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Review Article

STREAMLINING REGULATORY DOCUMENTATION: EXPLORING THE COMMON TECHNICAL DOCUMENT (CTD) AND ELECTRONIC SUBMISSION, WITH EMPHASIS ON M SERIES ACCORDING TO ICH GUIDELINES

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ABSTRACT

A number of regulatory bodies have worked together to create the Common Technical Document (CTD), including the United States Food and Drug Administration, the European Medicines Agency, and the Japanese Ministry of Health. This standardized format facilitates the collection and submission of regulatory documentation pertaining to applications for new medicines. Since its inception in 2000, the CTD has been widely adopted internationally, including by nations such as Canada, Australia, and India. The CTD aims to streamline the submission process, reduce duplication of effort, and facilitate regulatory evaluations by providing a uniform structure for technical documentation. This article outlines the guidelines and organization of the CTD, including its modules covering administrative information, quality, non-clinical studies, and clinical trials. The CTD's significance lies in its ability to improve regulatory efficiency, promote data transparency, and expedite the availability of new medicines to patients. However, challenges persist, such as variations in regional requirements and the need for continued adaptation to evolving technological standards. Electronic submissions and improved information management are two ways in which the new electronic CTD (eCTD) has improved submission procedures. Despite some ongoing issues, the CTD and eCTD represent significant advancements in regulatory documentation, with the potential for further innovation and global adoption in the future.

Keywords: Common technical dossier/document, Electronic common technical dossier, International Conference on Harmonization, M4 series.

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INTRODUCTION

In the year 2000, representatives from the European Medicines Agency, the FDA, and the Japanese Ministry of Health, Labor, and Welfare drafted a set of rules regarding the format and content of a new medicine application dossier. These rules are in place to make sure that all three groups follow them. These notions are now part of the International Conference on Harmonization (ICH) recommendations, a set of guidelines put together with the help of the ICH. The Common Technical Document (CTD) aimed to streamline the process of collecting applications for human medicine registration by creating a uniform format for technical information that would allow for the establishment of electronic submissions. In addition, if all regulatory authorities could use a single, standard document, it would speed up regulatory reviews, contact with the applicant, and the exchange of regulatory information [1,2].

There are now four guidelines from the ICH on the CTD in addition to four questions and answers documents. The initial set of ICH CTD regulations was issued in 2002. ICH developed CTD, but several other nations, including Canada, Australia, and India, have embraced it as well. In 2003, CTD was made mandatory for NDA filings in Japan and Europe. Although CTD is not yet required, the FDA has highly recommended it [3]. CTD has already been a smashing success by saving businesses a ton of money and time by eliminating the need to reformat and rearrange data into other forms. CTD makes it easier to submit applications simultaneously in several locations using an identical format for filing NDAs. By defining the CTD as "a collection of data comprising scientific, manufacturing, clinical, and non-clinical information presented in a standardized format and with identical content," the FDA aimed to simplify the procedure of registering new pharmaceuticals in the US, EU, and Japan [4].

GUIDELINES FOR PREPARATION OF CTD

The data contained in the CTD must be clearly and transparently displayed, just like in all other documents. According to the CTD organization's ICH M4 guidelines document, tables and text should have margins that enable printing on both 8.5 × 11" (USA) and A4" (EU and Japan) paper. It is advised that narrative compositions be composed using the Times New Roman 12-point font. The Unified Criteria for Manuscript Submitted to Scientific Journals states that each module must provide a list of references to relevant material and that acronyms and abbreviations must be defined wherever they appear. Except for cited works, where the present journal pagination is considered sufficient, all CTD publications should have page numbers starting on page 1. The ICH M4 guidelines state that page numbers need not be constantly displayed as "1 of n," where n is the total number of pages in the book. This is an interesting exception from the norm. Every page of a publication has its own header or footer that summarizes its contents (for instance, 2.7 Clinical Summary would be an abbreviation for the whole subsection number and title). For the purpose of avoiding fifth, sixth, and so on level subheadings (for example, 2.6.6.3.2.1) from being shown inside a document, the M4 standards provide shorter numbered strings. The condensed section numbers of the document (for example, 2.6.6 Toxicology Written Summary) are required to be shown in the footer or at the top of the page, after the document number and the name of the document [5].

