DRUG INFORMATION ASSOCIATION

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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

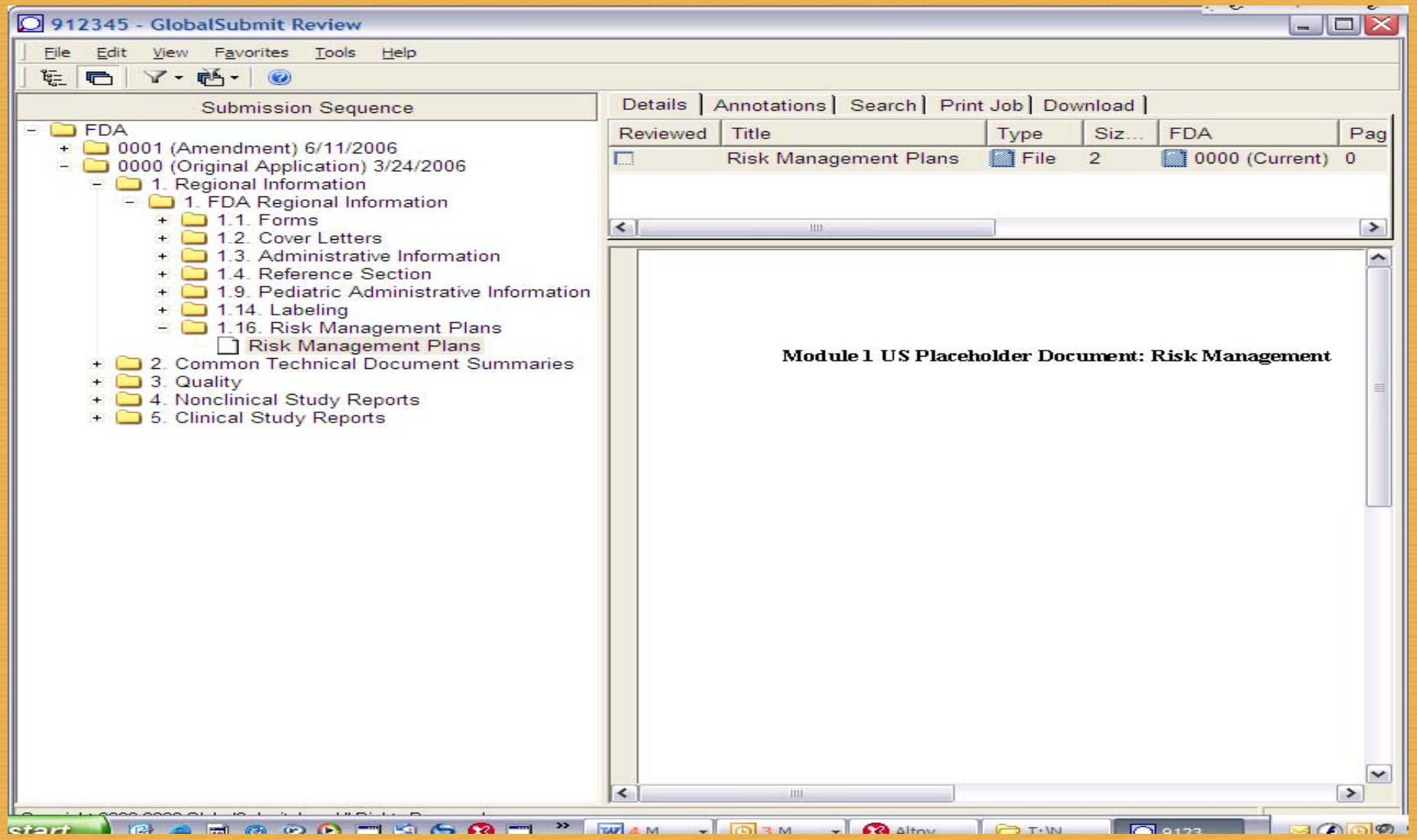
Fewer Technical Issues

- 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

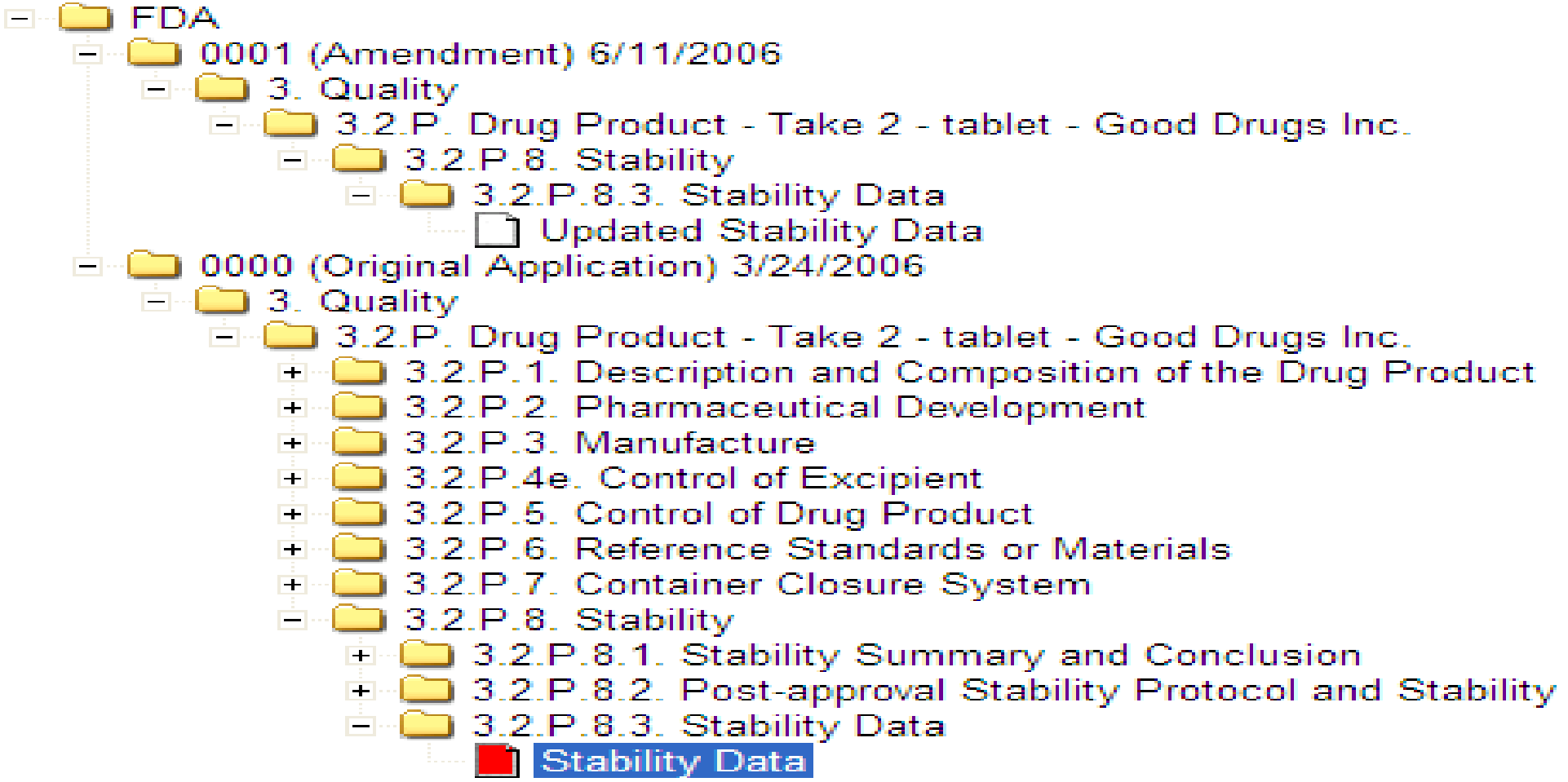
- Media is loaded to server, validate program is run
- Directory compare tool is run
- If review of your submission cannot proceed, you are contacted
- Otherwise, reviewers are notified that submission is available for review
- Reviewer performs the detailed audit

