Getting started with the eCTD

Donovan Duggan, MBA
Office of Business Process Support
Center for Drug Evaluation and Research

Overview

- Background Information
- eCTD Guidance and Specifications
  - eCTD Guidance Document
  - eCTD Specifications
- eCTD Guidance
  - Changes from eNDA Guidance
  - Continuation of eNDA Guidance
- Sample Process
- Common Mistakes to Avoid
- Waiver Process

Background

- CTD is an ICH standard that FDA adopted in a consensus process, as a member of ICH, together with other member regions, Europe & Japan
- As of 1/1/08, eCTD standard is the only acceptable format for *new* electronic submissions to CDER (Exceptions: electronic applications actively under review on 1/1/08 and/or applications with a waiver)
- eCTD is not a creation of FDA

Submit in eCTD Format

- We are working to standardize ASAP
- By the end of PDUFA IV, we need to be paperless
- Begin the process of converting now if you haven't already
- Any new application, supplement, or DMF
- Normally not within a review cycle
- Submit a sample first

Definitions

- CTD: common technical document
- eCTD: electronic common technical document
- Backbone: the master table of contents of the eCTD
- Esub: any electronic submission
- ICH: International Conference on Harmonisation

Getting Started

- Get back to basics
  - Understanding eCTD requires understanding the CTD
- Educate the organization
  - CTD requires new ways of authoring documents
- Examine your internal practices
  - eCTD requires new ways of publishing submissions

Use All Available Reference Material

- CTD Guidances
  - International Conference on Harmonisation - Joint Safety/Efficacy (Multidisciplinary)
- eCTD Guidances
- Specification Documents
  - Module 1 Regional
  - Module 2 through 5
  - Study Tagging File
  - Study Data Specifications
  - PDF Specifications
    - Very Import to Read This
  - eCTD Table of Contents
  - Heading and Hierarchy Document

eCTD Guidance

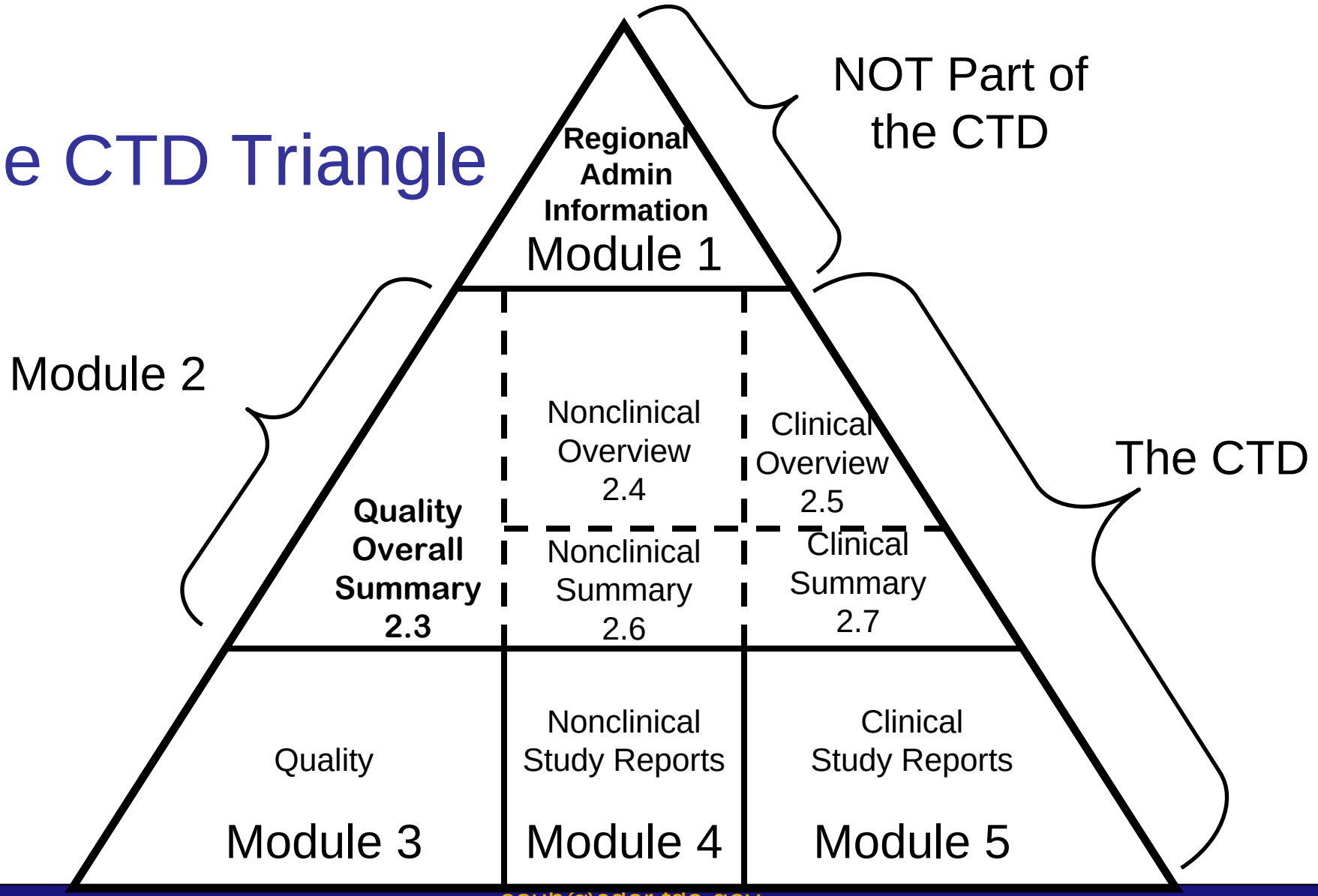
- Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions
  - All submission types
    - NDA, ANDA, BLA, IND, DMF, Annual Reports, Periodic Safety Reports, Advertising and Promotional Labeling
  - Last Published as Final June 2008

