eCTD: More than a Document

Heather Crandall
Division of Data Management Services and Solutions
Office of Business Informatics
CDER | US FDA

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Learning Objectives

- Understand where to find new information for eCTD submissions
- List the most common errors made when submitting in eCTD format
- Know resources available for common questions asked about eCTD submissions

What's New?

- Submission Standards location
  - New webpage as of December 2022
- Addition of Structure-Data Files information
  - Section 3.3.3 of the Technical Conformance Guide (updated November 2022)

What's New?

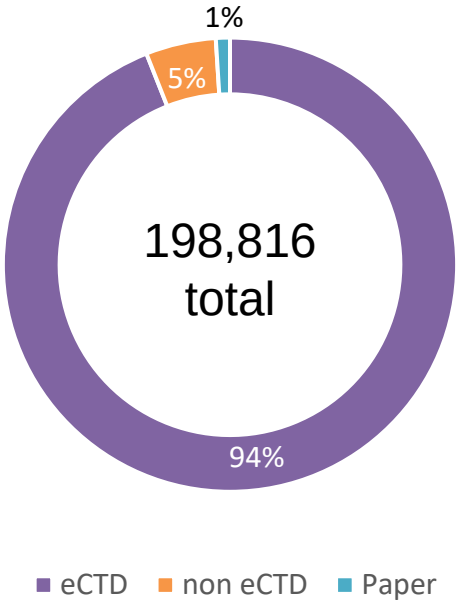
- New 1738 error
  - Study ID should match between STF and ts.xpt files
  - Medium level
- 1737 check every m4 and m5 section where an STF is required
  - Does not include 4.3, 5.2, 5.4, and 5.3.6

Number:	1738
Group:	General
Description:	STF Study ID should match STUDYID or SPREFID listed in the referenced Trial Summary (ts.xpt) file
Severity Description:	Medium
US DTD Version	3.3
Effective Date:	3/16/2023
Problem:	The STF Study ID does not match the STUDYID or SPREFID listed in the referenced ts.xpt file (not an exact match).
Corrective Action:	Ensure ts.xpt is referenced under the correct STF. If ts.xpt is under the correct STF, update the STUDYID or SPREFID in the ts.xpt and other referenced study data files. Modify your SOPs to ensure that a consistent Study ID (exact match) is used.
Guidance Source:	The eCTD Backbone File Specification for Study Tagging Files; Providing Regulatory Submissions in Electronic Format – Standardized Study Data; Study Data Technical Conformance Guide; General good practice to ensure reviewability.

eCTD Submission Metrics

CDER Submissions October 1, 2022 through April 30, 2023

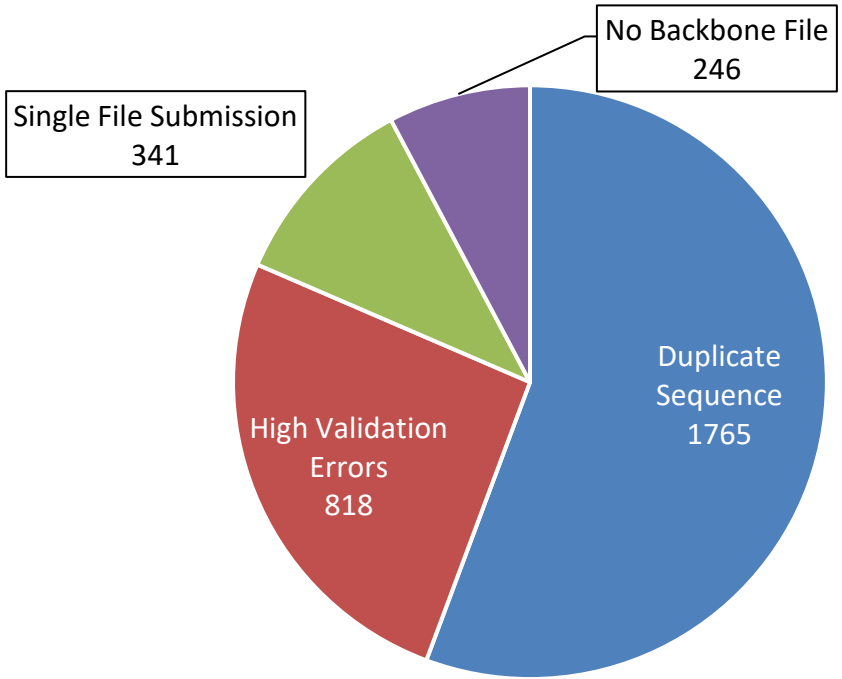
Percent of Submissions by Electronic Format



