



THE COMMON TECHNICAL DOCUMENT: TAKING INDIAN NDA PROCESS TOWARDS GLOBALIZATION

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ABSTRACT

Demonstration of safety and efficacy of the drug product for use in humans is essential before the drug product can be approved for import or manufacturing of new drug by the applicant by Regulatory authority in any country. Once preclinical and clinical trial data have been collected, a New Drug Application must be submitted to the regulatory authority for approval. Although the requirements for this submission have similarities around the world, until now, the applications have been different. Substantial documentation and data are required in these types of submissions, resulting in large, complex applications. Till date, applicants have used many different approaches in organizing the information and the differences in organization of data in each application has made reviewing more difficult and can also lead to omission of critical data or analyses. Such omissions can result in unnecessary delays in approvals. Thus, a common format of submission will help in overcoming these hurdles. Through the International Conference on Harmonisation (ICH) process, the Common Technical Document (CTD) guidance's have been developed for Japan, European Union, and United States. The CTD drug application format is now favored by the US Food and Drug Administration (FDA) as well as worldwide regulatory authorities. Hence, Central Drugs Standard Control Organization (CDSCO), India has also decided to adopt CTD format for technical requirements for registration of pharmaceutical products for human use. Implementation of CTD is expected to significantly reduce time and resources needed by industry to compile applications for global registration.

Keywords: Common Technical Document, International Conference on Harmonisation, Central Drugs Standard Control Organization, New Drug Application, Globalization.

INTRODUCTION

Drug approval is the goal of the long process of drug development. Once preclinical and clinical trial data have been collected, a New Drug Application must be submitted to the regulatory authority for approval.¹

Every drug, before receiving approval for marketing in India, or indeed many other countries, must undergo rigorous scientific testing and scrutiny to ensure that it is safe and effective for its intended use. Drug development starts with *in vivo* animal studies that primarily evaluate the pharmacology and potential toxicities of a product. Once these studies are complete, the sponsor of a drug submits an Investigational New Drug application (IND) for review. The IND contains the preclinical data and proposed plans for study in a human population. The information submitted in an IND is reviewed in the India by DCGI – CDSCO and a decision is made whether to allow a sponsor to begin clinical trials in humans.¹

During the clinical trials, products typically undergo three phases of study: Phase I, Phase II and Phase III, which represent the giving of the new drug to increasing numbers of patients in an effort to characterize safety and efficacy. Once the clinical trials are completed, the results are tabulated and analysed by the sponsor and then submitted as a New Drug Application (NDA) to the DCGI – CDSCO. The NDA presents to DCGI – CDSCO reviewers the entire history of the development of a drug product. It is the job of the DCGI – CDSCO to review the

data and determine whether the product meets the criteria for marketing in India.¹ (See Figure – 1).

The regulations under Drugs and Cosmetics Rules 122A, 122B and 122D and further Appendix I, IA and VI of Schedule Y, describe the information required for approval of an application to import or manufacture of new drug for marketing.²

Substantial documentation and data are required in these types of submissions, resulting in large, complex applications. Till date, applicants have used many different approaches in organizing the information and the differences in organization of data in each application has made reviewing more difficult and can also lead to omission of critical data or analyses. Such omissions can result in unnecessary delays in approvals.²

Globalization of the pharmaceutical industry has created the need to harmonize the recommendations for the development of new pharmaceuticals, as well as the regulatory requirements of various countries.¹

Thus, a common format of submission will help in overcoming these hurdles. Through the International Conference on Harmonisation (ICH) process, the Common Technical Document (CTD) guidance's have been developed for Japan, European Union, and United States.²

Most countries have adopted the CTD format. Hence, CDSCO has also decided to adopt CTD format for technical requirements for registration of pharmaceutical products for human use.²



This guidance is developed by CDSCO based on,

- The ICH Harmonised Tripartite Guideline on “Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use”. M4, Step 4 version dated January 13, 2004, and
- Drugs & Cosmetics Act 1940 and Rules made thereunder.²

OBJECTIVE OF ICH TO PREPARE THE CTD

The primary objective of the ICH is to avoid duplicative animal and human testing and to reach a common understanding of the technical requirements to support the registration process in the three ICH regions. These objectives are achieved through harmonized guidelines and result in a more economical use of human, animal and material resources, as well as the elimination of

unnecessary delays in the global development and availability of new medicines, whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health. With the development of the Common Technical Document (CTD), the ICH hopes to accomplish many of its objectives.¹

EVOLUTION OF THE COMMON TECHNICAL DOCUMENT

Efforts over the past 15–20 years by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have resulted in a unified dossier for drug applications, the Common Technical Document for the registration of Pharmaceuticals for Human Use (CTD).³

The evolution of The Common Technical Document is illustrated in figure - 2.