eCTD Specifications

- eCTD Specifications
  - FDA Module 1 Specification
  - FDA Modules 2 to 5 Specification
  - Study Tagging File Specification
- FDA eCTD Table of Contents Headings and Hierarchy
- Documentation Available On-Line

  http://www.fda.gov/cder/regulatory/ersr/default.htm

The CTD Triangle



Going In-House - Select a Tool

- Publishing eCTDs without a tool will often lead to frustration and delays
- Build versus Buy Decision
- Ensure tool is as flexible as your submission process requires

Many Have Used a Contractor

- Many contractors have a good deal of experience
- Can provide a fast track to success
- Can serve as a training resource
- Can give a false sense of accomplishment if you don’t learn from them

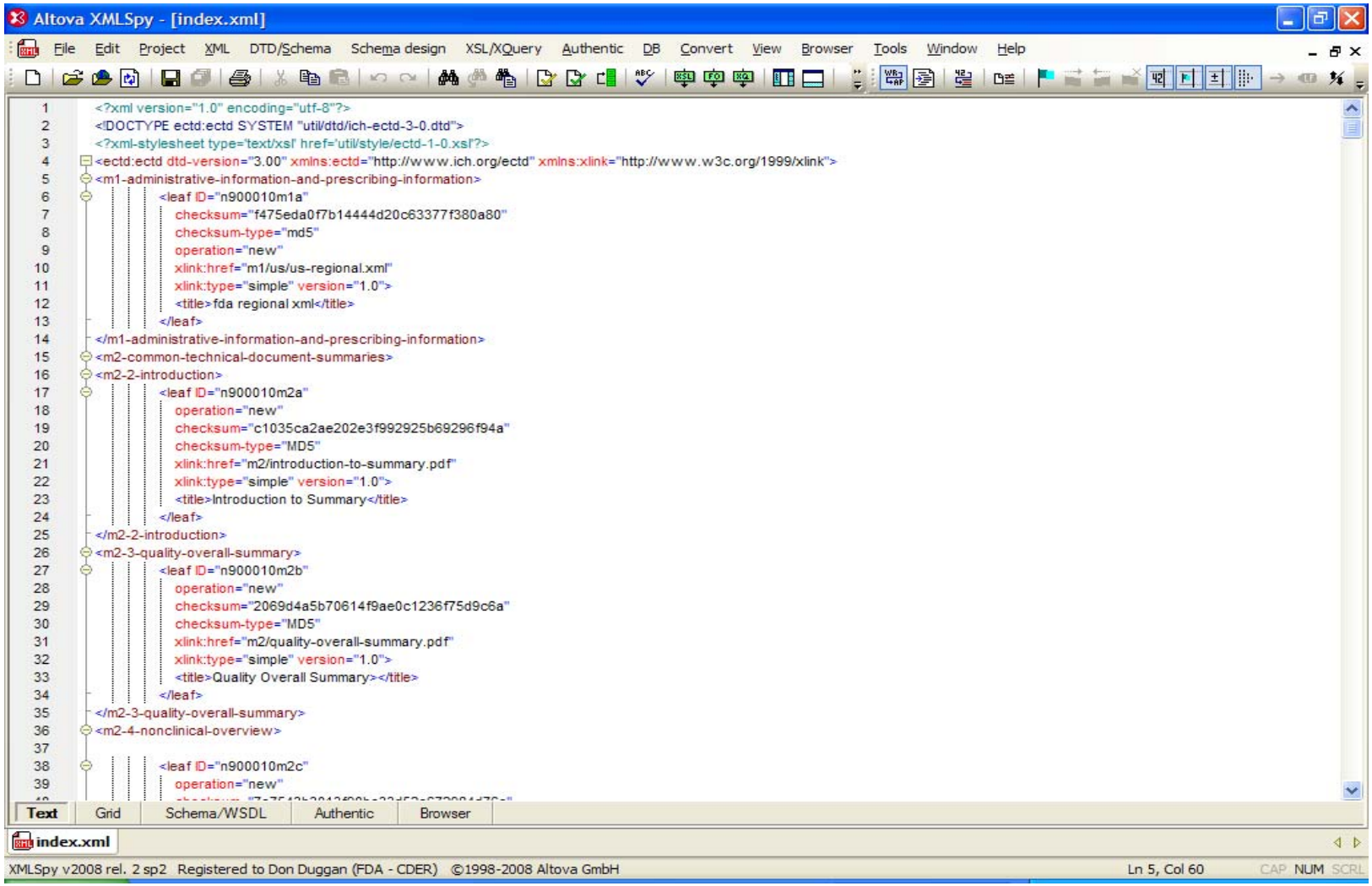
Do I Need Reviewer Approval?

- No!
- Communication of your intent very helpful though
  - Helps with training
  - Helps alleviate any anxiety

