



42nd
Annual Meeting



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eSUBS and eCTDs: Practical Advice and Pitfalls to Avoid

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Overview

- CDER's eCTD processing
- How our tools look and work
- Frequently encountered issues
- Examples
- How to ensure success



Fewer Technical Issues

- eCTD submissions continue to increase steadily
- Number of technical errors/issues has decreased
- You're doing a great job!



How CDER EDR Staff Checks Your eCTD Submission

- Media is loaded to server, validate program is run
- Directory compare tool is run
- If review of your submission cannot proceed, you are contacted
- Otherwise, reviewers are notified that submission is available for review
- Reviewer performs the detailed audit



General Sample – Module 1 -Risk Management

912345 - GlobalSubmit Review

File Edit View Favorites Tools Help

Submission Sequence

- FDA
 - + 0001 (Amendment) 6/11/2006
 - 0000 (Original Application) 3/24/2006
 - 1. Regional Information
 - 1. FDA Regional Information
 - + 1.1. Forms
 - + 1.2. Cover Letters
 - + 1.3. Administrative Information
 - + 1.4. Reference Section
 - + 1.9. Pediatric Administrative Information
 - + 1.14. Labeling
 - 1.16. Risk Management Plans
 - Risk Management Plans
 - + 2. Common Technical Document Summaries
 - + 3. Quality
 - + 4. Nonclinical Study Reports
 - + 5. Clinical Study Reports

Details | Annotations | Search | Print Job | Download |

Reviewed	Title	Type	Siz...	FDA	Pag
<input type="checkbox"/>	Risk Management Plans	File	2	0000 (Current)	0

Module 1 US Placeholder Document: Risk Management



Life Cycle Sample – Stability Data Replaced

Navigation Pane

- FDA
 - 0001 (Amendment) 6/11/2006
 - 3. Quality
 - 3.2.P. Drug Product - Take 2 - tablet - Good Drugs Inc.
 - 3.2.P.8. Stability
 - 3.2.P.8.3. Stability Data
 - Updated Stability Data
 - 0000 (Original Application) 3/24/2006
 - 3. Quality
 - 3.2.P. Drug Product - Take 2 - tablet - Good Drugs Inc.
 - + 3.2.P.1. Description and Composition of the Drug Product
 - + 3.2.P.2. Pharmaceutical Development
 - + 3.2.P.3. Manufacture
 - + 3.2.P.4e. Control of Excipient
 - + 3.2.P.5. Control of Drug Product
 - + 3.2.P.6. Reference Standards or Materials
 - + 3.2.P.7. Container Closure System
 - 3.2.P.8. Stability
 - + 3.2.P.8.1. Stability Summary and Conclusion
 - + 3.2.P.8.2. Post-approval Stability Protocol and Stability
 - 3.2.P.8.3. Stability Data
 - Stability Data



Life Cycle Sample – Stability Data Replaced

Detail Panel

Details Annotations Search Print Job Download						
R...	Title	Type	Size...	Pages	FDA	
[-] Stability Data						
<input type="checkbox"/>	Updated Stability Data	 File	124	4	 0001 (Current)	
<input type="checkbox"/>	Stability Data	 File	3	0	 0000 (Replaced)	



The Top Technical Issues

- Listed from least to most important
- Most all errors stem from one or more of these items



Use of Elements

- Not necessary to use every element in the eCTD Specification
- Use only the elements you need
- Placeholder documents are not necessary, and can divert reviewers' time and attention



Leaf Titles

- Should be informative and succinct
- Should not include the eCTD numbering
- Should immediately reveal to the reviewer what's inside



Clinical Reports – Long and Short Leaf Titles in Navigation

-  Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
 -  Placebo Control
 - +  Study ID: ABC 330 - Take 2 in Migraines - A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy of Take 2
 - +  Study ID: ABC 999 - Take 2 in Migraines/hypertension -Randomized, Double-Blind, Multicenter
 - +  Study Reports of Uncontrolled Clinical Studies
 - +  Reports of Analyses of Data from More than One Study



Always Reference All Files in the XML Backbone(s)

- Unreferenced Files Result from
 - Missing/Mislocated Directory references in xlink:href
 - “Extra” files
 - Failing to Repeat Complete Directory Structure on each media component in a set
- Unreferenced Files may not be located by reviewers



Include Module 1 in All eCTD Submissions

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



Make Sure All Application Numbers are 6 Digits

- Application-number values must be 6 digits -
 - No Alpha Characters
 - No “-” “,” or other punctuation
 - No spaces
 - Six Numbers – pad left “0” if 5 digits are given
- Application number is key - ties all submissions together as an application



