

FDA Considerations for eCTD INDs

**Constance Robinson-Kuiperi
Regulatory Information Specialist**

Division of Regulatory Review Support

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Agenda

- **Acceptable IND Formats**
- **Why submit in eCTD format?**
- **Getting Started**
- **General Considerations for eCTD INDs**
 - **The “DO” List**
 - **The “DON’T List**
 - **Top Ten Issues for Success**
 - **References**



Acceptable IND Formats

- Paper
- eCTD to CDER
- eCTD or eIND w/roadmap to CBER



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Why submit in eCTD format?

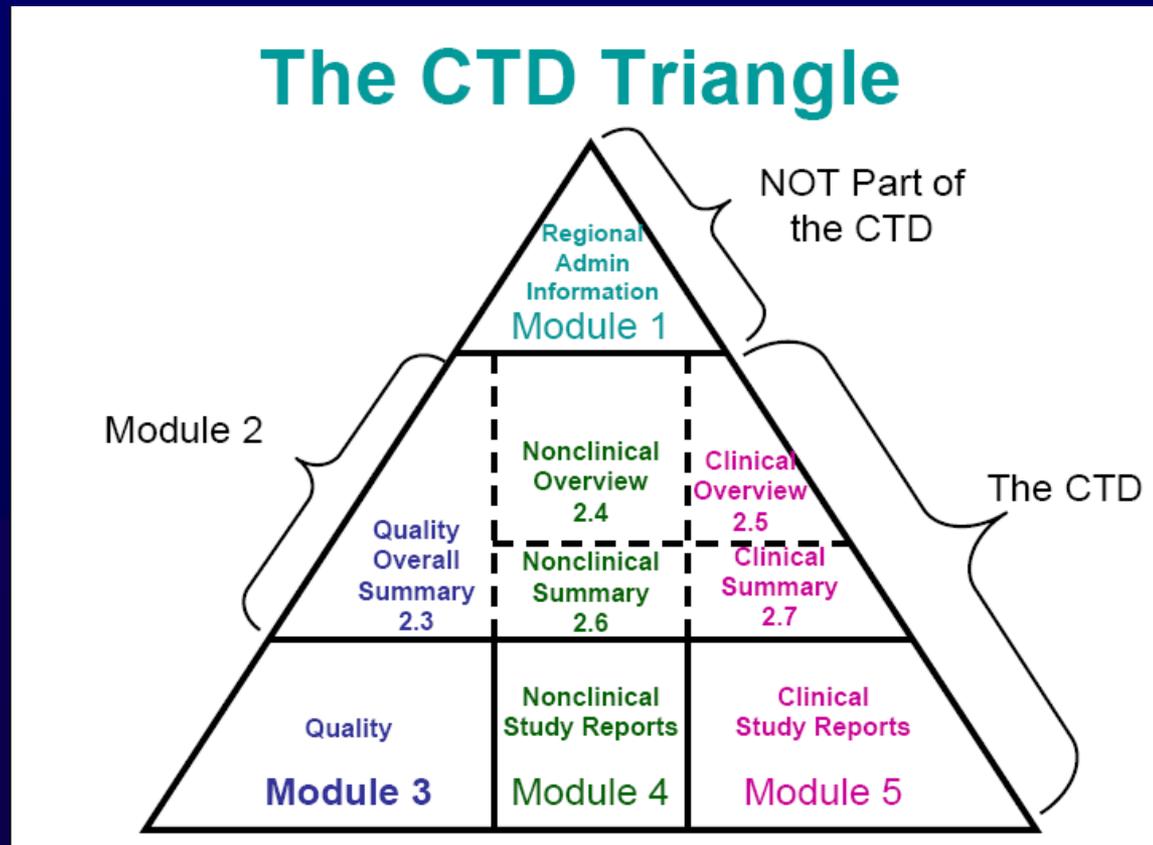
- eCTD is the FDA-preferred format
- Most FDA reviewers prefer electronic vs. paper
- Opportunity to use Part 11 Compliant Electronic Signatures
- eCTD can be sent to FDA via the gateway and can be received via our automated processing, paper can't
 - Electronic format can help expedite the review process



