An overview of the Common Technical Document (CTD) regulatory dossier

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Abstract

The Common Technical Document (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. The CTD dossier is divided into five main modules: Module 1 – Administrative information and prescribing information; Module 2 – Overviews and summaries of Modules 3–5; Module 3 – Quality (pharmaceutical documentation); Module 4: Non-clinical reports (pharmacology/toxicology); Module 5: Clinical study reports (clinical trials). Detailed guidelines are provided describing the content of each module and the majority of submissions must now follow the CTD format for submission dossiers.

Keywords: Common Technical Document, Harmonisation, ICH M4, Regulatory submissions

Background

Prior to the implementation of the Common Technical Document (CTD) in 2002, each of the three major regulatory regions (European Union (EU), USA, and Japan) had its own set of guidelines and format for the submission of a regulatory dossier to obtain marketing approval for a new drug or a variation to the licensing of an existing drug. In Japan, the GAIYO was required, which organised and presented a summary of the technical information; in Europe, Expert Reports and Tabulated Summaries were required and Written Summaries were recommended; and in the USA, the Food and Drug Administration (FDA) had guidance documents regarding the format and content of the New Drug Application (NDA). To complicate things further, countries within the EU also had their own guidelines and formats, making submission to multiple countries and multiple regions a time-consuming and repetitive process.

In 2000, representatives from the European Medicines Agency (EMA), the USA FDA, and the Ministry of Health, Labour, and Welfare in Japan developed a set of guidelines defining the structure and content of the dossier for an application for the registration of a new medicine that could be used across all three regions. These guidelines were developed under the umbrella of The International Conference on Harmonisation (ICH) and have become part of the family of ICH guidelines. The aim of the CTD was simple – it would provide a common format for the technical documentation that would significantly reduce the time and resources needed to compile applications for registration of human pharmaceuticals and would ease the preparation of electronic submissions. In addition, regulatory reviews and communication with the applicant would be facilitated by a standard document of common elements and the exchange of regulatory information between Regulatory Authorities would be simplified.[1]

The first set of ICH CTD guidelines were published in 2002, and currently there are four ICH guidelines on the CTD (M4, M4Q, M4S, and M4E), along with four question and answer documents. In July 2003, the CTD became the mandatory format for NDAs in the EU and Japan, and the strongly recommended format for NDAs submitted to the FDA. Since the implementation of the CTD format in the EU, USA, and Japan, the CTD has also been adopted by several other countries including Canada and Switzerland. The paper CTD is now destined to be replaced by its electronic counterpart, the eCTD,[2] with the eCTD being mandatory for the centralised procedure in the EU since 2010.

General principles

As for all documents, the display of information in the CTD should be unambiguous and transparent. The ICH M4 guidance document on the

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organisation of the CTD[1] recommends that text and tables are prepared using margins that allow the document to be printed on both A4 paper (EU and Japan) and 8.5×11" paper (USA). Times New Roman, 12-point font, is recommended for narrative text. Acronyms and abbreviations should be defined the first time they are used in each module and literature references should be cited at the end of each module in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.[3]

Every document included in the CTD should be numbered starting at page 1, except for individual literature references where the existing journal page numbering is considered sufficient. It is of note that the ICH M4 guidelines state that it is not necessary to display the page numbers as '1 of *n*', where *n* is the total number of pages in the document. All pages of a document should include a unique header or footer that briefly identifies its subject matter (e.g. an abbreviation of the full section number and title, i.e. 2.7 Clinical Summary). To avoid fifth, sixth etc. level subheadings (e.g. 2.6.6.3.2.1) within a document, the M4 guidelines[1] allow a shortened numbering string. In this case, the document number and the name (e.g. 2.6.6 Toxicology Written Summary) should appear in the page header or footer and then an abbreviated section numbering used within the document, e.g. 1, 1.1, 2, 3, 3.1, 3.2 etc.

Overall organisation of the CTD

The overall structure of the CTD is detailed in the ICH M4 guidelines[1] and includes a granularity section that provides guidance on document location and pagination within the CTD dossier. This granularity information is particularly useful if the dossier contains multiple indications or multiple components of the investigational medicinal product (IMP). In addition to the M4 guidelines, a set of questions and answers is also provided to address the most common issues raised.[4]

The CTD dossier is divided into five main modules (see Figure 1):

Module 1: Administrative information and prescribing information
Module 2: Overviews and Summaries of Modules 3–5
Module 3: Quality (pharmaceutical documentation)
Module 4: Non-clinical reports (pharmacology/toxicology)
Module 5: Clinical study reports (clinical trials).

Module 1 is not strictly included in the CTD since it contains documents that are specific to each region, e.g. application forms or the proposed label. This module will not be discussed in any further detail in this article since the content and format of this module is specific to individual Regulatory Authorities.