Figure 1: The Drug Approval Process: Drug approval involves passing a number of steps, including preclinical and clinical studies, and later, post-marketing research.¹

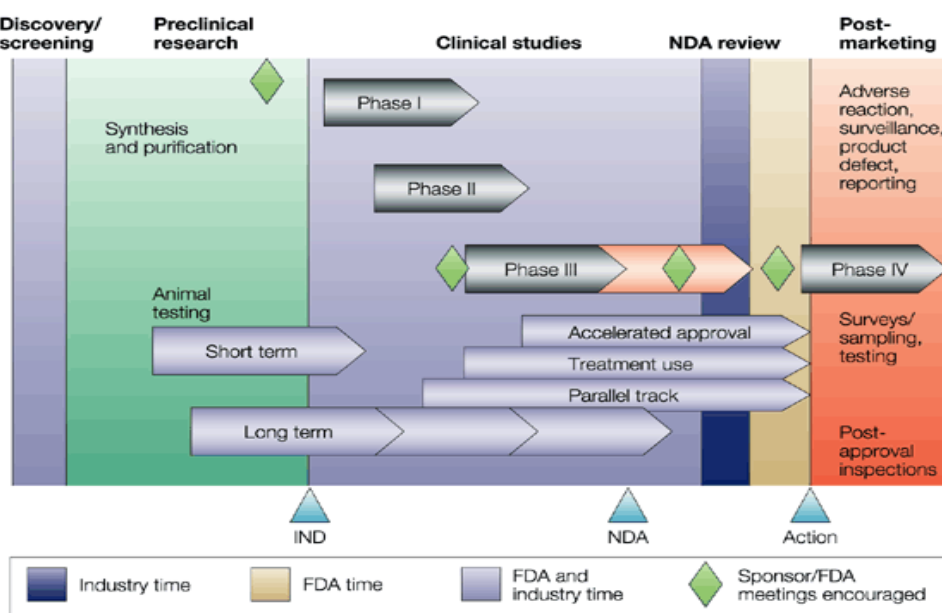
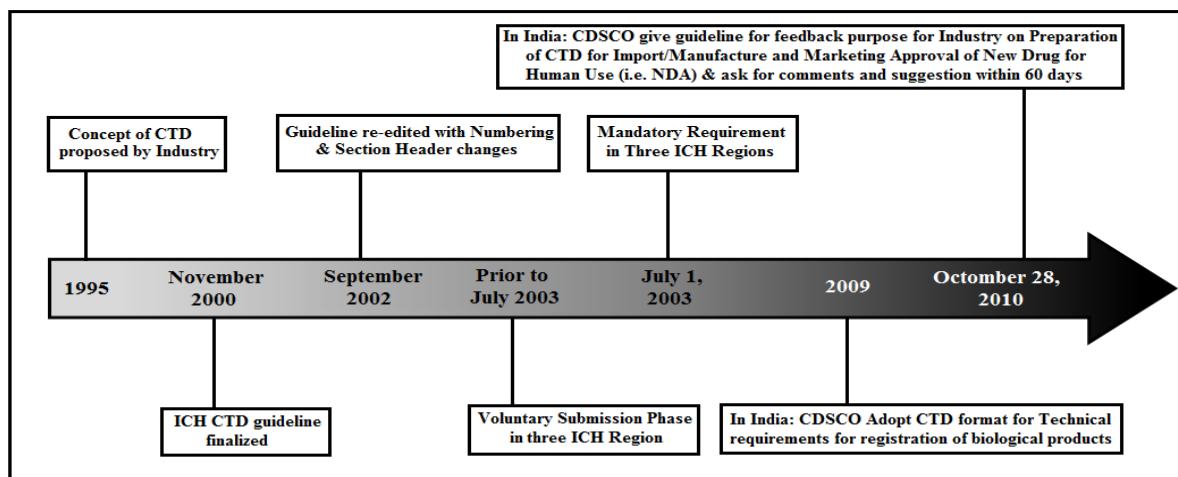


Figure 2: Evolution of the CTD.^{1, 2}



In ICH Region¹

1995: Concept of CTD proposed by Industry.