General Sample – Module 1 -Risk Management



Life Cycle Sample – Stability Data Replaced

Navigation Pane



Life Cycle Sample – Stability Data Replaced

Detail Panel

Details | Annotations | Search | Print Job | Download

	R...	Title	Type	Size...	Pages	FDA
⊟ Stability Data						
	☐	Updated Stability Data	File	124	4	0001 (Current)
	☐	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

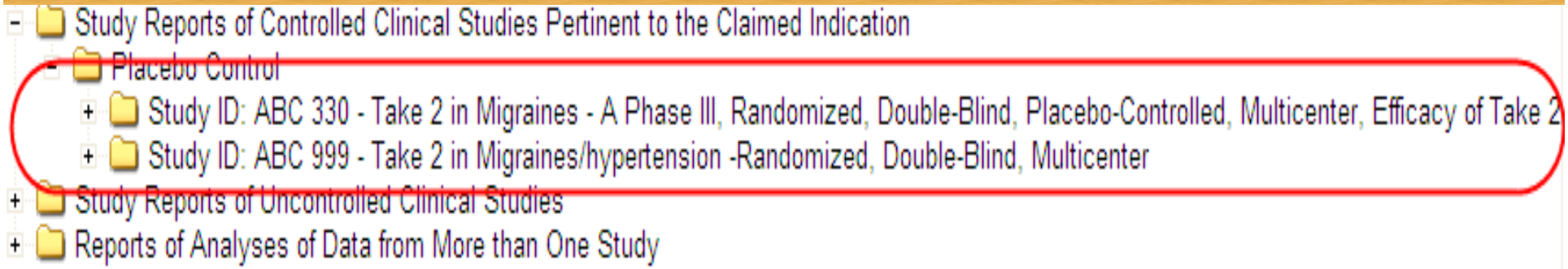
Use of Elements

- 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



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

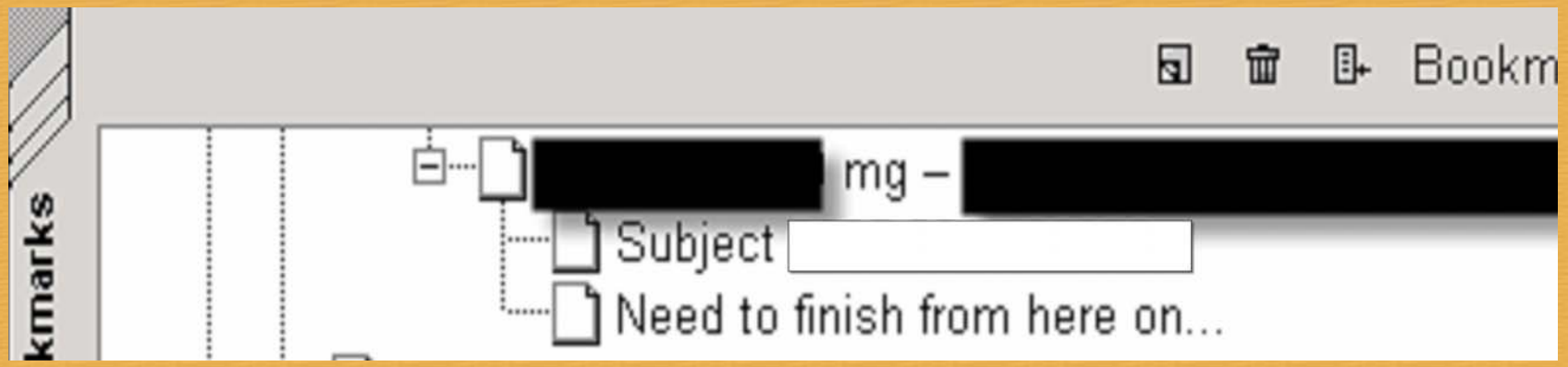
UTIL Folder

- 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)