ORGANIZATION OF CTD

The ICH M4 guidelines 1 give a general definition of the CTD as well as specific instructions for pagination and document placement within the CTD. Particularly useful is this level of detail if the dossier covers more than one indicator or component of the IMP. A series of inquiries and responses is also included to deal with the most frequently brought-up topics, together with to the M4 rules [6].

The applicant must abide by a few general guidelines when processing an application. The applicant should provide the data and information in CTD in an open and transparent manner. No information should be

concealed from regulatory bodies by the application. "CTD must be developed in accordance with the ICH recommendations" [7]. CTD is an arrangement where you should only add pertinent data. If the applicant considers that it is necessary to incorporate any extra information not contained in CTD to support his application [8].

Five primary modules of CTD dossier	
Module 1	Data related to administration and prescription
Module 2	Synopsis and overview of modules-3-5
Module 3	Quality (Pharmaceutical records)
Module 4	Non-clinical reports (pharmacology/toxicology)
Module 5	Clinical study reports (clinical trials)

Module 1: Regional administrative information

Since Module 1 is region-specific, CTD does not strictly include it. It includes application forms, labeling information, and administrative data [15]. The content and formats for Module 1 vary throughout nations [16,17].

For instance, in the United States, Module 5 gives detailed information on the investigator, but in Europe, Module 1 covers clinical specialists (researchers and quality assurance), while in the United States, Module 1 only hits on financial disclosure. While Module 1 in Europe does not require a statement of waiving off data for *in vivo* investigations, it does in the USA [18,19]. In the USA, an environment assessment statement must comply with the EPA, whereas in Europe, an environment risk certificate is necessary [20]. In contrast, pharmacovigilance is included into Phase IV trials and the risk management system in the United States, but it is not a part of Module 1 of the European Clinical Trials Declaration (CTD) [21,22].

Module 2: CTD overviews and summaries

2.1	Table of contents
2.2	Introduction
2.3	Quality overall summary
2.4	Non-clinical overview
2.5	Clinical overview
2.6	Non-clinical written and tabulated summaries
2.7	Clinical summary

Module 2.2: Introduction

Module 2.2 should provide an IMP summary, including the drug's pharmacological class, action mechanism, and proposed clinical use [23]. The standard recommendation is that the introduction stays within one page [24].

Module 2.3: Quality overall summary

In the case of chemicals, pharmaceuticals, biological and biotechnological commodities, and other technologies that are pertinent, a quality overall summary, also known as a QOS, provides an evaluation of the information included in the dossier at a high level [30]. The ICH M4Q standards specify the format of the QOS, and a follow-up document answers the most often-asked questions. In general, the information in the QOS follows the same format as the data presented in Module 3 [31]. Nothing that is not already covered in the 3rd module or other CTD sections should be included in the QOS. In addition to discussing the product's important parameters, the QOS should address difficulties that developed during development and offer explanations for any instances in which guidelines were not followed, etc. [32,33]. The regular length of the QOS, excluding tables and figures, is 40 pages of text; however, for biotech items and those made using more intricate processes, this may be increased to 80 pages [34].

Module 2.4: Non-clinical overview

The content and organization of Module 2.4 are defined by the ICH M4S regulations. A discussion of the data's interpretation and analysis, as well as an evaluation of their clinical relevance, should be part of the Non-Clinical Overview (Module 2.4) [35]. In addition, it should investigate whether there is a connection between the non-clinical results and the IMP's quality components, and what these results mean for the safety of the IMP when tested on humans [36]. If there are relevant protocols that need to be followed for carrying out the research, they should be noted and any discrepancies should be explained. An explanation and justification of the non-clinical testing technique should be included, in addition to an assessment of the studies' compliance with Good Laboratory Practice [37]. Pay close attention to the characteristics of similar goods and provide references to relevant scientific articles (e.g., if a certain discovery has been made with a drug that is classified as the IMP, it must be mentioned). In terms of animal testing, the Non-Clinical Overview provides a thorough and critical evaluation of the IMP's toxicological, pharmacokinetic, and pharmacological characteristics. In most cases, the length of non-clinical overviews is restricted to thirty pages [38].

