Tips for Preparing a Successful eCTD

March 10, 2011

RPI Regulatory Professionals, Inc.
Topics

- Overview of the eCTD
- Planning the eCTD
- eCTD Publishing
- Biometrics Tasks for eCTD
Overview of the eCTD
CTD is an ICH standard that was adopted in a consensus process by US, Europe, Japan and other member regions.

eCTD is the only acceptable format for new electronic submissions to CDER and CBER
eCTD - The New Standard

- eCTD is “highly recommended” by FDA
- NDAs, BLAs, DMFs and INDs
- Required by EMEA for Centralized Procedures
- Transparency of entire submission
- Ease of navigation and review
What is an eCTD?

- Electronic transfer of information to Agency based on common format (CTD)
- PDF documents linked via XML backbone
- Increased document granularity
- Relies on formatted files, leaf titles, hyperlinks and bookmarks for ease of navigation
The CTD (as a pyramid)

Module 1

Module 2 Summaries

Module 2.2 Introduction

Module 2.4 Nonclinical Overview

Module 2.5 Clinical Overview

Module 2.3 Quality Overall Summary

Module 2.6 Nonclinical Summary

Module 2.7 Clinical Summary

Module 3 Quality

Module 4 Nonclinical

Module 5 Clinical

Module 1 is Region specific & is Not part of the CTD

Modules 2-5 contain the CTD:
- Intro, Summaries
- Quality (CMC)
- Nonclinical
- Clinical
eCTD Submission Strategy
Plan Your Approach to Win
Planning for a Successful Submission

The Challenge

- CTD prep requires experienced and dedicated resources
- Demand for resources far exceeds what is required for drug development phase
- Resource gaps exist that stand between the sponsor and a high quality, on-time, on-budget CTD

The Solution

- Have a clear understanding of eCTD requirements
- Identify needed expertise early in the process
- Monitor activities closely to identify and address potential issues so they have low/no impact on timeline
- Increase quality of the eCTD to speed FDA review
- Increase chances of approval after first review cycle
Resource Planning

- Comprehensive analysis to identify resource gaps
- Identify and evaluate essential external partners
- Set up systems to allow access to information
- Start planning at least 12 months in advance of eCTD
Assemble the CTD Team

- Assign Team Leader
- Identify Team members
- Agree on CTD content; get Mgmt. and Agency buy in
- Agree on the timeline
- Agree on how information will flow among team members & between team and senior mgmt
  - Document/Data deliverables
  - Changes in timelines
  - Budget
Seek Regulatory Guidance

- Sponsors benefit from early regulatory guidance by defining hurdles to registration
- Review pertinent guidance documents and prior precedents
- Integration of regulatory strategy with business, marketing and clinical development strategies is key to successful NDA
Regulatory Considerations

- **Submission Type**
  - **Combination Product – who is the lead center?**
    - Is the device component approved?
    - If not, have the testing requirements for devices been met?
  - **505b1, 505b2**
  - **Orphan drug, accelerated approval, Fast Track, Rolling NDA, Priority Review, Subpart H & E**
  - **Special Protocol Assessment**
    - Phase 3, Carcinogenicity, Stability
Milestone FDA Meetings

**EOP2**
- For Phase 3
  - Nonclinical safety data
  - Clinical safety data
  - Phase 3 CMC strategy
- For NDA
  - Long term tox requirements
  - Size of clinical safety database
  - Pediatric Plan

**Pre-NDA**
- Submission structure
- Acceptability of clinical data
- REMS
- Agreements on post NDA submissions e.g., supplemental stability
- Label
- Pediatric Plan
- Data pooling strategies
Module 1 – Tips

- Debarment Certification
  - Request your accounting group to prepare a list of all vendors who were paid

- Financial Disclosure
  - Request your accounting group to prepare a list of payments made to investigators that were not for direct clinical study costs (e.g., consulting fees, research grants)

- Labeling
  - The label should not have data presentations or analyses that are not also presented in clinical summaries or CSRs
  - Ensure format conforms with SPL guidance

- Trade name
  - Can be submitted under IND; submit no later than the NDA
  - FDA will re-confirm acceptance 90 days before PDUFA date
Module 2 – Tips

- Nomenclature for the drug should be unified in M2
  - Mod 3-Mod 5 may use earlier research names for the drug
- Need a single editor to review Mod 3 and unify writing styles
- The SCE (2.7.3) and SCS (2.7.4) are not substitutes for the ISS and ISE (Mod 5).
  - SCE and SCS are higher level summaries of the data (50-400 pages)
  - ISS and ISE are an analysis of the data
  - Omission of ISS and ISE should be agreed with FDA in advance
- Data pooling strategies for clinical summaries should be decided and agreed upon at the Pre-NDA meeting. This drives much of the work in preparing the NDA.
Module 3 – CMC Tips