Modules 2–5 though are common to all regions and these comprise the main body of the CTD. Module 2 contains the CTD overviews and summaries. It starts with a general introduction to the drug, including its pharmacological class, mode of action, and proposed clinical use. Module 2 then provides an overall summary of the 'quality'

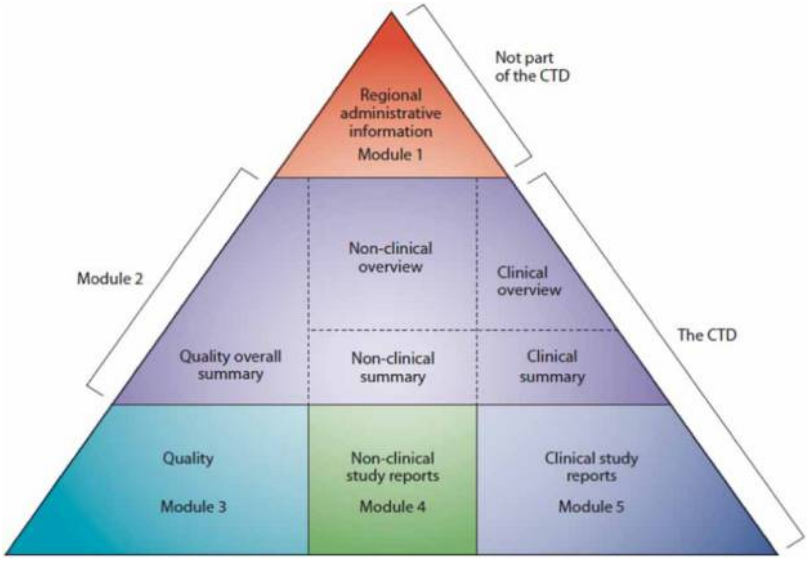

Figure 1: The CTD triangle.

information (i.e. the pharmaceutical documentation), as well as the Non-Clinical Overview and the Clinical Overview, the Non-Clinical Written Summaries and the tabulated summaries, and the Clinical Summary. The information provided in Module 2 is based on the foundation material that is provided in Module 3 for the quality information, Module 4 for the non-clinical information, and Module 5 for the clinical information.

Module 2: CTD overviews and summaries

Module 2 contains seven sections that should be maintained in the following order:

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

The introduction in Module 2.2 should be a general introduction to the IMP, including its pharmacological class, mode of action, and proposed clinical use. In general, the introduction should not exceed one page.

Module 2.3: Quality overall summary

The quality overall summary (QOS) is a summary of the chemical and pharmaceutical data in the dossier (including data for biological/biotechnological products). Guidance on the structure of the QOS is provided in ICH M4Q guidelines,[5] with answers to the most common issues raised provided as a separate document.[6] The structure of the QOS broadly follows the structure of the data included in Module 3. The QOS should not include information that has not already been included in Module 3 or in other parts of the CTD.

The aim of the QOS is to discuss the critical parameters of the product, but it should also address issues that arose during development and provide justification for instances where guidelines were not followed etc. The QOS should normally not exceed 40 pages of text, excluding tables and figures (in cases of biotech products and products manufactured using more complex processes it can be longer but should not exceed 80 pages, excluding tables and figures).

Module 2.4: Non-clinical Overview and Module 2.6: Non-clinical Written and Tabulated Summaries

The structure and content of Modules 2.4 and 2.6 are specified in the ICH M4S guidelines,[7] with answers to the most common issues raised provided as a separate document.[8] The main purpose of the Non-Clinical Written and Tabulated Summaries in Module 2.6 is to provide a comprehensive factual summary of the non-clinical information on pharmacology, pharmacokinetics, and toxicology. The Non-Clinical Written Summaries are generally in the region of 100–150 pages long. A total of 34 templates are provided for the preparation of the Tabulated Summaries in the ICH M4S guidelines.

The interpretation of the data, the clinical relevance of the findings, any association between non-clinical findings and quality aspects of the IMP, and any implications of non-clinical findings for the safety of the IMP in humans should be addressed in the Non-Clinical Overview (Module 2.4). If relevant guidelines on the conduct of the studies exist, then these should be noted as being adhered to, or justification provided if there were any deviations. The non-clinical testing strategy should be discussed and justified and a comment on the Good Laboratory Practice (GLP) status of the studies should also be included. Reference to the scientific literature and characteristics of related products should also be taken into account (i.e. if a particular finding has been seen with a drug in the same class as the IMP this should be discussed). Thus, the Non-Clinical Overview is an integrated and critical assessment of the pharmacological, pharmacokinetic, and toxicological aspects of the IMP in animals. The Non-Clinical Overview should generally not exceed 30 pages.

Module 2.5: Clinical Overview and Module 2.7: Clinical Summary

These modules are usually the documents a medical writer is most likely to be asked to write. The structure and content of Modules 2.5 and 2.7 are specified in the ICH M4E guidelines,[9] with answers to common issues raised provided as a separate document.[10] The Clinical Overview is a short document that provides a Critical Assessment of the clinical data, whereas the Clinical Summary is a longer document that focuses on data summarisation and integration. The Clinical Summary and Clinical Overview provide the supporting information for the Summary of Product Characteristics (SmPC) or the product label (included in Module 1 of the CTD), so it is important these documents are consistent.

