APPLIED CLINICAL TRIALS

Global Regulatory Publishing Trends

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The Regulatory information is required to prepare the dossier of a drug product which differ according to the regulations of the local regulatory authority. To get a harmonized system, the International Council for Harmonisation (ICH) has developed a standard content format, the Common Technical Document (CTD), organized with consistent sections and headings. Apart from the US, Europe, and Japan, various other countries like Australia, Switzerland, Canada, etc. have adopted the ICH guidelines and followed the standard content format. Most countries and their regulatory authorities have migrated to the electronic Common Technical Document (eCTD) submission format.[1] The United States Food and Drug Administration (USFDA), the Medicines and Healthcare products Regulatory Agency (MHRA), and the European Medicines Agency (EMA) (majority of the European Union regions) have started accepting only eCTD submissions for all the application types. The eCTD is a standard format for submitting applications, amendments, supplements, and reports to various regulatory agencies. The Non-eCTD Electronic Submissions (NeeS) format still exists in a few countries across the European Union and Gulf Cooperation Council.[2]

Global regulatory publishing process

The regulatory requirements of various countries across the globe differ based on the local agencies. One of the primary challenges for authorities is to ensure that the pharmaceutical products are developed as per the regulatory requirement of that specific country. A regulatory submission includes data and information that need to be compiled and managed for thoroughness, accuracy, and integrity against agency requirements. Regulatory agencies require these to establish whether a product can progress to clinical testing and to confirm if the product is safe and efficient for marketing. A typical submission process flow includes Submission Management, Document Level Publishing, Submission Level Publishing, Validation and Verification, and Dispatch to Agency.

Submission Management - Source documents are received from the sponsors, and a submission planner is prepared based on the application and submission type.

Document Level Publishing – It includes PDF conversion, document formatting, bookmarking, and hyperlinking, ‘Table of Content’ (ToC) creation, pagination of the documents, document properties setting as per the agency, and ICH criteria and specifications.

Submission Level Publishing – This phase includes creating a submission outline in the publishing software, uploading the documents as per the CTD structure and submission planner, and compiling and generating the output of the published submission.

Verification and Validation – The published output is set to run in a validation tool to verify and validate the submission that fulfils the agency's need. Any errors or warnings must be fixed before proposing the submission to the regulatory authority.

Dispatch to Agency – Error-free and validated submissions are dispatched to the agency through CD/DVD for paper submissions and the respective gateways for NeeS/eCTDsubmissions.

Submission formats

Non-eCTD electronic submissions

A NeeS is a submission of electronic information sent by an applicant to an agency and it is merely a collection of electronic files either as a “bunch” of files or organized in folders. The NeeS format was developed in Europe and was intended as a steppingstone to the eCTD. It uses the same files and folders as the eCTD but simplifies the navigation by using a PDF ToC with hyperlinks. NeeS is an electronic submission without XML and SPL. It does not have metadata and no life cycle of the documents is maintained. Even EU and other RoW regions have started their transition from NeeS to eCTD. NeeS is still acceptable in the EU by a few member states for national, decentralized, and mutual recognition procedures.[3] The US does not accept the NeeS format, whereas other RoW regions which do not accept eCTD versions and are getting transitioned from the paper version or previously submitted applications, the NeeS format is still accepted.

electronic Common Technical Document (eCTD)

The eCTD is a specification for an electronic submission created by the ICH.[4] The intention is to give a common format for the electronic version of the CTD dossier. This means there is a common dossier structure provided by the CTD and the regional content requirements. One of the key features of the eCTD is “Lifecycle Management,” which provides information about the relationship of one document to another (represented by the “operation” attribute such as new, replace, append, and delete) and about the relationship of one submission to another (represented by “related sequence” attribute). An eCTD is the submission of mostly PDF documents stored in the eCTD directory structure, crucially accessed through the XML (Extensible Markup Language) backbone (index.xml), and with the file's integrity guaranteed. The eCTD is defined as an interface for the industry to transfer regulatory information while considering the facilitation of the creation, review, lifecycle management, and archival of the electronic submission. It follows a common structure for Modules 2 to 5, and country or region-specific requirements for Module 1. It is submitted as a “Baseline Submission” when getting transitioned from the paper or NeeS format. The benefits of the eCTD are easy to distribute and review highly organized electronic ToC, more efficient use of resources, less cost and stress to the organization, cross submission integration, etc.

eCTD is different from other formats in the following aspects:

- Overall ToC provided in XML (Extensible Markup Language)
- Utility files to enable technical conformance and viewing
- Submission folders, XML, and utility files are created automatically if an eCTD builder is used
- High level of granularity in documents
- More precise structure
- Easier lifecycle management of the submission

The eCTD is widely accepted by the US, EU, UK, a few GCC countries, Canada, and other RoW regions such as Australia, New Zealand, Russia, South Africa, and the Asia Pacific are getting transitioned from the paper and NeeS format.

Paper

The structure of a paper submission must be in accordance with the sequence of documents as referenced in either the XML backbone of the eCTD or the overall ToC of the NeeS. The location of each document in the paper submission dossier must be marked by a tab identifier. The name for the tab identifier should be the name of the document. The paper format is only accepted in countries where the NeeS and eCTD versions are not available.

Conclusion

Although there is a continuous process of harmonization across the globe, there are challenges to be overcome by the pharmaceutical industry due to the heterogeneity in the regulatory authorities of various countries. Initially, the submissions were processed in a paper format, which transitioned to NeeS, and now, most of the countries are accepting eCTD submissions for the benefits therein. Irrespective of the format, the most common of all three is a standard content format, the CTD, which is organized with consistent sections and headings that were developed by ICH.

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