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Significance of Common Technical Document in Pharmacy Regulation: A Review

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ABSTRACT
The Common Technical Documents (CTD) was designed to provide a common format between Europe, USA, and Japan for the technical documentation included in an application for the registration of a human pharmaceutical product. Electronic Common Technical Documents (eCTD) is a topic of increasing interest in the pharmaceutical environment. Electronic Common Technical Documents (eCTD) is an interface for the pharmaceutical industry to agency transfer of regulatory information. Since, June 2003, applicants have had the option of submitting an eCTD in parallel with the paper submission (Common Technical Documents), following sign-off by the International Conference on Harmonisation Steering Committee of the eCTD Specification documents at step 4. It is designed to make regulatory submissions easier and more efficient for drug makers and for regulations.
When it comes to eCTD submission, there continues to be differences among different countries and even ICH regions. The standardization that electronic submission will bring will allow for much greater consistency not only for regulators but also for organizations. It is important that eCTD ready document Prepared by authoring them in eCTD complaint templates.
Keywords: Common Technical Documents, ICH , Benefits, Challenges, Harmonisation.

I. INTRODUCTION

After decades of using paper, the goal is the electronic transfer of drug applications and their review across submission formats, procedures, and regions came in. Electronic Common Technical Document (eCTD) is a topic of increasing interest in the pharmaceutical environment. The eCTD is the electronic equivalent to the Common Technical Document (CTD) format. The eCTD is defined as an interface for industry to agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, lifecycle management and archival of the electronic submission. The eCTD specification lists the criteria that will make an electronic submission technically valid. The focus of the specification is to provide the ability to transfer the registration application electronically from industry to a regulatory authority. It was developed by the International Conference on Harmonisation (ICH) Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG). In November 2003, the ICH M2 group revised the specification for the eCTD to version, which remains the current version. ICH eCTD is an internationally driven standard designed to reduce cost in the administration, assessment and archiving of applications for marketing authorization of medicinal product for human use, to reduce the use of paper and streamline the assessment process making the system more efficient. It provides a common global standard for companies to electronically submit the quality, safety and efficacy information required for approval of a new drug to regulatory agencies in the United States(US),European Union (EU), Canada and Japan etc. that imposes minimal restriction to the industry and agencies (1). The primary technical components are:

a. A high level folder structure (required)
b. An EXtensible Markup Language(XML) “backbone" file which provides metadata about content files and lifecycle instructions for the receiving system.
c. An optional lower level folder structure (recommended folder names are provided in respective modules of the eCTD specification below)
d. Associated document type definitions (DTDs) and style sheets that support the presentation and navigation

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II. HISTORY

The steadiness of the submission format 'paper' in the past might not apply for the electronic submission formats in the future (six standards in the last 20 years - SEDAMM, MERS, MANSEV, CANDA, DAMOS, eCTD). Today submitting to ICH countries might be as eCTD, Non-eCTD electronic Submissions(NeeS), eSubmission or paper. Submissions to non-ICH countries offer even a greater variety of electronic or paper formats. The concept of electronic regulatory submissions is not new, and has been evolving in America and Europe since the late 1980s. The Food and Drug Administration (FDA) and others has worked with electronic submissions for more than a decade CANDA –(Computer Aided New Drug Application), Initiated in 1985 by FDA in US (2). It was seen as a way for FDA reviewers to have rapid access to report and data together, in a format that allowed efficient and high-quality analysis of data. Unfortunately, the CANDA era led to a proliferation of unique and proprietary formats for CANDAs, most of which required a stand-alone desktop computer on the desk of each regulatory reviewer (3). A whole variety of strategies for CANDAs emerged, from simple to complex. Each CANDA required a reviewer to learn a new system for accessing the data, a daunting task in many cases that few reviewers had time for. There were no standards for the structure of a CANDA and no common software platform or file format for the data. The results were mixed, many reviewers and sponsors were delighted with the efficient review that CANDAs provided, but others were unwilling to train on and use multiple different systems, sometimes simultaneously. The FDA soon called a halt to the unstructured CANDA era. But this was certainly not the end of the submission of electronic data.

a. DAMOS-Drug Application Methodology with Optical Storage; Initiated by European regulatory Europe in 1989.
b. SEDAMM - SoumissionElectronique de Dossiers d'Autorisation de Misesur le Marché; Initiated by France in 1993.
c. MERS- Multiagency Electronic Regulatory Submission Project; Initiated by USA, Newzea land, and Australia in 1994.
d. MANSEV - Market Authorisation by Network Submission and Evaluation; Initiated by UK, Denmark, France, Italy and EMEA in 1997.