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eCTD Getting Started

The CTD Triangle



eCTD Getting Started IND Mapping Table

<u>CTD-Modules</u>	<u>IND-Items</u>	
Module 1 -- Regional Admin	IND-Item 1. → FDA-1571-Form IND-Item 2. → Table-of-Contents-(N/A) Item 3. Environmental-Assessment Item 3. Clinical-Supply-Labels IND-Item 4. → General-Investigational-Plan IND-Item 5. Investigator-Brochure	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Module 2 -- Summaries	IND-Item 3-Introductory-Statement IND-Item 7-CM&C-Introduction IND-Item 7-Nonclinical-Summary IND-Item 9-Previous-Human-Experience--Clinical-Summary IND-Item 10-Additional-Information Drug-Dependence-and-Abuse	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Module 3 -- Quality	IND-Item 7-Chemistry-Manufacturing-and-Control IND-Item 7-Drug-Substance IND-Item 7-Drug-Product IND-Item 7-Placebo	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Module 4 -- NonClinical Safety	IND-Item 8-Pharmacology/Toxicology-Information IND-Item 8-Nonclinical-Reports	<input type="checkbox"/> <input type="checkbox"/>
Module 5 -- Clinical Efficacy	IND-Item 6. Protocol FDA-Form-1572 Investigator-CV Sponsor's-CV Item 9. Previous-Human-Experience-Clinical-Reports	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>



eCTD Getting Started eCTD Specifications, Guidance, and Other Information

- **Visit the FDA eCTD website and review the information (specifications and guidance)**
 - **FDA presentations**
 - **ICH M2 EWG eCTD Specification**
 - **The Comprehensive Table of Contents Headings and Hierarchy (CTOC)**
 - **mapping sections (IND, NDA, ANDA) on page 12 of CTOC**
 - **Review the Validation Specifications**



eCTD

Getting Started

Training
Tools
Templates
Obtain information & clarification
Submit a sample

**Three Important Steps When Submitting
an eCTD:**

Build it, Validate it and View it



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eCTD

Getting Started

**PreIND and IND number are the same
eCTD application number**

**To obtain an eCTD application number,
please visit**

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



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General Considerations for eCTD INDs

For questions and guidance, consult with FDA E-Sub group and your review division!

- **Initiate contact prior to assembling application**
- **Include IND format on pre-IND meeting agenda**
- **Submit eCTD Sample**
- **Contact addresses:**
 - **Cder-edata@fda.hhs.gov**
 - **esub@fda.hhs.gov**



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General Considerations for eCTD INDS continued...

Submitting Electronic Submissions -

- For CDER: –ALL electronic submissions should be sent to the CDER Central Document Room
- For OGD–All electronic submission to the OGD document room•
- Use the correct electronic media and choose type appropriate to size of submission
- If Part 11 compliant electronic signatures are available otherwise only documents requiring original signatures



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General Considerations for eCTD INDS continued...

Reviewability and Navigation is very important!

Bookmarks and Links enhance navigation & can improve reviewability

When to provide links? Anytime the text refers to a reference (table, figure, section, etc.) that is not on the same page

–Provide cross reference links to other documents if necessary

–Check your links

–When there are changes reported in a summary provide links, if it would be helpful to the reviewer



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General Considerations for eCTD INDs continued...

Leaf titles - Short, meaningful & indicative of the contents

Scanned images, text, tables and figures are very difficult, frustrate reviewers and can impede a review. Source documents converted to pdf or OCR'd pdfs are much more user-friendly from a reviewer's perspective.



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General Considerations for eCTD INDs continued...

Create document level Tables of Content with appropriate bookmarks

- Include a TOC for any document more than a few pages long**
- If the document in paper needs a TOC, the electronic version needs one too**



General Considerations for eCTD INDs continued...

**Use Appropriate Operation attributes
for the leaf element (New, Append,
Replace, Delete)**

**Do not use “New” if you should be
using “Replace”**



General Considerations for eCTD INDs continued...

The screenshot displays a software interface with a file tree on the left and a table of file details on the right. The file tree shows a hierarchy of folders, including 'Life Cycle', 'Current', 'Submission Type', and 'Sequence'. The table lists files with columns for 'Review...', 'Title', 'Type', 'Status', 'Submitted In', 'File Extensi...', 'Pages', and 'Size (KB)'. A red arrow points to the 'Current' status in the table, with a callout box that says 'Operation attribute for the leaf element'.