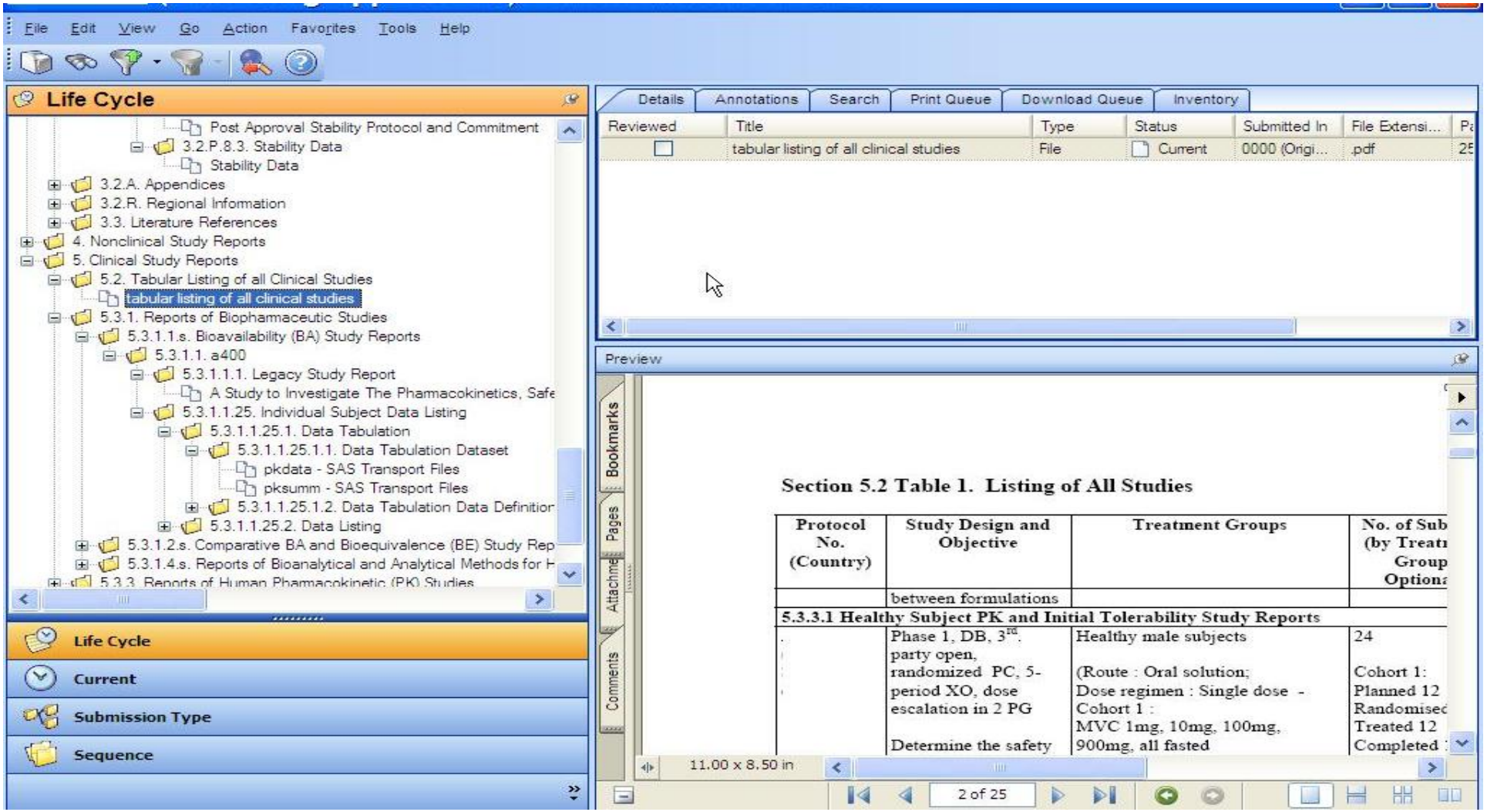
eCTD Changes

- XML-based eCTD Backbone replaces PDF Table of Contents
- Increased document granularity in accordance with ICH eCTD agreements

An index.xml file



FDA Reviewer View of an eCTD



eCTD Changes

- eCTD Validator tool performs rigid validation of backbone against DTD
  - Requires strict adherence to specifications
  - Do not add or modify leaf nodes within the backbone
- Once a submission is sent in eCTD format all future submissions for the application should be in eCTD format
- Opportunity to use Part 11 Compliant Electronic Signatures

Understand the eCTD Lifecycle

- Can be intimidating – but shouldn't be
- Three well defined options
  - New*
  - Replace
  - Delete
- One less defined option
  - Append

* Effectively everything was New prior to eCTD

Lifecycle Operators

- When you replace a document it would helpful to outline a summary of changes
- This saves the reviewer time and speeds up your review
- Replace and Delete are when information changes - not just for correcting mistakes

Lifecycle Operators contd.

