WHITE PAPER

HOW TO EFFECTIVELY DEVELOP CLINICAL DOCUMENTS IN THE EU/US AND CHINA NDA DOSSIER

Dr. Julia Cooper
Vice President, Head of Global Medical Writing Services
PAREXEL International

Dr. Cooper outlined the development process of clinical documents for regulatory submissions, comparing the clinical content requirements for Europe and the US with that for China FDA (CFDA) submissions. She also highlighted the integral role that medical writers play in designing, planning, managing and preparing documents for regulatory submissions.

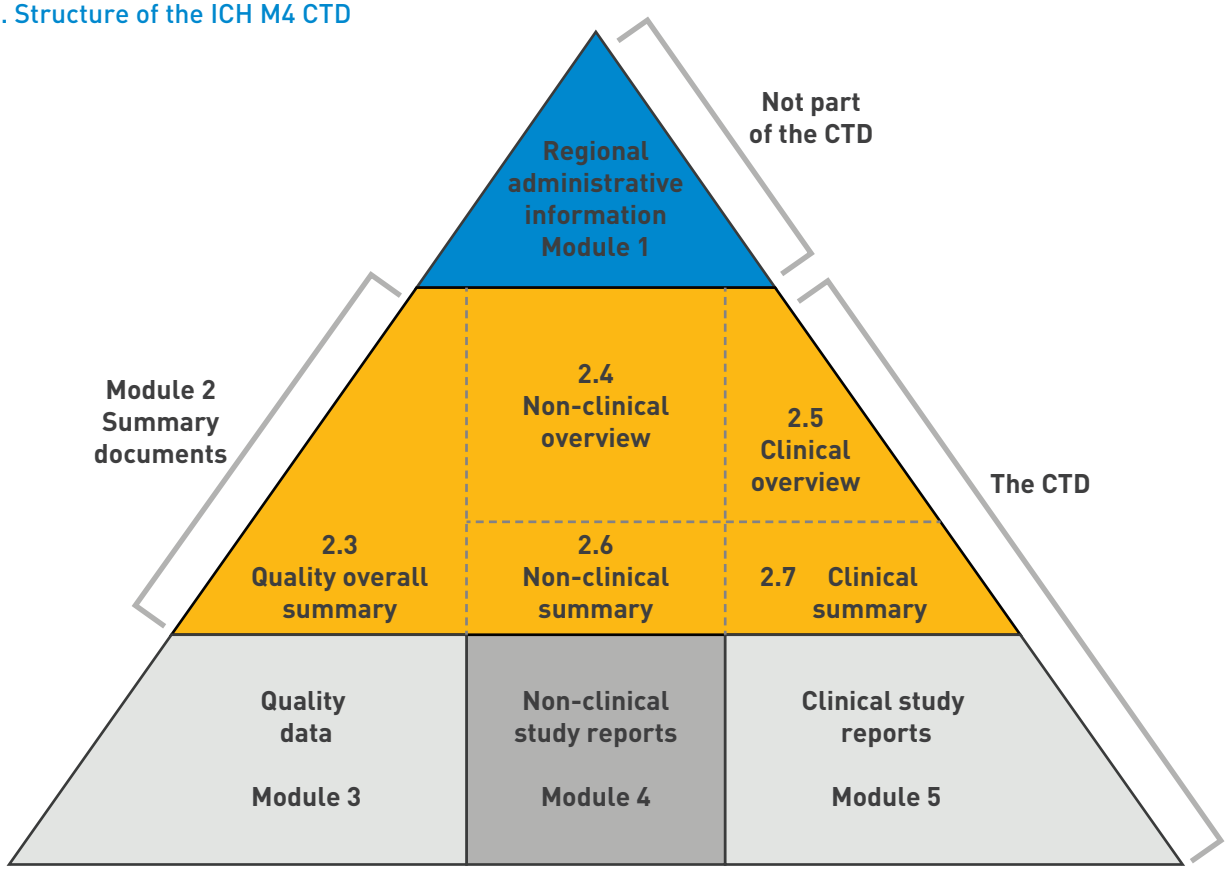
PAREXEL®
YOUR JOURNEY. OUR MISSION.®

EU/US SUBMISSIONS UTILIZE THE COMMON TECHNICAL DOCUMENT

The Common Technical Document (CTD) is the result of the joint efforts of industry and the European Medicines Agency (EMA), US Food and Drug Administration (FDA) and Japanese Ministry of Health, Labour and Welfare via the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The CTD rationalizes submission requirements across regions into a single guidance document (ICH M4) on the presentation and format of a dossier for regulatory submission. The CTD was initially adopted by the European Union and Japan in 2003, and is strongly recommended for New Drug Applications (NDAs) submitted to the US FDA. It is now used in a number of other countries, greatly simplifying the process of submitting drug approval applications in multiple markets.