In 1997, ICH M2 Expert Working Group (EWG) started working closely with M4 (CTD), the ICH guideline that presents the agreed upon common format for the preparation of a well structured Common Technical Document for applications that will be submitted to regulatory authorities. Simultaneously the FDA revealed the beginnings of a new method of electronic submission (4). The increasing volume of NDAs and the need for expedited review caused by the 1992 Prescription Drug User Fee Act (PDUFA) initiatives demanded that the FDA develop an approach for the efficient review of electronic data. The FDA was looking for a way to deal with the accumulating volumes of paper in its file rooms and the logistical problem of distributing sections of regulatory submissions to appropriate reviewers. By means of a series of guidance documents, the agency intended to carefully define the structure and technology that was acceptable for electronic submissions. In this way, the FDA could ensure a consistent set of electronic submission documents and reviewers could be comfortable that any electronically submitted data would be viewable in a familiar format. As a result, in 2002, eNDA and eANDA Guidance issued by FDA. Shortly after the first guidance documents were issued, electronic submission of New Drug Application(NDA) and Abbreviated New Drug Application(ANDA) documents became an emerging standard for many pharmaceutical sponsors, eliminating the need for manual printing, duplication, pagination, and other processes (5).

A significant milestone was the adoption in 2003 of the ICH eCTD Guideline v3.0 on the electronic Common Technical Document (eCTD), which is the electronic counterpart of the Common Technical Document (CTD; a harmonized structure and format for regulatory submissions). Following developmentof eCTD by ICH which is a start of transition to standards based submission has provided support for all application types including IND, NDA, BLA, ANDA, and Master Files. After that in 2004, ICH eCTD Guideline v3.2 was implemented in all ICH regions, In 2006 Withdrawal of eNDA and eANDAguidances took place. 3 It must be noted, however, that when it comes to eCTD submission, there continues to be differences among different countries and even ICH regions. For example, the FDA began accepting eCTD submissions in 2003; Japan began accepting in 2004, yet the EU Heads of Medicines Agencies committed themselves, in 2005, to be

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ready for eCTD submissions by 2010. The approach of the different health authorities also continues to be different. For example, Japan has accepted eCTD since 2004 but eCTD submissions of active pharmaceutical ingredient (API) dossiers are not possible; in Europe, some agencies continue to require paper submissions for specific sections. Outside the ICH region, countries are continuing to adopt the eCTD initiative and there is potential for eCTD to become the standard for non-ICH countries. Internationally, the eCTD has been required for Centralised Procedure applications to the European Medicines Agency (EMA) since 2010. Use of the format is also strongly encouraged in Canada, Japan and other developed markets around the globe. Therefore, anyone who works on drug regulatory submissions needs to understand the format well (6). In the US, the 2012 reauthorization and update of the Prescription Drug User Fee Act (PDUFA), within the Food and Drug Administration Safety and Innovation Act (FDASIA), elevates the eCTD format to a requirement for all New Drug Applications (NDAs), Biologics License Application (BLAs) and Abbreviated New Drug Applications (ANDAs). It also will be required for most Investigational New Drug Applications (INDs) within the next few years, depending on when FDA finalizes the pending guidance document (7).