eCTD	94%
non eCTD	5%
PAPER	1%

Top Reasons for eCTD Rejection

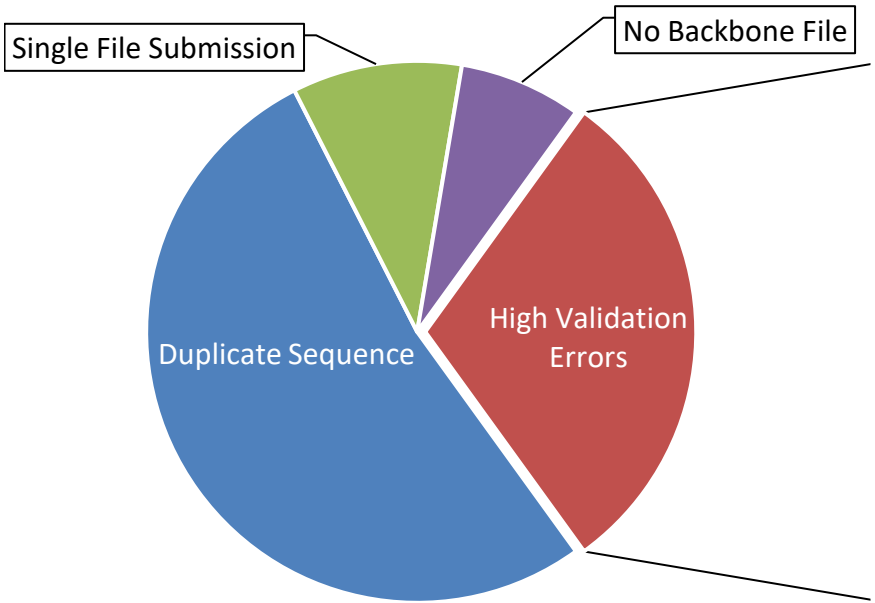
Approximately 1% of eCTD submissions are rejected



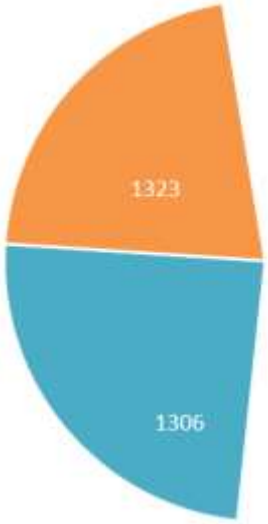
October 1, 2022 through April 30, 2023

Top 10 High Errors

eCTD Submission Errors October 1, 2022 through April 30, 2023



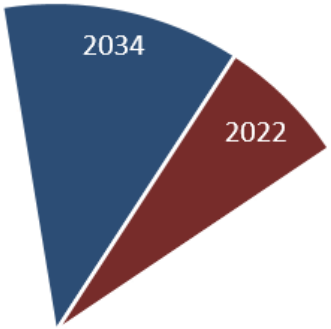
Leaf Element Errors



46% of High Errors are:

- Code 1306 – No leaf element for file
- Code 1323 – No file for leaf element

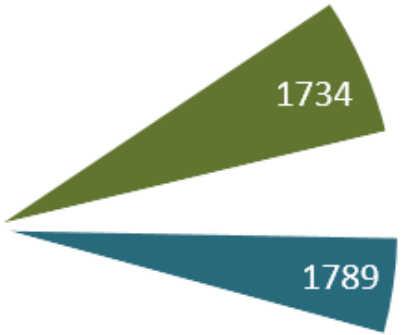
Submission Type Errors



18% of High Errors are:

- Code 2034 – Submission Type invalid for Application Type
- Code 2022 – Submission Sub-Type is invalid for Submission Type

Study Data Errors



10% of High Errors are:

- Code 1734 – A dataset named ts.xpt with information on study start date must be present for each study in Module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4, and in Module 5, sections 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2

- Code 1789 – A file has been submitted in a study section without providing an STF file. STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports

Challenge Question #1

Most eCTD submission failures are due to:

A. Duplicate sequence number

B. eCTD validation error

C. Missing backbone file

D. A single file submission

Challenge Question #2

The majority of High Validation Errors are due to:

A. Missing ts.xpt file

B. Invalid submission type or sub-type

C. Leaf elements and files missing each other

D. Data not referenced in an STF

eCTD Common Questions

- Where do I place content?
- How do I cross-reference to another application?
- What file formats are recommended?
- Do I need a digital signature on my 1571/356h?
- What file-tag should I use?

eCTD Common Questions

Where do I place content?