The CTD dossier comprises five main modules (Figure 1) that contain all the quality, safety and efficacy information pertinent to a NDA. Module 1 – containing administrative and prescribing information – is region-specific, but Modules 2 to 5 are intended to be common to all regions.

Figure 1. Structure of the ICH M4 CTD



ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; CTD, common technical document

Source: ICH; M4: The Common Technical Document (http://www.ich.org/products/ctd.html).

The role of medical writers in efficient CTD preparation

Within the CTD, content for modules related to clinical data are likely to garner the greatest input from the medical writing team. However, the contribution of the medical writers typically extends far beyond clinical writing services.

Dr. Cooper shared some of the lessons learned by PAREXEL's medical writers about how they can ensure that CTD preparation proceeds efficiently in terms of both time and resources. Medical writers should 'own' the document preparation and review process; they should lead timeline discussions, write or coordinate the writing of submission documents, and organize the internal review and approval processes. It is also prudent to involve medical writers in the discussion and review of the planned analyses, including table shells. As part of the CTD submission team, medical writers should assist in mapping out the full content of the clinical sections, including the topics for analysis/discussion in each document, deciding how best to select and condense the content formats for ongoing studies that may not require a full Clinical Study Report (CSR), and ensuring that redaction and transparency considerations have been addressed.

The contribution of the medical writing team typically extends far beyond clinical writing services

Their involvement must start as early as possible, potentially with protocol writing and/or review, as well as writing and oversight of pivotal CSRs to ensure they will meet dossier requirements. As they have the most comprehensive overview of the clinical data in the dossier, the medical writing team can also be involved in supporting related activities such as coordinating question lists for pre-submission meetings, preparing or contributing to briefing packages, reviewing related documents, eg, Risk Management Plan, and creating advisory board slides or responses to regulators' questions. The medical writing team should manage consistency across documents within the CTD, as well as proactively identify issues and risks, and assemble the right people to find appropriate solutions.

COMPARING THE CTD WITH THE CHINA NDA

For the China registration dossier, Dr. Cooper referenced the new guideline issued by CFDA in May 2016, "Requirement on registration dossier under the new categorization for chemical drug registration (tentative)". This is already being followed although it is still in draft stage. The dossier now comprises 5 sections:

1	Administrative and Summary Information
2	Pharmaceutical, Non-clinical and Clinical Summaries
3	Pharmaceutical Data
4	Non-clinical Data
5	Clinical Trial Data

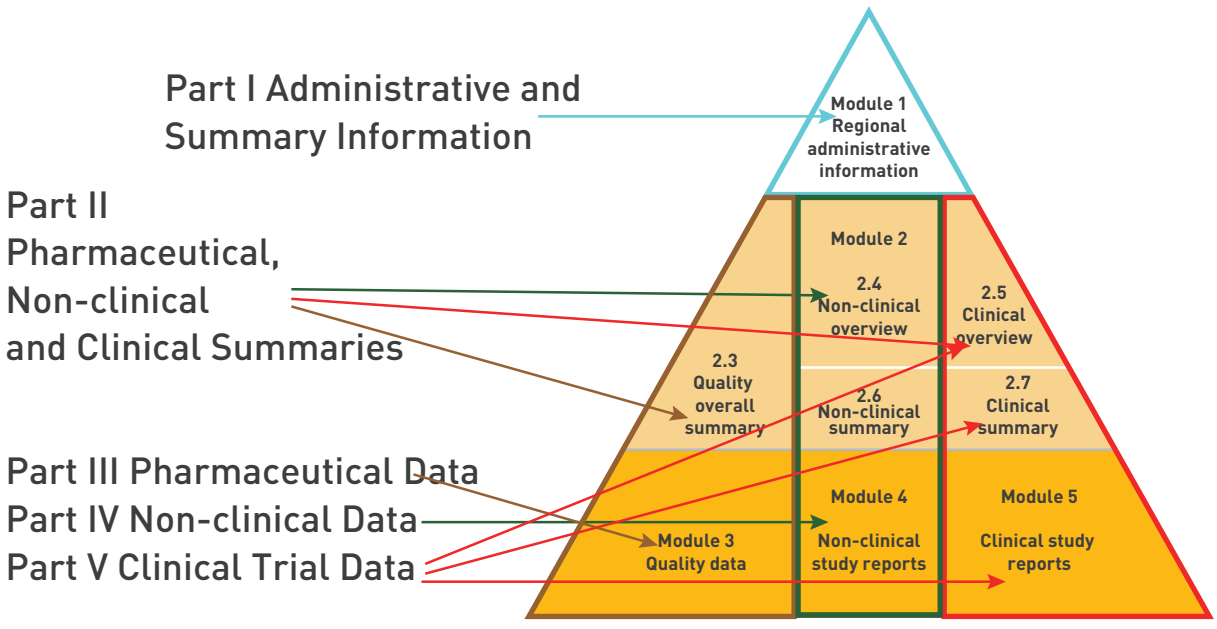
Part 5 Clinical Trial Data is structured as follows:

- 27: Summary of Clinical Trial Data
- 28: Clinical Trial and Research Programs
- 29: Data Management Plan, Statistical Analysis Plan
- 30: Investigator Brochure/Updates
- 31: Informed Consent Forms, Ethics Committee Approvals, Scientific Review Committee
- 32: Clinical Study Reports
- 33: Clinical Trials Database (original database, database analysis and derived variables documentation)
- 34: Data Management Report, Statistical Analysis Report

For marketing applications for drugs already marketed outside China (category 5 drugs), the CFDA announced that the CTD modules will be accepted instead, if supplemented by Module 1 (Administrative and Summary Information) from the CFDA guideline.

Dr. Cooper compared the China NDA format and content requirements with those of the CTD (Figure 2) to identify how an existing CTD could be efficiently leveraged during preparation of an NDA submission. These principles still apply to submissions for drugs other than category 5.

Figure 2. Relationship between the ICH M4 CTD and the China NDA



How do global pharma companies prepare clinical sections of the China NDA?

The new draft guideline for the CFDA dossier refers to a separate guideline "The guideline of the structure and content of summary documents for chemical drug – summary of clinical studies". The guidance in this document concerns how to present the clinical data in Section 27: Summary of Clinical Trial Data. In general, the approach is similar to that in Module 2.5 of ICH M4, CTD. If the company has a global CTD, content from that CTD that is relevant and acceptable can be reused or modified to generate the clinical sections of the China NDA.

If the company does not have a global CTD to use as the starting point, the clinical summary guidance may be followed, but the actual structure of the documents may need to be determined depending on the data to be presented. Preparation of clinical NDA sections may be led by the medical writing/scientific communications department or the regulatory affairs or submissions management departments, often with substantial input from medical writers. Thus the medical writer's role will include helping the team establish the best format to present the data, and mirrors the practice on global submission teams.

For category 5 drugs, the company may opt to submit the CTD modules supplemented by Module 1 from the CFDA dossier. Understanding of the extent to which the CTD modules may need further modification is still evolving, eg, on whether to include the comparisons of Chinese to non-Chinese data required by CFDA, and/or the addition of some of the documents specified in the new guideline, such as the data management plan and report.

Data in Chinese patients is required to obtain marketing approval from the CFDA. These data may be obtained from local Chinese trials and/or Chinese data from multiregional clinical trials (MRCT). A CFDA draft guideline specifies that comparisons between Asian versus non-Asian, and Chinese versus non-Chinese data must be included in the CSR. In the past, this was sometimes presented in a separate CSR or subgroup analysis report and the medical writer typically led the preparation of these documents. Going forward, CFDA may prefer to see the comparison within the main CSR, and the medical writer will need to ensure these sections are clearly presented.

Role of the medical writers in China NDA preparation

Dr. Cooper said that a China NDA is undoubtedly as complex to prepare as a CTD and the medical writer plays a very similar role in China as for global submissions. As the China NDA increasingly leverages the global CTD, China and global medical writing teams should work collaboratively to ensure that the CTD content is integrated into the China dossier as smoothly and efficiently as possible. In June 2017, China joined ICH as a full regulatory member of ICH. This may lead to further alignment of the China dossier with the ICH M4 structure in the future.

CONCLUSION

Clearly, medical writers play an essential role in dossier preparation and are frequently an integral part of the wider US/EU submission team. Dr. Cooper concluded that the increasing focus on quality may expand the role of the China medical writing team in preparing submissions for the CFDA.

WHEREVER YOUR JOURNEY TAKES YOU, WE'RE CLOSE BY.

CORPORATE HEADQUARTERS

195 West Street
Waltham, MA 02451
USA
+1 781 487 9900

Offices across Europe, Asia and the Americas

www.PAREXEL.com
apac@PAREXEL.com

PAREXEL®
YOUR JOURNEY. OUR MISSION.®