On May 5, 2015, the U.S. Food & Drug Administration published a final, binding guidance document requiring certain submissions in electronic (eCTD) format within 24 months. The projected date for mandatory electronic submissions is May 5, 2017 for New Drug Applications (NDAs), Biologic License Applications (BLAs), Abbreviated New Drug Applications (ANDAs) and Drug Master Files (DMFs).4

III. BENEFITS OF IMPLEMENTING ECTD AND CHALLENGES

The standardization that electronic submissions will bring will allow for much greater consistency not only for the regulators but also for organizations. Both parties will benefit from reducing automation and storage costs by having all data in a common electronic environment that will also allow them to manage the documentation and oversee products more efficiently, eliminating difficulties with accessing, searching through and finding data in paper format. A common global standard for electronic submission of quality, safety and efficacy information provides such benefits as:

a. Allows regulators to use computer-based tools such as searching, copying and pasting text, making the review process more efficient and can complete reviews online in less time than it would take offline, which also benefits sponsors.
b. Streamlines review process allowing for multiple reviewers and therefore a more efficient review process
c. Allows Reuse of documents and submission components with more ease for several different regions by sponsors,
d. Enhance ability to efficiently organize, prepare and manage submission content
e. Reduce storage costs associated with producing and storing paper dossiers
f. Streamlines workflows in development, regulatory and marketing departments while increasing collaboration between teams (8).

Despite these benefits, the mandatory switch to eCTD presents companies with several challenges. The costs, both in initial capital and annual expense of building, validating and operating an electronic publishing system, together with the training and administration required to develop organizational competency, present a significant barrier to adoption. The effort required to establish and maintain an in-house system can be substantial, technical tools and a team of trained technical experts is typically required to document the requirements; research and evaluate options; procure, install, configure and test the system; and validate documentation and execute the full solution. While each organization's implementation project plan is different, a typical timeframe to complete the required steps is estimated to be between 9 – 18 months depending on the system size and configuration complexity. Another barrier to adoption is the risk of failed submissions. A deep knowledge of global regulatory requirements and the specifications of eCTD, as well as the ability to configure and operate a publishing platform to correctly assign every submission level and document-level attribute, is required to produce compliant submission documents. While large Pharma companies have the required capital and regulatory expertise for full eCTD implementation, companies operating across their global business models in emerging markets may not, specifically when considering the dynamic nature of regulatory requirements across emerging and developed

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markets (9). The same can be said of small- to mid-sized Pharma companies operating in developed markets. For small - to mid-sized companies with modest annual submission requirements; it is clear that implementing an in-house system is difficult to justify. Apart from the above, different implementation approaches, varied regional rules, changes in way of working, Granularity in eCTD, working with PDFs and hyperlinks, not ease to make Last minute changes are several other challenges. Since the introduction of the eCTD, submissions to FDA using the format have continued to grow steadily. According to FDA, eCTD submissions to the agency have climbed each year since 2004. In fiscal 2007, they made up about 9% of NDAs. In fiscal 2014, eCTDs accounted for 85% of NDAs (10).

IV. MODULES OF ECTD

The eCTD has five modules in two categories. There are

1. Regional module which includes only Module 1 - Administrative information and prescribing information - not harmonized - different for each region; i.e., country, defined by each of the ICH regions(USA, Europe and Japan).

2. Common modules: which includes module 2 – 5 (Harmonized - common to all the regions)

a) Module 2 - Common technical document summaries
b) Module 3 - Quality
c) Module 4 - Nonclinical study reports
d) Module 5 - Clinical study reports

The specification for the eCTD is based upon content defined within the CTD issued by the ICH M4 EWG. The CTD describes the organization of modules, sections and documents. The structure and level of detail specified in the CTD have been used as the basis for defining the eCTD structure and content but, where appropriate, additional details have been developed within the eCTD specification. The ICH website includes an empty eCTD folder template as an example of an eCTD submission folder structure. It shows all of the possible modules 2-5 folders and can be populated with the applicant data and edited as appropriate (i.e. adding additional folders or removing unnecessary folders). The applicant should still add the relevant regional module 1 folders and content, add the appropriate utility folders and content, and create the XML (Extensible Markup Language) index files to complete a valid eCTD.**Fig-1**