Review...	Title	Type	Status	Submitted In	File Extensi...	Pages	Size (KB)
<input type="checkbox"/>	Final Protocol, June 200...	File	Replaced	0000 (Orig...	.pdf	55	763
<input type="checkbox"/>	* Amendment #1 Protocol	File	Replaced	0002 (Ame...	.pdf	59	868
<input type="checkbox"/>	* Final Protocol Amendment ...	File	Replaced	0009 (Ame...	.pdf	67	804
<input type="checkbox"/>	* Amendment # 09 O...	File	Current	0012 (Ame...	.pdf	74	627



eCTD INDs

The To Do List:

Follow Guidance & Specifications

6-digit application # and 4 digit sequence #

Take advantage of granularity

Send submissions to our Document Room

Include all required eCTD files

ALL files submitted are referenced in XML backbone

Only send 1 copy of the electronic submission

**Same application # is in the us-regional.xml, FDA form
and cover letter**



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eCTD INDs

The Do Not Do List:

Ensure what we receive is what you wanted to send

- X No blank electronic media**
- X No empty folder**
- X No unloadable media**



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eCTD INDs

The Do Not Do List:

- X Don't submit a duplicate sequence**
- X Don't use node extensions in preparing eCTD**
- X Don't send customized style sheets**
- X Don't send electronic desk copies**
- X Don't send paper, except for briefing packages**
- X Don't send Word files or file formats not specified in the guidance**



eCTD

Examples of Issues :

3 Real Examples of Issues

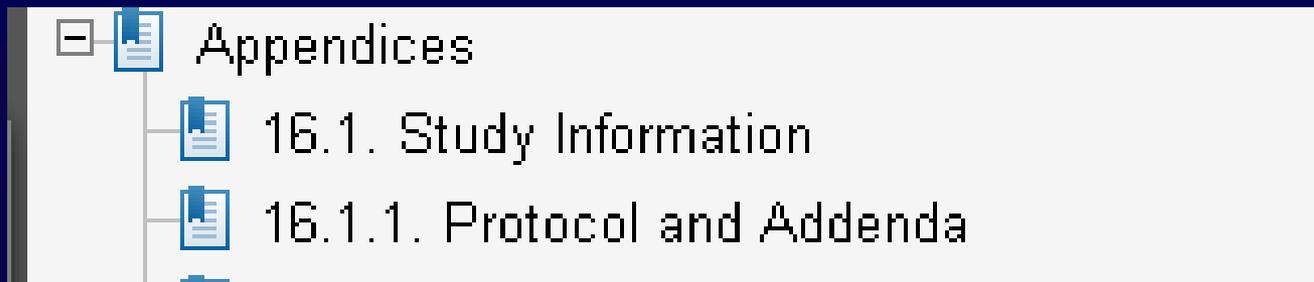
1. A single bookmark in a study that had 4 protocols
2. Perfect eCTD structure and titles, but missing almost all cross document reference links
3. Over 60 repeat dose toxicity study reports not grouped according to specifications and had inadequate leaf titles (only had study identifiers as leaf titles)



eCTD

Examples of Issues :

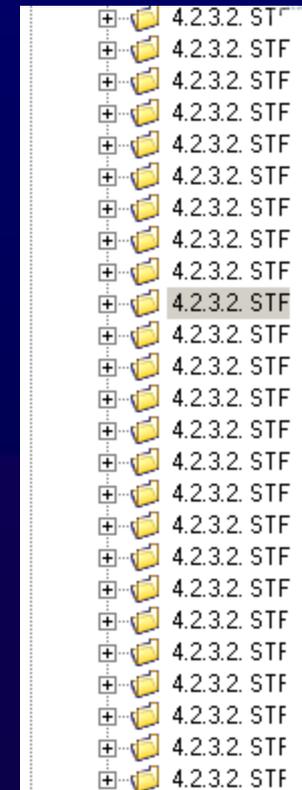
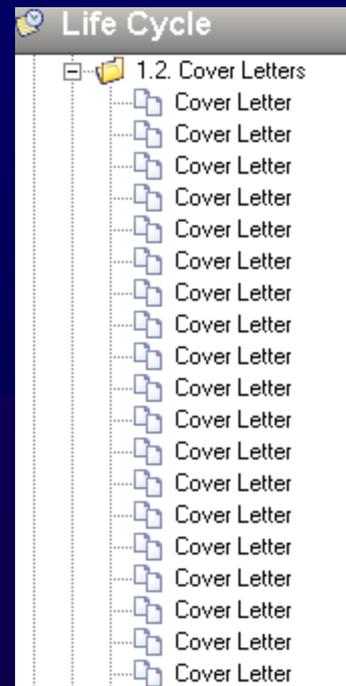
- If you have 4 protocols don't only provide one bookmark
 - Include a bookmark for each protocol and bookmarks for the TOC in each protocol
 - Below is a bad example that has one bookmark



eCTD

Examples of Issues :