November 2000: ICH CTD guideline finalized.

September 2002: Guideline re-edited with Numbering & Section Header changes.

Prior to July 2003: Voluntary Submission Phase in three ICH Region.

July 1, 2003: Mandatory Requirement in Three ICH Regions.

In India²

2009: CDSCO Adopt CTD format for Technical requirements for registration of biological products.

October 28, 2010: CDSCO give guideline for feedback purpose for Industry on Preparation of CTD for Import/Manufacture and Marketing Approval of New Drug for Human Use (i.e. NDA) & ask for comments and suggestion within 60 days.

THE COMMON TECHNICAL DOCUMENT & ITS COMPONENTS

The Common Technical Document (CTD) is a set of specification for application dossier for the registration of Medicines and designed to be used across Europe, Japan and the United States.⁴

Table 1 gives idea about what is CTD & what isn't CTD.^{5,6}

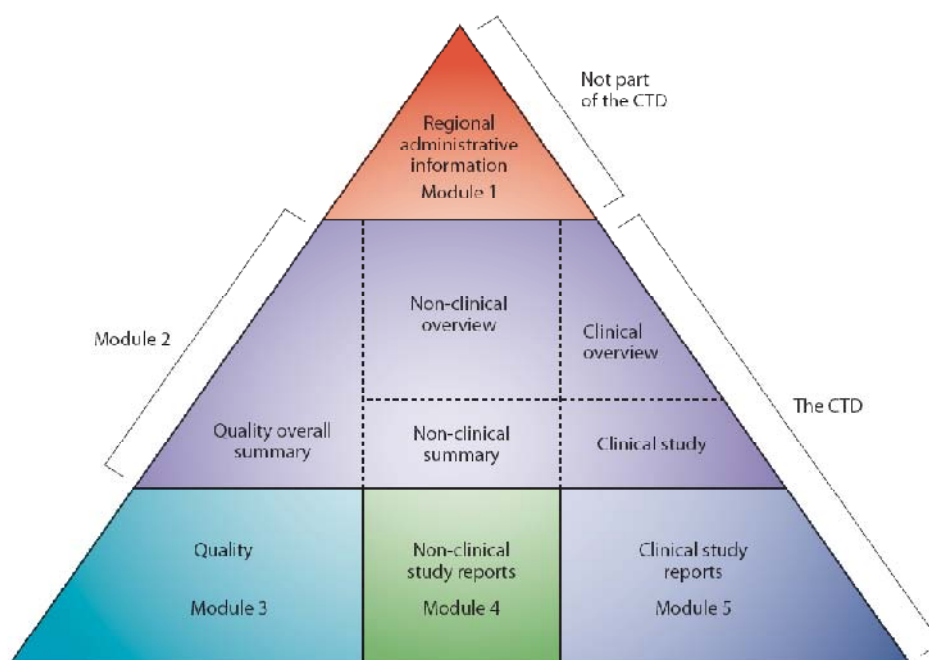
The Common Technical Document is divided into five modules:⁴

1. Administrative and prescribing information
2. Overview and summary of modules 3 to 5
3. Quality (pharmaceutical documentation)
4. Safety (toxicology studies)
5. Efficacy (clinical studies)

Components of the CTD

The CTD is organized into five modules. Module 1 is region specific and Modules 2, 3, 4 and 5 are intended to be common for all regions.⁷ The CTD triangle is illustrated in Figure - 3.⁸ The format of the CTD application is modular and organized according to the general outline in Table 2.^{2,3,9-12}

Figure 3: The CTD Triangle.⁸



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Table 1: What is CTD & What isn't CTD.^{5,6}

CTD IS	CTD IS NOT
A common harmonised FORMAT for applications for preparing marketing authorisations in the three ICH regions. It is a TEMPLATE for presenting data in the dossier.	A statement of data requirements for applications.
A guideline that merely indicates an appropriate format for the data that have been acquired.	A guideline that intended to indicate what studies are required.