Module 2.5: Clinical overview

A concise document referred to as the "Clinical Overview" comprises an exhaustive examination of the clinical data that are being evaluated. An integral part of any CTD dossier is the Clinical Overview [39]. The six parts that make up the Clinical Overview are as follows: Product development rationale, biopharmaceutics, clinical pharmacology, safety and efficacy, and conclusions on the product's advantages and disadvantages. The Clinical Overview, in contrast to its literal representation in the Clinical Summary, offers a comprehensive exposition of the medication manufacturing program and its yielded outcomes. In this investigation, clinical outcomes and other pertinent data are investigated and evaluated. For instance, pertinent animal data or product quality issues that potentially impact clinical outcomes are illustrations of pertinent data [40]. To reiterate, the Clinical Overview is not meant to repeat information that is already in the Clinical Synopsis or elsewhere in the CTD; rather, it is meant to draw attention to the findings and the relevance of the data. In addition to identifying areas where the research and development approach fell short, a strong Clinical Overview would also explain how the study's findings support important recommendations made in the prescription advice [41]. Included should be a statement about adherence to Good Clinical Practice, or GCP, and the caliber of the clinical programs and study performance. If a license is approved, the clinical overview ought to address the IMP's position in the clinical toolbox [42]. To contextualize the results, appropriate references to the literature should be given. Depending on the results of the clinical studies that are pertinent to the topic at hand, the Clinical Overview needs to additionally cover the advantages and disadvantages of the IMP. It is important to evaluate not just how other measures, such prescription information, would maximize benefits and minimize risks, but also how the safety and efficacy results support the indicated dosage and target indication. The intended length of the Clinical Overview ought to be around thirty pages [43].

Module 2.6: Non-clinical written and tabulated summaries

Module 2.6's Non-Clinical Textual and Tabled Reports strive to give accurate and thorough non-clinical information about pharmacology, drug kinetics, and toxicity [44-46]. Non-Clinical Written Summaries typically have a page count of 100–150. The ICH M4S standards contain a total of 34 patterns that can be used to prepare Tabulated Summaries [47,48].

Module 2.7: Clinical summary

The term "Clinical Summary" refers to a more extensive document that is primarily concerned with incorporating an overview of the data. Providing an accurate and thorough description of the clinical facts is the aim of the clinical summary [49,50]. This combines data from every accessible meta-analysis and other cross-study assessment carried out, as well as information on product sales in other areas [51]. Module 5's clinical trial reports and their accompanying data are also part of this. Just be sure to stick to true observations while comparing and analyzing the different research findings presented in this publication. The

Clinical Overview covers data interpretation [52]. Sections on clinical pharmacology, safety, efficacy, biopharmaceutics, and related analytical techniques make up the Clinical Summary. An electronic CTD (eCTD) containing the relevant hyperlinks is provided for every abstract of a case study report, which is also incorporated within this module. Typically, the clinical summary spans a length of 50 to 400 pages; nevertheless, the inclusion of a substantial number of indications may extend its length considerably [53].

Module 3 quality

The components of the product registration dossier that pertain to manufacturing, chemical, and control are shown in Module 3 [54-56]. All of the data required for Module 3 is already included in the ICH M4Q regulation [57-59]. This module has sections that cover the pharmaceutical ingredient and drug product. Below are illustrations of the various Module 3 components [60-62].

3.1	Table of contents
3.2	Body of data
3.2.S	Drug substance (s)
3.2.S.1	General information (name, manufacturer)
3.2.S.1.1	Nomenclature (name, manufacturer)
3.2.S.1.2	Structure (name, manufacturer)
3.2.S.1.3	General Properties (name, manufacturer)
3.2.S.2	Manufacture of drug substances (name, manufacturer)
3.2.S.2.1	Manufacturer (s) (name, manufacturer)
3.2.S.2.2	Description of manufacturing process and process control (name, manufacturer)
3.2.S.2.3	Control of materials (name, manufacturer)
3.2.S.2.4	Controls of critical steps and intermediates
3.2.S.2.5	Process validation and/or evaluation (name, manufacturer)
3.2.S.2.6	Manufacturing process development (name, manufacturer)
3.2.S.3	Characterization of drug substance
3.2.S.4	Quality control of drug substance
3.2.S.5	Reference standards or materials
3.2.S.6	Container closure system
3.2.S.7	Stability of drug substance
3.2.P	Drug product (name, dosage form)
3.2.P. 1	Description and composition of the drug product
3.2.P. 2	Pharmaceutical development
3.2.P. 3	Manufacture of drug product
3.2.P. 4	Control of excipients
3.2.P. 5	Control of drug product
3.2.P. 6	Reference standards or materials
3.2.P. 7	Container closure system
3.2.P. 8	Stability of drug product
3.3	Literature reference

Module 4: Non-clinical study reports

The presentation of dossier data that does not pertain to clinical matters is encompassed within Module 4. Module 4's structure and content are both determined in accordance with the ICH M4S criteria [63-65]. These are the main, unchanging headers of the section [66-72].

