Regulatory Submissions, Information, and Document Management Forum

February 8-10
North Bethesda, MD

DIA DEVELOP INNOVATE ADVANCE

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DIA DEVELOP INNOVATE ADVANCE

eCTD VALIDATION UPDATE

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DIA Electronic Document Management 2016
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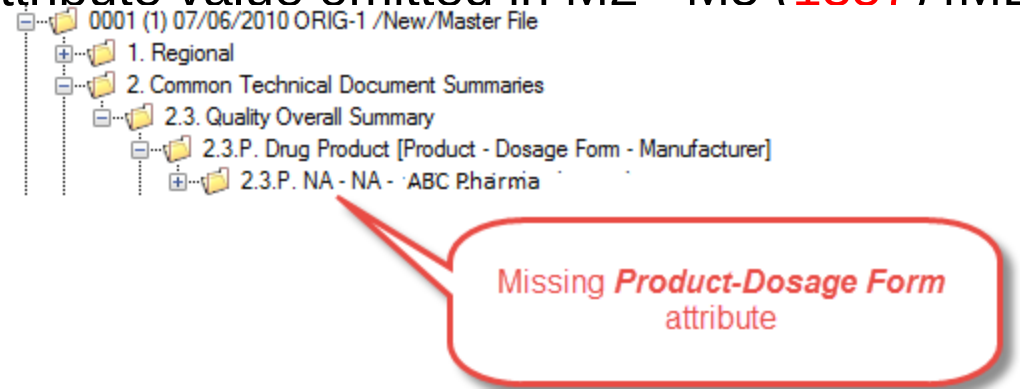
Agenda

- CDER eCTD
  - Top Ten Validation Errors
  - New M1: How are we doing?
  - Rejections
  - Helpful Tips

Top Ten Validation Errors

Description (Error Number) [Severity]

#10 Omitted leaf element title (1289) [MED]
#9 No leaf element for file (1306) [MED]
#8 Related submission type cannot have child sub (1595) [MED]
#7 No file for leaf element (1323) [MED]
#6 Non required file exists (1314) [MED]
#5 File submitted in study section without STF file (1789) [MED]
#4 Invalid file extension (1255) [MED]
#3 Submission type requires related sequence (1629) [MED]
#2 Failed to process PDF contents (3102) [MED]
#1 Required attribute value omitted in M2 - M5 (1357) [MED]



New M1: How are we doing?

How many new M1 submissions have been received?

Application Type	Total
ANDA	121
BLA	110
IND	836
DMF	140
NDA	429
EUA	3
Total	**1639***

*as of 2/1/2016

How many companies have used it?

117

New M1: How are we doing?

What submission types have been received?

Submission Type	Total	Submission Type	Total
Original Application	647	Periodic Safety Reports	60
Promotional Labeling Advertising	314	CMC Supplements	38
IND Safety Reports	265	Efficacy Supplements	30
Product Correspondence	148	PMR/PMC	25
Annual Reports	96	Labeling Supplements	16

*as of 2/1/2016

Rejections

- Most common reasons for rejection
  - Duplicate/Incorrect sequence
  - Submitted to the wrong center
  - Mismatched application/sequence type
  - Invalid file type
  - Not in standard eCTD format

Rejections (1%)*

FY 2015 Total Number and Percent of Standards-Based Electronic Submission Failures

Problem Type	BLA	IND	NDA	Total
Duplicate Sequence Received	10 (2%)	354 (74%)	115 (24%)	479 (40%)
Sent to Wrong Center	32 (19%)	117 (69%)	20 (12%)	169 (14%)
Mismatched Application/Sequence/Type	8 (7%)	52 (46%)	54 (47%)	114 (10%)
Invalid File Type	7 (6%)	41 (38%)	60 (56%)	108 (9%)
Not in Standard eCTD Format	2 (2%)	70 (74%)	23 (24%)	95 (8%)
Duplicate Content Received	33 (39%)	51 (61%)	0 (0%)	84 (7%)
Sent in Error	8 (14%)	33 (59%)	15 (27%)	56 (5%)
No Data Received	7 (16%)	18 (40%)	20 (44%)	45 (4%)
Broken / Corrupted Media	2 (7%)	10 (37%)	15 (56%)	27 (2%)
Invalid Application/Sequence	3 (33%)	4 (44%)	2 (22%)	9 (1%)
Multiple Application / Sequence / US-Regional.xml	1 (50%)	0 (0%)	1 (50%)	2 (0%)
eCTD High Validation Error	0 (0%)	1 (100%)	0 (0%)	1 (0%)
Total	113 (10%)	751 (63%)	325 (27%)	**1,189**

*1,189 out of 115,275 eCTD Submissions into CDER/CBER

Helpful Tips

- Avoid Insufficient Hyperlinks
- Double Check Your PDFs
- Hitting the Mark with Bookmarks
- Getting Files to Correct Destintation
- Leaf Titles
- Annual Reports
- Cover Letter and FDA Forms
- Life Cycle Function

Avoid Insufficient Hyperlinks

HELPFUL TIPS!