Table 2: Modular Organization of CTD.^{2, 3, 9-12}

The Common Technical Document	
Module 1: Administrative Information and Prescribing Information	
1.1	Table of Contents of the Submission Including Module 1
1.2	Documents Specific to Each Region
Module 2: Common Technical Document Summaries	
2.1	CTD Table of Contents
2.2	CTD Introduction
2.3	Quality Overall Summary
2.4	Nonclinical Overview
2.5	Clinical Overview
2.6	Nonclinical Written and Tabulated Summary <ul style="list-style-type: none"> ↳ Pharmacology ↳ Pharmacokinetics ↳ Toxicology
2.7	Clinical Summary <ul style="list-style-type: none"> ↳ Biopharmaceutics and Associated Analytical Methods ↳ Clinical Pharmacology Studies ↳ Clinical Efficacy ↳ Clinical Safety ↳ Synopses of Individual Studies
Module 3: Quality	
3.1	Module 3 Table of Contents
3.2	Body of Data
3.3	Literature References
Module 4: Nonclinical Study Reports	
4.1	Module 4 Table of Contents
4.2	Study Reports
4.3	Literature References
Module 5: Clinical Study Reports	
5.1	Module 5 Table of Contents
5.2	Tabular Listing of All Clinical Studies
5.3	Clinical Study Reports
5.4	Literature References

The CTD is organised into five modules:

MODULE 1: Regional Administrative Information:

Module 1 is for administrative information and prescribing information, and should contain documents that are specific to each region; for example, 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.⁷

In India: This module should contain documents specific to India; for example, Form 44, Treasury challan fee or the proposed label for use in India.²

MODULE 2: Overview and summary of modules 3 to 5:

Module 2 contains the CTD summaries and should begin with a general introduction to the drug, including its pharmacological class, mode of action and proposed clinical use. Module 2 should also provide the overall summary of the 'quality' information provided, the non-clinical overview and the clinical overview, as well as the

non-clinical written summaries and the tabulated summaries, and the clinical summary.⁷

In India: 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.²

MODULE 3: Quality (Pharmaceutical Documentation):

The Quality section of the Common Technical Document (M4Q) provides a harmonised structure and format for presenting CMC (Chemistry, Manufacturing and Controls) information in a registration dossier. The table of contents includes sections on Drug Substance and Drug Product. There are also sections for regional specific information as well as some appendices.⁷

MODULE 4: Safety (Toxicology Studies – Non Clinical Study Report):

The CTD Safety (M4S) Guideline delineates the structure and format of the nonclinical summaries in Module 2 of the Common Technical Document, and provides the



organisation of Module 4, the Nonclinical Study Reports. The Nonclinical Overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the pharmaceutical, and generally should not exceed 30 pages. The Nonclinical Written Summaries (100 - 150 pages) are recommended to provide more extensive summaries and discussion of the nonclinical information on pharmacology, pharmacokinetics and toxicology.⁷

MODULE 5: Efficacy (Clinical Study Report):

CTD-Efficacy (M4E) describes the structure and format of the clinical data in an application, including summaries and detailed study reports. There are two high level clinical summaries in Module 2 of the CTD: the Clinical Overview, a short document that provides a critical assessment of the clinical data; and the Clinical Summary, a longer document that focuses on data summarization and integration. Clinical Study Reports and raw data (where applicable) are included in Module 5 of the CTD.⁷

CLARIFICATION OF CDSCO – INDIA ON GUIDANCE FOR INDUSTRY ON PREPARATION OF COMMON TECHNICAL DOCUMENT

- This guideline applies to import / manufacture and marketing approval of new drugs including new chemical entity, new indication, new dosage forms, modified release form, new route of administration etc. under the definition of new drug under Rule 122E of Drugs & Cosmetics rules, as a finished pharmaceutical product.²
- This guideline is not intended to advice on the design of studies that are required for product registration, but it indicates an appropriate format for submission of the data that have been acquired. Drugs & Cosmetics Act and Rules there under, defines the 'content requirements' for the specific type of submission and hence, this guidance document has to be read along with Drugs and Cosmetics Act 1940 and Rules made thereunder.²
- The CTD is only a format for submission of information to CDSCO. It does not define the content.²
- Although adherence to overall CTD structure is necessary, it should be noted that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, applicants can modify the format at some of the subsection levels, if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation.²
- Clear and unequivocal information should be provided.²

POINT TO BE CONSIDERING WHEN PREPARING THE CTD

A drug application organized according to CTD format is not any more difficult than a standard NDA; guidance provides much assistance. However, in places, there can

be significant advantages to considering the "art" of the presentation as well as the science.³