The primary purpose of the clinical summary is to provide a comprehensive factual summary of the

clinical data. This includes information provided in the clinical study reports located in Module 5, information from any meta-analyses or other cross-study analyses that have been conducted, and post-marketing data for products that have been marketed in other regions. The comparisons and analyses of results across studies provided in this document should focus on factual observations and should not provide any interpretation of the data – this is covered within the Clinical Overview. The Clinical Summary is divided into sections covering biopharmaceutics and associated analytical methods, clinical pharmacology, efficacy, and safety. The synopsis from each study report is also included in this module (or appropriately hyperlinked in an eCTD). The clinical summary is between 50 and 400 pages long, although it may be longer if more than one indication is included.

The Clinical Overview is a key document in the CTD dossier. The Clinical Overview is divided into six sections: product development rationale, biopharmaceutics, clinical pharmacology, efficacy, safety, and risk/benefit conclusions. In contrast to the factual presentation in the Clinical Summary, the Clinical Overview provides a critical analysis of the drug development programme and its results, including discussion and interpretation of clinical findings, and the relevance of other information (e.g. pertinent animal data or product quality issues that may have clinical implications). It is important to remember that the Clinical Overview presents the conclusions and implications of the data and it should not repeat the information presented in the Clinical Summary or elsewhere in the CTD. The Clinical Overview should present the strengths and limitations of the development programme and study results, analyse the benefits and risks of the IMP in its intended use, and describe how the study results support critical parts of the prescribing information. The quality of the clinical programme and performance of the studies, including a statement regarding Good Clinical Practice (GCP) compliance, should also be included. The clinical overview should also discuss the place of the IMP in the clinical armamentarium if approval is given for a licence. Appropriate reference should be made to the literature to put the results into context. Finally, the Clinical Overview should provide an evaluation of the benefits and risks of the IMP based upon the conclusions of the relevant clinical studies, including interpretation of how the efficacy and safety findings support the proposed dose and target indication and an evaluation of how prescribing information and other approaches will optimise benefits and manage risks. The Clinical Overview should be a relatively short document of approximately 30 pages.

Module 3: Quality

Module 3 presents the chemistry, manufacturing, and controls reports for the product included in the registration dossier. Full details of what should be included in Module 3 are provided in the ICH M4Q guideline.[5] Sections on both drug substance and drug product are included in this module. The main headings in this section (that must not be altered) are as follows:

- 3.1 Table of contents of Module 3
- 3.2 Body of data
  - 3.2.S Drug Substance
  - 3.2.P+ Drug Product
- 3.3 Literature references used in Module 3

Module 4: Non-clinical study reports

Module 4 presents the non-clinical reports included in the dossier. The structure and content of Module 4 is specified in the ICH M4S guidelines.[7] The main headings in this section (that must not be altered) are as follows:

- 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 4.

Module 5: Clinical study reports

Module 5 presents the clinical reports included in the dossier. The structure and content of Module 5 is specified in the ICH M4E guidelines,[9] which provided a specific placement of clinical study reports and related information to simplify preparation and review and to ensure completeness. The placement of a report is determined by the primary objective of the study, with each report appearing in only one section. If there are multiple objectives, the study should be cross-referenced in the various sections. The main headings in this section (that must not be altered) are as follows:

- 5.1 Table of contents of Module 5
- 5.2 Tabular listing of all clinical studies
- 5.3 Clinical study reports
  - 5.3.1 Reports of biopharmaceutic studies
  - 5.3.2 Reports of studies pertinent to pharmacokinetics using human biomaterials

5.3.3 Reports of human pharmacokinetic (PK) studies
5.3.4 Reports of human pharmacodynamic (PD) 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.

Issues

Although the development of the CTD has been largely successful and all dossiers now use the CTD format (with newer dossiers moving to the eCTD format), some regions still persist in retaining some of their original pre-CTD dossier requirements. The most common example of this is the FDA requirement to submit an Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) in the USA submission, even though the intent was that the Clinical Summary would replace them (Module 2.7.3 Summary of Clinical Efficacy was the replacement for the ISE and Module 2.7.4 Summary of Clinical Safety was the replacement for the ISS). The guidance provided is therefore to include the full ISE and ISS in Module 5 and then condense this into a summary format for the Module 2.7 documents.[10]

The CTD has been largely successful in meeting its objectives of providing a common format for the information included in a submission dossier. However, it is of debate whether this has resulted in the suggested reductions in time and resources needed to compile applications.

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Debbie Jordan has 25 years' experience in the pharmaceutical industry. She worked as a CRA, then a project manager, before setting up a medical writing group in a large CRO. Since 1999 she has run her own business providing medical writing, training, and clinical research services to the healthcare industry.