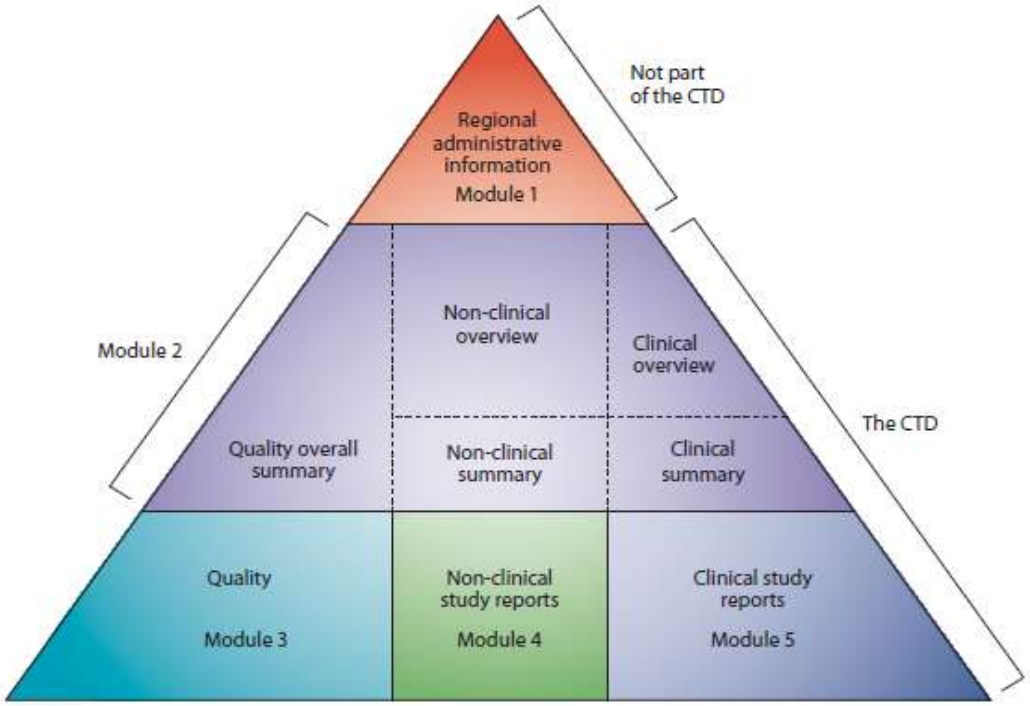

Fig: 1 The CTD triangle.

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Module 1

Module 1 is region specific due to which it is not strictly included in CTD. It contains administrative information, labeling information, and application forms. Different countries have different formats and content for Module 1. Different types of cover letters, forms (e.g., in US 356 h is used), field copy, patent information, and application information are used. Administrative information in case of Europe depends on type of procedure to be followed. In case of mutual or decentralized procedure, cover letter for specific member state, application form applicable for specific country, proof of payment to clinical investigators, proof of establishment of the applicant in European Economic Area, etc., are required. Information about drug product is known as a summary of product characteristics (SPC) in Europe while it is known as package insert in the USA. Information regarding the experts (clinical, i.e., investigators and quality) is provided in the Module 1 in Europe, whereas in USA only financial disclosure is mentioned in Module 1 and detailed information about investigator is provided in Module 5. Module 1 in the USA includes waiver off information for in vivo studies while no such mention is required in Europe in Module 1. Environment assessment statement should be compliant with EPA in the USA, whereas environment risk certificate is required in case of Europe. Separate section on pharmacovigilance is provided in Module 1 of European CTD while in USA, it is a part of risk management system and Phase IV trials. Side-by-side labeling of drug product compared with reference listed product is mentioned in Module 1 of the US FDA whereas in Europe, it is not required. All information is given in SPC (11).

Module 2: CTD Overviews and Summaries

Module 2 contains 7 sections as given below (12):

2.1. CTD table of contents (Modules 2-5)
2.2. CTD introduction
2.3. Quality overall summary
2.4. Non-clinical overview
2.5. Clinical overview
2.6. Non-clinical written and tabulated summaries
• Pharmacology
• Pharmacokinetics
• Toxicology.
2.7. Clinical summary
• Biopharmaceutic studies and associated analytical methods
• Clinical pharmacology studies
• Clinical efficacy
• Clinical safety
• Literature references
• Synopses of individual studies.