Make Sure All Sequence Numbers are 4 Digits

- Sequence-number values must be 4 digits
 - No Alpha Characters
 - No “-” “,” or other punctuation
 - No spaces
- Sequence number is key and relates all submission components together
- Sequence numbers need not be received/submitted in “sequence”



Do Not Use Node Extensions

- Node Extensions are Unwanted
 - ICH and FDA do not recommend NEs
 - At best they are ignored; at worst they defeat the standard headings
- Node Extensions are Unneeded
 - Leaf Title can be used to differentiate between documents at the same level



Verify That All MD5 Checksums are Correct

- MD5 Checksum values should be
 - Coded as a leaf attribute in either us-regional.xml or index.xml
- Except
 - The MD5 Checksum value is provided in a one-line text file – index-md5.txt - in each sequence number directory



All Documents Should Conform to eCTD Granularity

Avoid combining documents at higher parent leaf level (allowed by Module 3)

- Tempting - small initial savings in combining
- Large cost in life cycle complexity
- “Legacy” Study Reports make for life cycle issues down the road



All XML must use Standard Components

UTIL Folder

- 3 Standard DTDs
 - 3 Standard Styles Sheets in UTIL folder
 - Custom components create issues in FDA Processes – Defeat standards efforts
- Avoid GIFs, custom CSS, custom DTDs, custom elements with standard DTDs

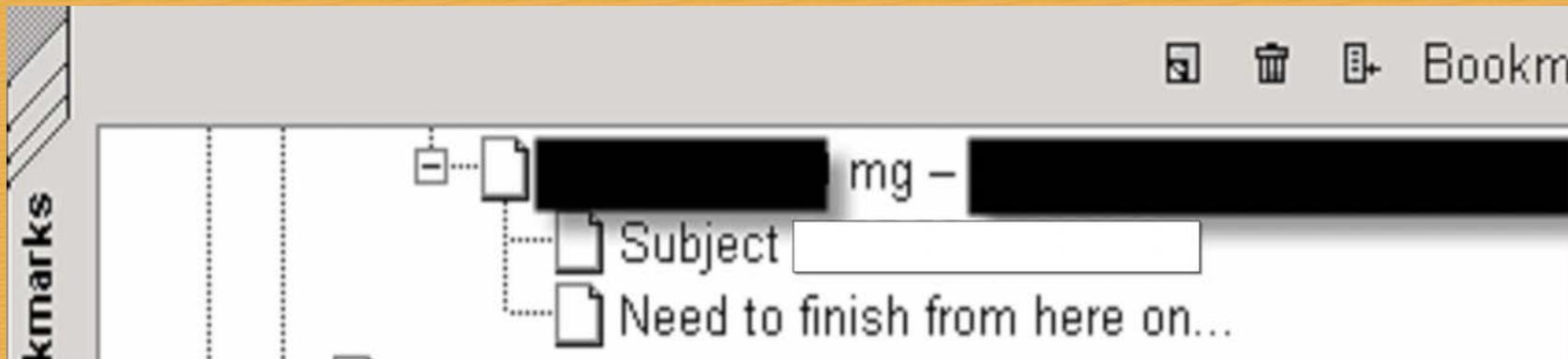


Be Sure All PDF Hyperlinks & Bookmarks are Correct

- Validate all Hyperlinks and Bookmarks
- Broken hyperlinks and bookmarks diminish reviewer confidence in the submission
- Test before you submit



Book Mark Example to Avoid



Include TOCs In All PDF Documents

For each Document -

- If a paper document needs a TOC, a PDF document needs a hyperlinked TOC
- TOCs should begin a PDF document if possible
- Include both bookmarks and hyperlinks
- Cross Document Links work in an eCTD



To Summarize

- Correct use of elements and leaf titles
- Always Reference All Files in the XML Backbone(s)
- Include Module 1 in All eCTD Submissions
- Make Sure All Application Numbers are 6 Digits
- Make Sure All Sequence Numbers are 4 Digits
- Do Not Use Node Extensions
- Verify That All MD5 Checksums are Correct
All Documents Should Conform to eCTD Granularity
- All XML must use standard components
- Be Sure All PDF Hyperlinks & Bookmarks are Correct
- Include TOCs In All PDF Documents



Ensuring Success

- Submit a Sample eCTD prior to your real eCTD (contact info next slide)
- Follow the specifications and guidances and/or use an experienced consultant
- Follow the advice outlined in this presentation to avoid common problems



References

- **CDER Contact for information on eCTD and CTD submissions:** eSub@fda.hhs.gov
- **Electronic Regulatory Submissions and Review website**
www.fda.gov/cder/regulatory/ersr/default.htm
- **International Conference on Harmonization**
www.ich.org
- **Regulatory Review Support Staff, Office of Business Process Support, CDER (headed by Gary Gensinger)**