- No hyperlinks provided
- Hyperlinks go to incorrect destination or do not work
- Inadequate description (i.e. if link doesn't work, Reviewer does not have enough information to find the referenced document)
- Table of Contents does not contain hyperlinks
- Reviewers appreciate links instead of searching for a reference (table, figure, etc)
- Hyperlinks should be in blue text and/or outlined with rectangles

Double Check Your PDFs

HELPFUL TIPS!

Make sure…

- You have a TOC, bookmarks and links in your PDF files
- Documents are legible and viewable
- Avoid scanning (if you find that you have to scan then correct any pages that needs to be rotated and perform OCR)
- Reviewers have the ability to copy and paste text, tables and figures
- Blue text are reserved for links
- Letter size paper are used for US Submissions – do not send A4 page formats

Hitting the Mark with Bookmarks!

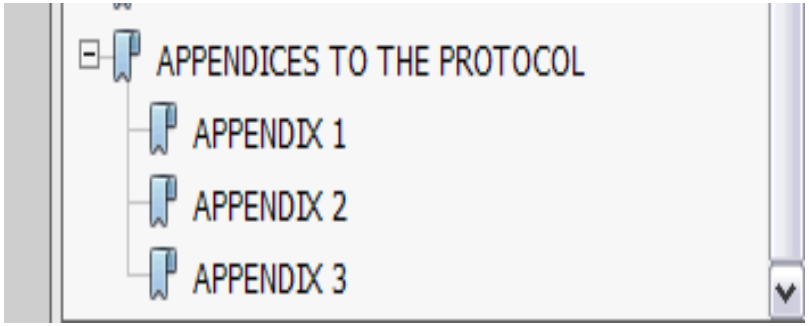
HELPFUL TIPS!

- Set the Navigation Tab to open to "Bookmarks Panel and Page"
- Provide bookmarks if documents are 5 pages are more
- Match table of contents with bookmarks
- Bookmark naming should be helpful

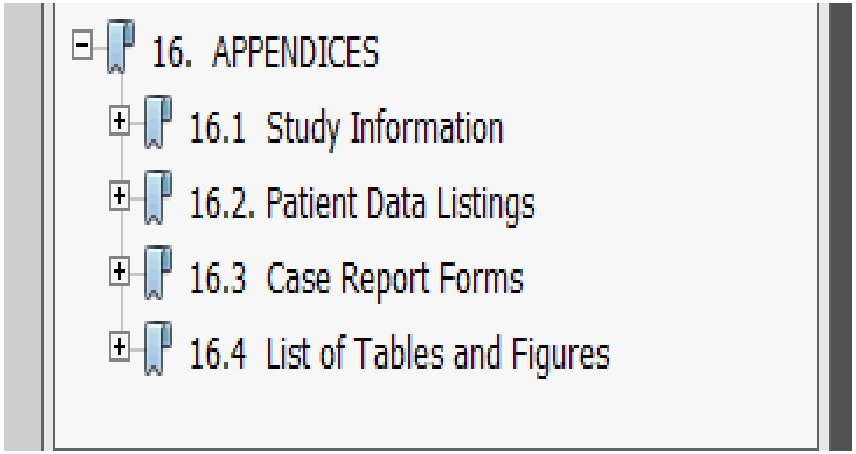
Helpful bookmarks - don't make Reviewers guess…

HELPFUL TIPS!

Not so helpful



Helpful



Getting Files to Correct Destination

HELPFUL TIPS!

Comprehensive Table of Contents Headings and Hierarchy (CTOC)

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163175.pdf

Module 1

- **Cover letter – Section 1.2**
- **Forms – Section 1.1**
- **Labeling – Section 1.14**

Module 2

- Quality of Overall Summary (QOS) – 2.3
- Drug Product – 2.3.P
- Drug Substance – 2.3.S
- Nonclinical Overview – 2.4
- Clinical Overview – 2.5

Use CTOC as your map!

Module 3 – Chemistry Manufacturing Control\Quality related information

Module 4 – Non-Clinical related information

Module 5

- Clinical Study and its components (protocol, synopsis, report, etc.,)
- Integrated Summary of Safety/Efficacy – 5.3.5.3
- Periodic Adverse Drug Event Report or Periodic Safety Update Report – 5.3.6. (reports only, no 3500A Forms)

Leaf Titles (not to be confused with reading tea leaves!)

HELPFUL TIPS!