It is clearly evident from different sections of Module 2 that it describes the overall summaries and overview of Modules 3-5. It gives a brief idea to the regulators and application reviewers regarding the content of Module 3-5. It contains written and tabulated summaries related to quality, non-clinical, and clinical data.

Module 3: Quality

Module 3 provides information on the chemistry of drug product and drug substance, their manufacturing, and controls. Different sections of Module 3 are depicted below:

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 substance (name, manufacturer)
3.2. S.2.1 Manufacturer(s) (name, manufacturer)
3.2. S.2.2 Description of manufacturing process and process controls (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

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3.3. Literature references.

Module 4: Non-clinical Study Reports
Module 4 describes the format and organization of the non-clinical (pharmacotoxicological) data relevant to the application. Main sections of module 4 are:
4.1. Table of contents
4.2. Study reports
4.2.1. Pharmacology
4.2.2. Pharmacokinetics
4.2.3. Toxicology
4.3. Literature references.

Module 5: Clinical Study Reports
Module 5 includes clinical data of a drug product required for marketing approval on its efficacy, safety, pharmacokinetic, pharmacodynamics, and other relevant data. Main heading of Module 5 are given below (13):
5.1. Table of contents
5.2. Tabular listing of all clinical studies
5.3.1 Reports of biopharmaceutical studies
5.3.2 Reports of studies pertinent to pharmacokinetics using human biomaterials
5.3.3 Reports of human pharmacokinetic studies
5.3.4 Reports of human pharmacodynamics 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.

V. ECTD

Paper CTD may comprise more than one lakh of pages. It is very difficult for regulatory agencies to go though and review this huge data. It will take lot of time for review process. Moreover, to find out some particular topic of CTD during its review becomes very tedious as reviewer has to physically locate that particular file. It is also difficult for the applicant to prepare number of copies of this huge CTD application. Applicant has to spend a lot of money, technical skills and time on hard copies, and their color coding and arrangement in modules. These limitations of CTD encouraged ICH for the development of electronic version of CTD. ICH M2 EWG prepared a list of requirements for input into the HL7 RPS Project. ICH got together the Expert Working Group for eCTD and endorsed them for the eCTD development in 2010 and assigned the topic code M8. ICH M8 has responsibility to further develop eCTD guidelines. Draft eCTD Implementation Guide (v.2.0) and related documents were released under Step 2b of the ICH process and are made available for regulatory consultation until May 22, 2015. eCTD became mandatory for centralized procedures in 2010.(14)eCTD is mandatory in the USA while it is not compulsory in Europe. eCTD is submitted along with the paper submission for MAA.

VI. SIGNIFICANCE OF CTD

To make the reviewing of each application easier and to avoid omission of critical data or analyzes, a common format has been implemented in all countries. Omissions of such data that are mandatory may result in unnecessary delays in approvals. It saves time and resources and facilitates regulatory review and communications. It provides appropriate format for the data which is easy to understand and also helps in evaluation of data. CTD is applicable to all types of products. It is more consistent format that helps in easier analysis for reviewer also. CTD also helps in simultaneous submission of documents for approval in three regions and facilitates exchange of regulatory information. Moreover, it facilitates electronic submissions and faster availability of new medicines to patient population (15).

VII. CONCLUSION

For registration of Pharmaceutical Product in any of the Exporting country it‟s important to compile the documents in the format which is accepted internationally for Regulated and Non-Regulated Market. Due to major difference in the regulatory requirement for registration of dossier for Pharmaceutical Product CTD and ACTD format was introduced. This helps to compile the documents in the defined format as mentioned above as per the requirement of the registering country (16). The process for smooth registration of drug product becomes easier by complying all the requirements to get approval of global market at the same time and to launch the product at once in different market. So before introducing the product in any of the country one should understand the requirement.

Abbreviations
Electronic Common Technical Document (eCTD), Common Technical Document (CTD), International Conference on Harmonisation (ICH), United States(US),European Union (EU),EXtensible Markup Language(XML), Document Type Definitions (DTDs), Non-eCTD

electronic Submissions(NeeS),New Drug Application(NDA) and Abbreviated New Drug Application(ANDA)

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Conflict of Interest
The authors declare that they have no conflict of interest.

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