- Operation Attribute
  - New
    - Referenced file is being used in a new context
  - Append
    - Referenced file is being used to add information
    - Append only files introduced as New or Replace
  - Replace
    - Referenced file is being used to replace a previous file
  - Delete
    - Used to signal that a previously submitted leaf is no longer to be considered relevant to the review

Lifecycle Operators contd.

- After numerous appends it may make sense to replace the document
- Again it is helpful to outline the changes for the reviewer

What doesn't change

- Data files submitted in SAS XPORT format
- Draft labeling submitted in MS Word
- Documents submitted in PDF Format
- Hyperlinks and Bookmarks are still Critical

eCTD Sample Process

- Contact CDER ESUB prior to generating sample submission
- No-Risk way to validate your eCTD understanding
- Sample submission evaluated for technical compliance only unless directed otherwise
- Accepting all submission types, e.g., IND, NDA, Amendments, Master Files, Annual Reports…
- Generally not required if using experienced submission publisher

What to Include in a Sample

- Include all modules
- Include cross-document hyperlinks
- Include a STF
- No need for dummy files under all headings
- No need for real data
- Will not be reviewed by a reviewer; only ESUB staff – reviewers/clients are not notified of sample success or failure

What to Include in a Sample cont.

- We take special requests – tell us anything specific you would like evaluated
- Provide a technical contact
- To obtain a Sample Number contact: esub@fda.hhs.gov
- Submit your sample well in advance of your eCTD submission – 30 day turnaround

How to get a Waiver

- Contact Person Name - This will be the main contact
- Contact Person's Company Name
- Contact Person's Mailing Address
- Contact Person's Phone Number
- Contact Person's Email Address
- Relevant Submission Types and Numbers
- A description of the submitters plan to become compliant with the guidance:
  - "Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications", ***including relevant timeframes .***

Submissions 101

All eCTD Submissions Include Module 1

- Each and Every eCTD Submission Requires Module 1
- Module 1 Identifies important information
  - Company Name
  - Drug Name
  - Submission Type
  - Submission Date
  - Application Number
  - Sequence Number

No Duplicate Submissions of mixed paper/electronic applications

- Once you have submitted an eCTD, do not submit additional paper or electronic copies
- When submitting paper documents requiring signatures it is preferable to send in electronic copies with your eCTD
- Duplicate submissions can trigger re-review or be rejected
- If you are planning to cross reference to other eCTD's it is wise to submit a sample first

No Electronic Desk Copies

- Do not send electronic desk copies
- Meeting briefing packages are OK
- Contact ESUB@fda.hhs.gov if you have a concern

Everything you Submit is “Official”

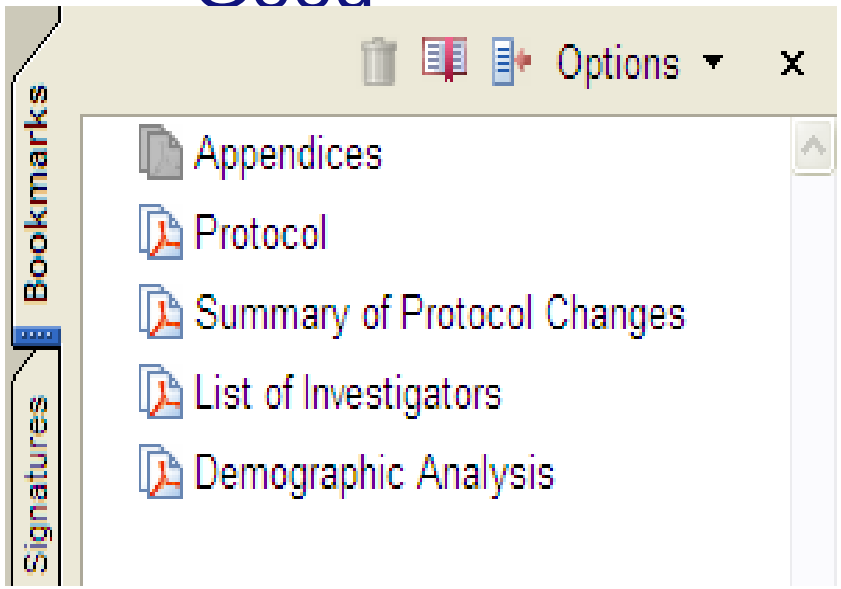
- Extra copies are also the “official copy”
- Everything you submit will be archived