4.1	Table of contents of Module 4
4.2	Study reports
4.2.1	Pharmacology
4.2.2	Pharmacokinetics
4.2.3	Toxicology
4.3	Literature references used in Module

Module 5: Clinical study reports

Module 5 gives an overview of the clinical reports that make up the dossier. Module 5's content and organization are predetermined by the ICH M4E standards [73-75]. These guidelines delineate a precise progression for clinical research reports and provide supplementary materials to aid in their submission, evaluation, and finalization [76,77]. The main goal of the research determines where each report appears, and each report only appears in one section [78]. If the research has more than one goal, it must be cross-referenced between parts. In this part, the following are the main sections that cannot be changed [79,80].

5.1	Table of contents of Module 5
5.2	Tabular listing of all clinical studies
5.3	Clinical study report
5.3.1	Reports of biopharmaceutics studies
5.3.2	Reports of studies pertinent to pharmacokinetic using human biomaterial
5.3.3	Reports of human pharmacokinetic studies
5.3.4	Reports of human pharmacodynamic studies
5.3.5	Reports of efficacy and safety studies
5.3.6	Reports of post-marketing experience
5.3.7	Case report forms and individual patient listings
5.4	Literature references
4.3	Literature references used in Module

SIGNIFICANCE OF CTD

A standard format has been implemented on a national level to facilitate the examination of all applications in a more streamlined manner and to ensure that no information or analyses are ignored [81-83]. If such mandatory data are omitted, approvals may be delayed needlessly [84]. It streamlines regulatory review and interactions while saving time and money [85,86]. It offers a suitable style for the data that are simple to comprehend and aids in data evaluation [87]. CTD works with many kinds of products. Its more uniform format facilitates easy analysis for the reviewer as well [88]. In addition, CTD promotes the exchange of regulatory data and makes it easier for papers to be submitted simultaneously for clearance in three different places [89,90]. In addition, it makes electronic submissions easier to do and speeds up the process of delivering new medications to medical professionals [91,92].

ISSUES OF CTD

Despite the fact that the CTD has had positive outcomes and that its format has been extensively embraced (the most recent dossiers have switched to the eCTD format), there are still segments of the pre-CTD dossier requirements that are still in place in specific regions [93]. An example of this is the need to provide a synopsis of both the safety and effectiveness of the product. Among these organizations are the FDA [94]. Regardless, the original plan called for the Clinical Summary to take the place of these two parts: in Module 2.7.3, a Summary of Clinical Efficacy was supposed to replace the ISE, and in Module 2.7.4, a Summary of Clinical Safety was supposed to take the place of the ISS [94]. Therefore, it is advised to cover all of the ISE and ISS in Module 5 before condensing it for the articles in Module 2.7 [95,96]. The CTD's goal of providing a standard structure for the data contained in a submitted dossier has mostly been accomplished. However, whether this has reduced application development time and resources as anticipated are debatable [97].

eCTD

The eCTD is a means of information exchange between regulatory agencies and the pharmaceutical industry [98]. The underlying structure for the main content is the CTD format. The organization ICH M2 EWG, which was formally referred to as the ICH, was in charge of its inception [99]. The electronic CTD, commonly referred to as eCTD, serves as a conveyance format to facilitate the submittal of electronic documents and may be incorporated into an organization's review process [100]. In addition to serving as a conduit for the transfer of regulatory data between businesses and government bodies, the eCTD will make it easier to create, assess, manage, and archive the electronic submission [101]. The requirements that must be fulfilled for an electronic submission to be considered technically valid are outlined in the eCTD standards. The eCTD represents a significant advancement in terms of data offered for novel medical applications. Companies could eventually be able to electronically submit paperwork to many regulatory authorities by just pressing a single key in the not-too-distant future [102].