Throughout the CTD, the display of information should be unambiguous and transparent, to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents.¹³

Even though CTD applications are typically huge, often hundreds of thousands of pages in length, there are opportunities to be creative, to tell a story, and to craft cohesive arguments to help regulatory bodies to understand your product. The modular format, with several layers of lesser or greater detail, allows for the presentation of the overall picture while making available all the supportive details. Because of the large size and complexity of CTD applications, it is important to cross-reference sections carefully within and between modules.³

Although each module of the CTD has a specific function, the key areas for creative and informative content are Modules 2 and 3. These sections allow for integration of data between studies, presentation of both the strengths and limitations of the data, and giving the reviewer an opportunity to see the big picture at any of several levels of detail. Clear and compelling presentations in these two modules are critical to the success of the application.³

The most important approach to maximize the chance that the CTD application is received favorably to strive for clarity, to avoid exaggerations, and to discuss rather than hide negative findings and deficiencies. Avoid claims that cannot be substantiated, and keep in mind the advice that if something is not documented it is rumor.³

If reviewers look favorably on an application's content and presentation and can follow the trail from statement to documentation, there is the best chance for the most rapid approval. A further benefit of a high-quality CTD application is that regulatory body's requirements for additional data, which become imposed at the time of review, may well end up as a post market requirement as opposed to a preapproval obligation. If the reviewers are generally uncomfortable with the CTD, review issues are more likely to result in new preapproval data obligations that delay approval.³

THE ELECTRONIC CTD – MODERN CONCEPT

The electronic Common Technical Document (eCTD) is an interface for the pharmaceutical industry to agency transfer of regulatory informations. The content is based on the Common Technical Document (CTD) format.¹⁴

It was developed by the International Conference on Harmonisation (ICH) Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG).¹⁴

Essentially, the electronic Common Technical Document (eCTD) will be a transport format intended to be moved into an agency's review environment and will facilitate electronic submissions. The eCTD will serve as an interface for industry-to-agency transfer of regulatory



information, and at the same time take into consideration the facilitation of the creation, review, life-cycle management and archiving of the electronic submission. The eCTD specification lists the criteria that will make an electronic submission technically valid. The eCTD represents a major advance in the submission of information to support a new drug application. In the future, companies might be able to send their submissions to several regulatory authorities simultaneously with the single stroke of a computer key.¹

ADVANTAGES OF CTD

- The main aim behind implementing a common format of submission is to make the reviewing of each application more easy and also to avoid omission of critical data or analyses. Omissions of such data can result in unnecessary delays in approvals.¹⁵
- A common format for the technical documentation will significantly reduce time and resources needed to compile applications for registration of human pharmaceuticals and will ease the preparation of electronic submission.¹⁵
- Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements.¹⁵
- Implementation of CTD is expected to significantly reduce time and resources needed by industry to compile application for global registration.¹⁵
- CTD not only help in raising the Indian standard but also will help to bring a proper structure to the whole process of filling an application.¹⁵
- In addition, exchange of regulatory information between regulatory authorities will also be simplified.¹⁵

SILENT BENEFITS OF CTD

- Global harmonization of applications.¹⁶
- Provides standards to prepare submission-ready documents in the IND phases.¹⁶
- Standardization assists project management and information management.¹⁶
- Facilitates life cycle management.¹⁶
- Facilitates drug development planning.¹⁶

HOW TO ACHIEVE PERFECT HARMONY

Further training of reviewers and industry will be based on practical experience with submissions. Companies are therefore being encouraged to submit applications in the new format to build up this experience. The ICH Steering Committee wants to see the benefits of the CTD realized by both the industry and the regulators. Much work has also been done on the eCTD. The CDSCO - India is committed to implementation of the CTD; however, implementation must be carried out as a coordinated effort, and industry and regulators must work together to make the benefits of the CTD a reality. The CDSCO is

prepared to accept and review NDAs and INDs in the CTD format; industry must take the next step and submit applications for review.^{1,2}

ABBREVIATIONS

CDSCO: Central Drugs Standard Control Organization
 CTD: Common Technical Document
 DCGI: Drug Controller General of India
 eCTD: Electronic Common Technical Document
 FDA: Food and Drug Administration
 ICH: International Conference on Harmonisation
 IND: Investigational New Drug application
 NDA: New Drug Application
 USFDA: US Food and Drug Administration

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