All PDF HyperLinks & Bookmarks are Correct

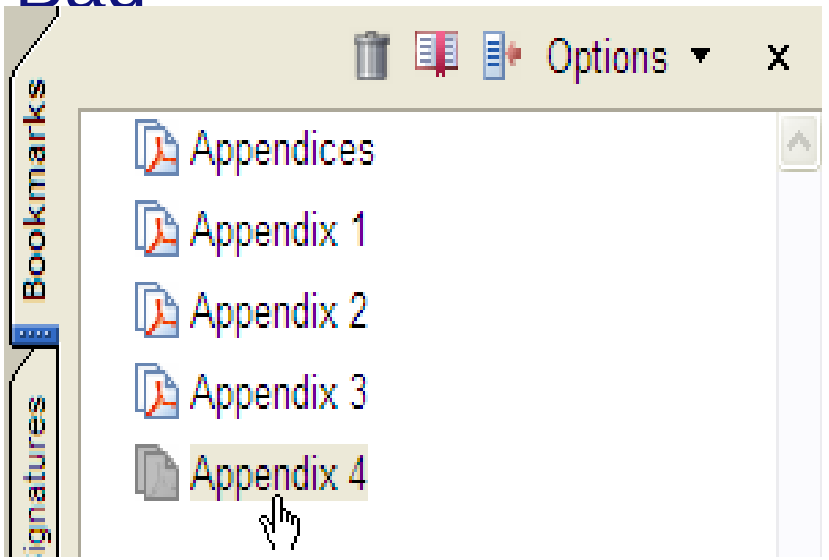
- Validate all Hyperlinks and Bookmarks before you send in your submission
- Incorrect Targets Unnerve Reviewers
- Reviewer Thinks: "What else is wrong with the submission?"
- Bad Hyperlinks have resulted in a RTF

Provide Bookmarks with Intuitive Names

- Good



- Bad



We are seeing more and more fundamental errors

- Careless mistakes (wrong numbers, missing information)
- Mismatched forms - e.g. 356h with an IND application
- Not following guidance or specifications
- Duplicate submissions

Please Remember…

- Your application number is 6 numeric characters
  - 99-909 is bad
  - 099909 is good
- Your sequence number is 4 numeric digits
  - 909 is bad
  - 0909 is good
- Your sequence number must be unique

Just say no…

- No paper
- No Word files or file formats not specified in the guidance
- No electronic submissions or records sent directly to a reviewer or project manager
- No electronic desk copies

Just do it…

- Do Follow the Guidance & Specifications
  - Don’t use node extensions in preparing eCTD
  - Don’t send customized style sheets
  - Don’t combine multiple documents into single PDF

Remember….

1. Files Referenced in the XML Backbone(s)
2. eCTD Submissions Include Module 1
3. Application Numbers are 6 Digits
4. Sequence Numbers are 4 Digits
5. Ensure we receive what you intended
6. Do not send in one submission to be applied to multiple applications
7. XML must be Standard Components
8. PDF contains Recognizable Text
9. PDF Hyperlinks/Bookmarks are Correct
10. PDF Documents include TOCs

References

- CDER Contact for information on eCTD submissions

  esub@fda.hhs.gov
- CDER Contact for information on SDTM submissions

  cder-edata@fda.hhs.gov
- Electronic Regulatory Submissions and Review website

  http://www.fda.gov/cder/regulatory/ersr/default.htm
- International Conference on Harmonization

  http://www.ich.org
- All FDA Guidances on Electronic Submissions

  http://www.fda.gov/cder/guidance/index.htm#electronic_submissions