- Anything not per the guidance or compendium should be agreed to with FDA in advance.
- Be careful about making commitments in the NDA for further experiments because it might help explain something.
- Starting materials – make sure they are defined and agreed with FDA in advance of the NDA. FDA is asking for more details on the manufacture of starting materials because they are seeing recalls involving changes to starting materials (esp. for foreign suppliers).
- Drug Development Report
  - Include only pertinent aspects of history that support the planned commercial product.
- Get marketing involved with commercial packaging early so that sufficient stability data can be generated, e.g. physician samples.
- Expiration dating will be based on stability data available on registration batches – if you plan to do something different be sure to get FDA agreement.
Module 4 – Tips

- Preparation of M4 can begin as soon as the sponsor decides to file an eCTD.
  - Legacy studies may require additional formatting
  - Have functional expert review legacy reports or reports coming from a partner to ensure agreement on conclusions
  - Certified translations are needed for reports not in English
- Start preparing CTD summary tables
- Carcinogenicity datasets need to be included
- Nonclinical references - Mod 4.3
Module 5 – Tips

- Identify the patient CRFs that will be included early
  - SAEs, deaths, drop-outs, others
  - Bookmarked and hyperlinked
  - Preparing the CRFs can be resource intensive

- TQT study
  - Clin Pharm Highlights Table
  - Waveforms – ECG Warehouse

- Datasets – need involvement from data mgmt early in the process (CSR, PopPK, ISS, ISE)

- References – Mod 5.4
  - Copies of papers cited in eCTD
  - Bibliography of literature search
Keys to a Successful eCTD

- Plan the eCTD early (12-18 mos before target submission date)
  - Get the eCTD publisher onboard early
  - Have authors work from standardized templates and style guides
  - Map out the data deliverables for the submission
- Dedicated Team – including internal and external resources
- Agreement on content (internally and with FDA)
  - Identify critical path items early
  - Create a solution, no/minimal impact on timeline
- Manage information and communication flow
- Review Agency commitments/recommendations
- Get internal agreement on NDA messages early
- Build QC steps into the review process
- Obtain thorough knowledge of FDA standards
Understand Regulatory Expectations and Plan Accordingly
eCTD Publishing

The Tools and the Process
The CTD: Managing a Mountain of Information
Know Your Tools

- Templates
- Style Guide
- Properly formatted Word files
- Compliant PDFs
- Publishing
What Do We Need to Get Started?

The Goal:
Provide the Agency with a submission where they can focus on content and be able to navigate the eCTD with ease. This means providing them with high quality formatted documents, as well having a process that ensures quality.

Electronic Submission Tools:
- Tracker Sheet
- Templates
- Style Guide
- QC Sheet
Tracker Sheet – The tracker sheet is used for multiple purposes.

- Gather information about submissions (metadata)
- Helps define submission content
- Lists documents to be submitted in an application
- Keeps track of progress on each document
Templates – authoring in templates allow writers to focus on content and less on formatting.

- Word content templates should be regulatory-compliant.
- Word documents that contain formatting, styles, headers, footers, and instructional text.
- Templates come in granular parts based on CTD structure.
Style Guide – The style guide is a tool which provides authors and publishers with a guide on format and consistency for word documents

- It outlines formatting for headings, body text, figures, tables, punctuations, abbreviations, margins, etc.
- Standardizes nomenclature e.g., drug name
- It should be used in conjunction with the Word templates
- It allows the authors to create submissions that are consistent in style, appearance, and functionality
**Quality Control (QC) Sheet** – is a tool provided to reviewers to keep a list of QC findings

- QC is an important part of any submission project. QC process for eCTD submissions takes place after the submission is published and the publishers have done their QC. During a final QC, focus is on **quality**.
RPI/Client eCTD timeline

- Tracker Sheet completed by Client
- Begin providing any final documents (e.g., M4 reports) to RPI
- Authors write eCTD sections in templates
- Internal review of drafts (2 rounds)
- Versions are returned to RPI for formatting
- Docs finalized
- Docs provided to publishers
- Client QC submission
- Revisions noted on QC Sheet
- ReQC. Ensure all findings are resolved, submission is finalized.

Client/Authors activity
- Templates & Styleguide provided to Client
- Begin formatting PDFs available

RPI Publisher activity
- Publishers format draft versions. Draft versions returned to authors for finalization.
- Final formatting on docs
- Publishing of submission, Links created – creation of xml backbone
- RPI QC
- Resolve QC findings
- Republish
- Submission metadata finalized
- Final generation of eCTD
- Validation of eCTD
- Submission sent to FDA via ESG or CD/DVD.
- Source and final docs provided to Client
Preparing the eCTD

Granularity, Leaf Titles, and Life Cycle
The eCTD structure

- Take time to understand the eCTD structure and how it applies to your submission
  - refer to FDA’s Headings and Hierarchies
- Some sections are easy to understand, while others take time to figure out.
  - For every submission, it’s worth thoughtfully choosing where documents are placed within eCTD tree. Once it is submitted in a particular location, it is not easily moved.
- When in doubt, work with regulatory publishers and FDA eSubs group.
eCTD Granularity - grasping its importance

- **What is granularity?**
  Level of hierarchy of the folders and files in the eCTD directory or the smallest unit of detail within the eCTD structure.