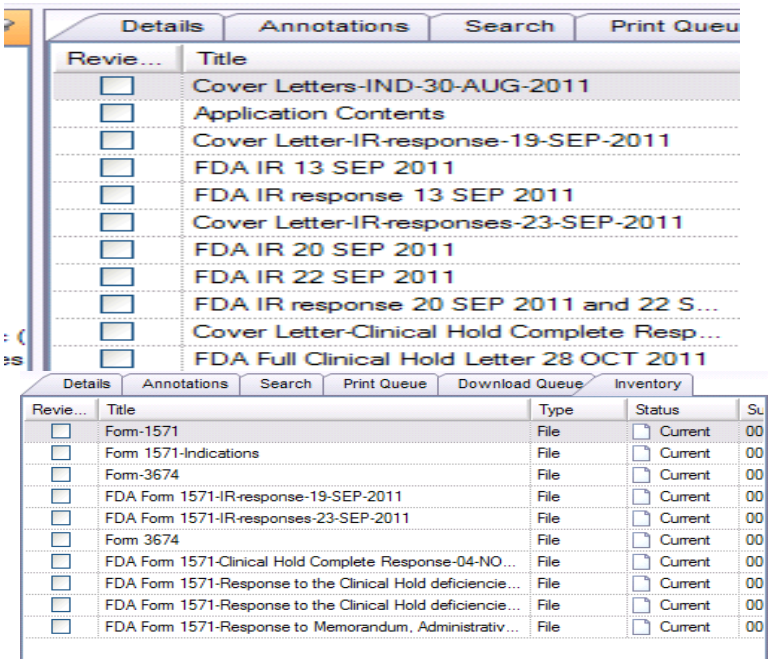
Leaf Titles…

- Different from file names
  - Leaf title displays on FDA's viewer tool
- Should be clear and indicative of the content
  - "Appendix 1" or "Attachment 1" is not a descriptive leaf title
- Same named document (e.g. cover letter and form)
  - adding the sequence number, date and\or brief description of the submission, helps the reviewers

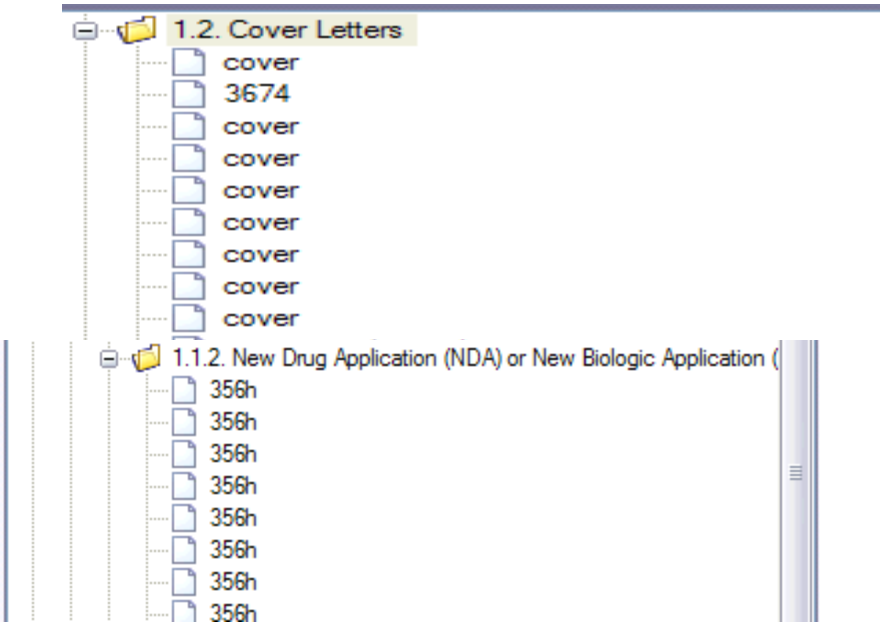
Don’t Make Reviewers Read Tea Leaves..

HELPFUL TIPS!

Useful



Not so useful



- **Leaf titles should be clear and indicative of the content**
- **Include date, sequence number and if possible, short description of the submission**

Annual Reports

HELPFUL TIPS!

- Standalone submissions
- Submit as ‘new’ regulatory activity at all times except when amending a previously submitted Annual Report
- Leaf titles should include reporting period (e.g. “AR-specifications-Oct-12-2014-Oct-11-2015)

Cover Letter and FDA Forms

HELPFUL TIPS!

- Send a cover letter with all submissions
  - Include brief description of submission content
  - Hyperlinks to referenced section(s) is recommended
  - Make sure you indicate technical point of contact information:- name, email address, correct fax and phone numbers
  - The cover letter and FDA Form should contain date, application and sequence number information

- Use Fillable FDA Forms – avoid scanning whenever possible to speed up reviewer accessibility

Life Cycle Function

HELPFUL TIPS!

- Life cycle functionality includes updates, additions and deletions of documents
- Replace and Append operators should be utilized when information changes – do not submit everything as "new" when it's not

Four well defined Life cycle operators

- New = Initial submission of documents
- Replace = Initial document plus updates
- Append = Updates only (use judiciously)
- **Delete** = No longer relevant to the review

- Outline summary of changes for reviewer in cover letter if possible, or in an appendix of a document

References

- eCTD Web Page: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm
- Electronic Submissions Gateway: http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm
- Electronic Submissions Presentations: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm229642.htm
- Questions about OPDP draft guidance or eCTD submissions to OPDP: OPDPeCTD@fda.hhs.gov
- Questions about submitting electronically to CDER: ESUB@fda.hhs.gov