Implications of eCTD errors

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Overview

- Common Errors we encounter
- Consequences of errors
- How to avoid errors

Consequences

- Our reviewers want to focus on the review – not submission problems
- Review Delays – Processing delays, time spent on unnecessary communication between the FDA and sponsors
- Rejection – Time sensitive submissions can be adversely affected
- RTF – can result from poorly formatted submissions

Rejection Notices

- Faxed to the sponsor
- A copy is sent to your Gateway inbox
- Email

From: CDER Electronic Document Room Staff

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Rd.
Beltsville, MD 20705
Mail/courier contact: (301) 827-4210

Contact Name:	Jim Zorn		Company Name:	Pharma Company			
Phone:	999-909-9999		Fax:	999-909-9998			
Application:	NDA 012345	Letter Date:	29-10-2008	Sequence:	N/A	Sent By:	GA

Problem with Electronic Submission sent to CDER

While processing your electronic submission, we encountered the issues stated below. Please review the issues below and take the appropriate corrective action.

☒ **RESUBMISSION REQUIRED**

This submission was received at CDER and is being rejected for the following reasons:

Letter Date: 29-Oct-2008
Application Number: NDA 012345
Sequence Number: N/A

Files can not be read from media. No data was found. Please re-submit a proper media with all required folders and files.

☐ **NO RESUBMISSION REQUIRED**

If you have any questions regarding this fax or electronic submissions in general, please email esub@cder.fda.gov or call Russell Livermore at (301) 796-0605.

For information about submitting electronic submissions to CDER, please review our public website: http://www.fda.gov/cder/regulatory/ersr/default.htm

Duplicate Submissions

- Often these occur when folks submit over the Gateway
- A duplicate sequence is determined by the sequence number in the us-regional.xml
- First sequence accepted
- Subsequent sequences are rejected

Duplicate Submission contd.

- Time To get an Gateway Acknowledgment
  - Small submissions 1 hour
  - Large Submission up to 4 hours
- In order to see the acknowledgement your must refresh your screen

PDF Document Legibility

- Legibility can be a problem with scanned documents
- Whenever possible be sure to send in searchable PDF's
- It can be frustrating to reviewers when they have to work hard just to read a document
- Reviewers often ask that documents be sent in again if the documents are unreadable

Table of Content Issues

- All documents require a table of contents
- They should be accurate and up to date
- Reviewers at times have asked that documents without table of contents be re-sent with a TOC included
- This delays the review process and can frustrate reviewers

Missing Files

- The severity of a missing file depends on which file is missing
- Some files are not as critical or particularly time sensitive
- Certain files are absolutely necessary for a review to move forward e.g. Study Report, Protocol, Methods Validation, etc..
- Verify your content before sending it to us

Truncated File Name

- Study-1234.pdf becomes Stu~4.pdf
- We have seen these coming in on cd-rom media
- The path designated in the index.xml is no longer valid
- The file is unavailable to reviewers
- Verify your content before sending in your submission

Hyperlinking Issues

- Severe Hyperlinking problems can result in a RTF
- Less problematic issues can result in a delay of the review and reviewer frustration
- Test and validate your hyperlinks
- Be sure to add hyperlinks between Module 2 and Module 5

One submission applied to more than One Application

- This situation occurs when the cover letter says to apply the submission to additional applications
- One submission can only be applied to one application
- An eCTD is self contained
- The application number listed in us-regional.xml is where the submission content will reside
- You can cross reference using the xml method or the cover letter method

Sent to Wrong Center

- This error often occurs in conjunction with the use of the ESG
- In the Gateway web application there is a drop down box to choose the Center
- CBER and CDER look similar – choose carefully
- All submissions sent to the wrong Center will be rejected

No us-regional.xml file

- The us-regional.xml file is an essential file for processing your submission
- Without this present it is impossible to process your submission

Single PDF Submission

- A key feature of the eCTD is its granularity
- Granularity aids in the review of the application
- Our ASR software cannot process a single PDF document

Empty Folder or Files can not be read from media

- Empty folders likely result from selecting an incorrect folder when utilizing the gateway
- Other times errors can occur when writing to a CD
- Always check the media before you send it to us
- Submissions with empty folders or unreadable media will be rejected

More than One Sequence through the Gateway

- Currently our software cannot process more than one sequence
- The software identifies the submission as having more than one 356h
- Submissions sent via the Gateway with more than one sequence will be rejected

Incomplete or missing application number in the us-regional.xml

- This error can occur from incomplete editing of the us-regional.xml file
- One of the most important steps you can do is to check the us-regional.xml file before sending in your submission
- A submission with an incomplete or missing application number is rejected

Mismatch in US-regional.xml between application type and form - an NDA with a 1571.PDF

- The application type is specified in the us-regional.xml
- When it does not match the form sent in the submission is rejected
- If the problem is not caught immediately then the processing of the submission is delayed

Non-Fillable Form

- Fillable forms allow the FDA to process your submission automatically
- Non-fillable forms require manual intervention delaying the processing of your submission

- http://www.fda.gov/opacom/morechoices/fdaforms/cder.html

No 356h, 1571, 2252, 2253

- While these forms are not required by regulation they are extremely useful to the FDA
- Process Manually

Spaces and characters not permitted by ESG specs in folder names

- Spaces and other characters not permitted by the ESG
- When an illegal character or space is found the submission is kicked out of automatic processing
- The submission is put in a queue to be processed manually
- The manual processing causes delays in getting the information to the reviewer

Mixed eCTD/esub (e.g., SPL folder or Word files submitted outside the sequence folder)

- Sometimes sponsors submit documents outside the eCTD
- Perhaps thinking that Word documents do not belong inside the eCTD
- All documents submitted outside the eCTD are rejected
- The documents submitted within the eCTD are accepted

Non-Standard eCTD or eCTD cannot be read

- We have received customized style sheets
- We have received us-regional.xml files created in MS Excel
- These types of eCTDs cannot be processed and will be rejected
- Follow the guidances

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
- FDA Forms Distribution Page for Center for Drug Evaluation and Research (CDER)http://www.fda.gov/opacom/morechoices/fdaforms/cder.html
- eCTD validation: http://www.fda.gov/cder/Regulatory/ersr/validation_specs.htm