- All modules (Modules 1-5) have granularity options. The most challenging are the Quality sections in Modules 2.3 and 3.

- **How granular do you go?**
  Do what makes sense, but within the guidelines.
  Because only entire documents in the eCTD can be replaced, not sections or pages within a document, your submission's initial granularity choices affect how information is updated in future submissions.
  (Refer to the Granularity Document, Annex to M4: Organization of the CTD)

- Once granularity is decided, it generally can’t be changed for the life of the dossier.
Granularity in Module 2 and 3

- No single granularity option for a compliant eCTD. It will depend on writing strategy.

- Publishers and Authors must work together to determine granularity prior to authoring and publishing, especially when a Drug has multiple dosage strengths or manufacturers.
  - In U.S., FDA doesn’t expect 2.3 to be updated after initial application, unlike in EU.
  - Generally, one 32P section per dosage form.
    (Do not create 32P sections for each strength)

- Attachments (e.g., COAs) – include within a document or as separate files
  - Good idea to submit attachments as separate files

- Excipients – determine granularity for this section (3.2.P.4)

- CMC MetaData (e.g., DS and DP Name and Manufacturers) – choose names that will most likely not change for the life of the application.
Module 2 Granularity

Documents rolled up to gray level are not considered appropriate.

One document may be submitted in Documents in the yellow level.
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One OR Multiple documents can be submitted in the orange level.
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Module 4 and 5

Preparation for Modules 4 and 5:

- Determine
  - Number of reports
  - eCTD location(s) for each report ahead of time
  - Naming Standards for reports and how they will be referenced in Module 2 (use CRO number vs. internal number)
  - Which literature references to submit

- Legacy vs. granular (ICH E3) study reports – avoid scanned reports.

- If outsourcing CSR writing, work with CRO ahead of time to ensure reports are formatted properly and eCTD ready.

- Work with data management groups regarding data expectations.

- If CRFs are included, know how many to expect and the level of complexity ahead of time. These can be resource intensive.

- Provide ready reports and literature refs to your publishers ASAP.

The more module 4 and 5 documents that can be prepared ahead of time, the more time there will be to process the M2 summary docs.
Module 1

- Differs by region (US, EU, etc.)
- Contains all forms and administrative information
- The label documents are also contained in this module
- Module 1 specifications will be changing in the near future. It is currently in draft at FDA.

Tips:
- PreIND – able to submit PreIND submissions in 1.6, as long as you know the IND application number.
- Form 3674 and Reviewers Guide – submit in 1.2 with Cover Letter
- DMFs - submitted in 1.4.1 not Module 3.
File Name vs. Leaf Titles

- Each document that is submitted in the eCTD tree has both a file name and a leaf title.

- File name is the actual name of the file – FDA doesn’t see this. (e.g., cover-letter.pdf & coa-tb-033a.pdf are the file names)

- Leaf Title is displayed when FDA views the submission. Short, meaningful, & indicative of the contents. Smart leaf titles provide efficiency for the reviewers.
FDA’s view on Navigation:

**DO:**

- Provide functional hyperlinks
- Provide sufficient number of hyperlinks. Err on the side of more hyperlinks to enhance navigation.
- Format Module 2 with sufficient hyperlinking to support docs in Modules 3-5.
- TOCs of a document should contain hyperlinks to the corresponding sections within the document.
- Supply descriptive and brief bookmarks. Have at least as many bookmarks as there are items in the TOC.

**DON’T:**

- Link to wrong document or the wrong page within a document.
- Avoid scanned documents – they typically aren’t searchable and don’t contain useful links.
- Avoid broken links!
Critical to understand operation attributes within the CTD to facilitate document authoring.

Lifecycle of documents:

- **New** – original or new documents
- **Replace** – replaces existing files
- **Append** – adds new info to an existing file (use carefully)
- **Delete** – No new file, flags an existing file as obsolete.

Establishing process for identifying appropriate operation attributes will help minimize mistakes – work with your publishers!

For example:
- Cover Letter – New
- Annual Reports – New
- Draft Labeling Text – Replace
- Amended Protocols – Replace
FDA’s Perspective

If I was a reviewer, could I……..?

- Easily locate the information/document
- Easily copy and paste from the document
- Print the document and see page numbers
- Easily differentiate between same type documents displayed in the eCTD tree
- Rely on a uniform, consistent format in your submission
- Easily navigate and access references in documents via bookmarks, links and the Table of Contents
- Easily identify the most current version of a document (protocol, IB, label, stability data, etc.)

The ultimate goal is to provide the agency with a reviewer-friendly eCTD so that the focus of their review is content, not on the format.
Benefits of eCTD

- Submission via ESG allows immediate receipt by FDA
- Can reduce time to approval
- Accessibility to documents across modules
- Allows for repurposing of docs for submission in other regions
- Improved handling and archiving of submissions (both sponsor and FDA)
- Search functionality and increased tracking ability
- Improves reviewer efficiency
Thank You!
Contact Information

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