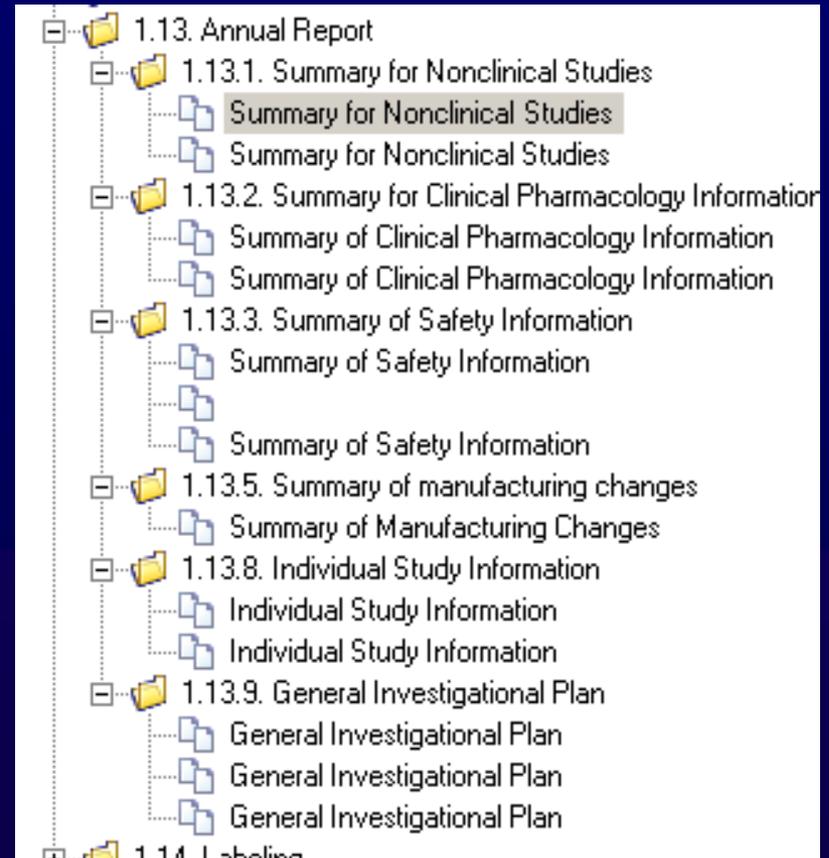
- See 2 examples of what not to do:
- Here is what you should do
 - Provide date, sequence for cover and forms
 - Provide study title or shortened study titles not study ID or STF with study ID



eCTD

Examples of Issues :

- Another example of what not to do:
- Here is what you should do
 - Provide date, time period or something that differentiates one from the other



Top 10 Issues for Success :

10. Files Referenced in the XML Backbone(s)
9. eCTD Submissions Include Module 1
8. Application Numbers are 6 Digits
7. Sequence Numbers are 4 Digits
6. Ensure we receive what you intended
5. Documents Conform to eCTD Granularity
4. XML must be Standard Components
3. PDF contains Recognizable Text
2. PDF Hyperlinks/Bookmarks are Correct
1. PDF Documents include TOCs



References

Guidance and Specifications listed on the FDA eCTD website : <http://www.fda.gov/cder/Regulatory/ersr/ectd.htm>

FDA presentations available on the FDA eCTD website:
at <http://www.fda.gov/cder/Regulatory/ersr/default.htm#Presentations>

Comprehensive Table of Contents Headings and Hierarchy:
at <http://www.fda.gov/cder/Regulatory/ersr/5640CTOC-v1.2.pdf>
Review the mapping sections (IND, NDA, ANDA) on page 12

eCTD validation:
http://www.fda.gov/cder/Regulatory/ersr/validation_specs.htm



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