BENEFITS OF eCTD

1. 1.Better management and preservation of submissions advantages of eCTD

Table 1: Module description[9-14]

Module	Guideline	Topic	Information contained	Date of finalization	Date of the new codification
1	M4 R3	Regional Administrative Information	• Documents for administration • Labels • Environmental evaluation • Information previously supplied	September 2002	November 2005
	M4 Document with Questions and Answers (R3)	Questions and Answers Document		June 2004	
2	M4Q R1	Overall Summary	• CTD Contents Table • Introduction to CTD • Quality in Context Summary • General data • Clinical Overview • Summary of Data in a Non-Clinical Setting • Summary of Clinical Practice • Synopses of individual studies.	September 2002	November 2005
	M4Q Questions and Answers Document (R1)	Questions and Answers Document		June 2003	
3	M4Q R1	Quality	• Table of Contents of Module 3 • Body of Data (Chemical, Pharmaceutical and Biological data) • Literature References	September 2002	November 2005
	M4Q Document: Questions and Answers (R1)	Questions and Answers Document		June 2003	
4	M4S R2	Summary of Non-Clinical Research	• Module 4's Contents Table • Study Reports (Pharmaco-toxicologial data) • Literature References	September 2002	November 2005
	M4S Questions and Answers Document (R2)	Questions and Responses Document		November 2003	
5	M4E R1	Clinical Study Reports	• Table of Contents of Module 5 Detailed Catalog of All Clinical Trials • Reports on Clinical Studies • Literature Reference	September 2002	November 2005 [9-14]
		Questions and Answers Document		June 2004	

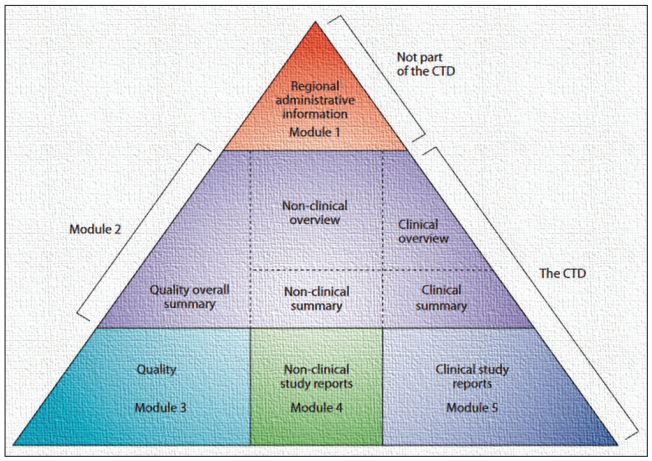

Fig. 1: Common technical dossier triangle[103, 104]

2. Improved data administration
3. Life cycle management support
4. Instant access to comprehensive and current data
5. Assessor search capabilities and enhanced tracking capacity
6. Facilitated assessment and increased process visibility
7. Less effort and information reuse for evaluation reports
8. Restrained dialogue with outside specialists
9. More efficient resource utilization
10. A more straightforward business procedure
11. Improved dialogue with business [103,104].

CONCLUSION

The common technical dossier is an essential tool for pharmaceutical companies seeking market authorization for new drug products. To assist regulatory agencies evaluate the drug's efficacy and safety, it provides detailed technical information on the product in a standard style. By providing a standardized format for submissions, the CTD streamlines the regulatory review process and facilitates comparisons between different drug products. The electronic common dossier (ECD) represents a significant step forward in streamlining the visa application process. Its benefits, such as efficiency, data security, and standardization, make this technology-driven approach an attractive option for visa authorities. However, challenges such as technical infrastructure, compliance, data validation, and interoperability must be addressed to ensure its successful implementation. The future of the ECD holds great promise, with potential global adoption, innovation, and improved decision-making through data analytics and artificial intelligence. As more countries embrace the ECD, the visa application process will become more efficient, reliable, and streamlined for applicants worldwide.

AUTHORS' CONTRIBUTIONS

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Mr. Rashyap Saraswat drafted this article and contributed in writing of the review article. Ms. Ankita Raikwar contributed in drafting and writing the significance and conclusion portion. Dr. Subhranshu Panda contributed in the compilation and review of the paper.

CONFLICTS OF INTEREST

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