Resources:

- ✓ The Comprehensive Table of Contents Headings and Hierarchy
- ✓ M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use Guidance fo Industry
- ✓ FDA Regulatory Project Manager
- ✓ esub@fda.hhs.gov

The Comprehensive Table of Contents Headings and Hierarchy

Module 1 Administrative information

- ***1.1 Forms***
  - Form [form-type]
- ***1.2 Cover letters***
- ***1.3 Administrative information***
  - 1.3.1 Contact/sponsor/applicant information
    - **1.3.1.1 Change of address or corporate name**
    - **1.3.1.2 Change in contact/agent**
    - **1.3.1.3 Change in sponsor**
    - **1.3.1.4 Transfer of obligation**
    - **1.3.1.5 Change in ownership of an application or reissuance of licens**
  - 1.3.2 Field copy certification
  - 1.3.3 Debarment certification
  - 1.3.4 Financial certification and disclosure
  - 1.3.5 Patent and exclusivity
    - **1.3.5.1 Patent information**
    - **1.3.5.2 Patent certification**
    - **1.3.5.3 Exclusivity claim**
  - 1.3.6 Tropical disease priority review voucher
- ***1.4 References***
  - 1.4.1 Letter of authorization
  - 1.4.2 Statement of right of reference
  - 1.4.3 List of authorized persons to incorporate by reference

eCTD Common Questions

How do I cross-reference to another eCTD application?

Resources:

- ✓ [eCTD Backbone Files Specification for Module 1]
- ✓ [esub@fda.hhs.gov]

b. Cross-reference-application-number element

This element should only be provided when an application makes reference to other applications. Cross references are unnecessary when the application(s) being referenced are in the ***application-set***.[2] A cross reference only needs to be identified once.

Provide the six (6)-digit application number in the ***cross-reference-application-number*** element. Only provide numeric digits, including any leading zeros for the application number, without letters or dashes.

Each ***cross-reference-application-number*** element requires an attribute of ***application-type*** and the attribute should be provided as a coded value from its corresponding attribute list (*application-type.xml*). The current valid codes for ***application-type*** are available in the eCTD Submission Standards on the FDA website: https://www.fda.gov/ectd.

The following is an example of a ***cross-reference-application-number*** element. In this example, the application NDA 456789 cross-references DMF 012345. The ***cross-reference-application-number*** element contains the attribute value of "fdaat5" for the ***application-type***, which indicates it is a Drug Master File (DMF).

```
…
<application-number application-type="fdaat1">456789</application-number>
<cross-reference-application-number application-type="fdaat5">012345</cross-reference-application-number>
…
```

eCTD Common Questions

What file formats are expected?

Resources:

- ✓ Specifications for File Format Types
- ✓ FDA Regulatory Project Manager
- ✓ esub@fda.hhs.gov

Specifications for File Format Types Using eCTD Specifications

File Type	File Format	Format Name	Accepted location in eCTD	Archive Format Copy	Permissible Uses
Documents					
	.pdf	Portable Document Format	M1 – M5		
	.doc	Microsoft Word document	M1.14, 1.16		
			M2.3, M2.7	PDF	ANDA
	.docx	Microsoft Word Open XML document	M1.14, 1.16		
			M2.3, M2.7	PDF	ANDA
	.txt	Text file	M3 - M5		
	.xls	Microsoft Excel document	M3 – M5	PDF	
	.xlsx	Microsoft Excel Open XML document	M3 – M5	PDF	
Images					
	.bmp	Bitmap	M1.15		

eCTD Common Questions

Do I need a digital signature on my 1571/356h?

Resources:

- ✓ Important Information About Digital/Electronic Signatures | FDA
- ✓ esub@fda.hhs.gov

Important Information About Digital/Electronic Signatures

FDA does not require submission of a paper copy for electronic submissions submitted using the FDA ESG.

FDA forms (e.g., 1571, 356h) and documents require a signature. Accepted signature methods by FDA are:

- Scanned signatures
- Digital signatures
- Flattened digital signatures. A flattened digital signature must include (*see example*):
  - the printed name of the signer
  - the date and time when the signature was executed
  - the reason for signature

eCTD Common Questions

What file-tag should I use?

Resources:

- ✓ The eCTD Backbone File Specification for Study Tagging Files
- ✓ Study Data Technical Conformance Guide_v5.0
- ✓ Valid values.xml file
- ✓ esub@fda.hhs.gov

Challenge Question #3

Where can I find recommended file formats?

A. Comprehensive Table of Contents of Headings and Hierarchies

B. Specifications for File Format Types Using eCTD Specifications

C. eCTD Technical Conformance Guide

D. The eCTD Backbone Files Specification for Module 1

Summary

- Check FDA's eCTD webpage, www.fda.gov/ectd for announcements, updates, and the Specifications
- Most common eCTD submission mistake is using a duplicate sequence number

Resources

- Web page for latest version of eCTD guidance, specifications, and validations
- eCTD Comprehensive Table of Contents Headings and Hierarchy
- M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use Guidance for Industry
- eCTD Technical Conformance Guide
- Interdisciplinary Review Team for Cardiac Safety Studies (formerly QT-IRT)
- The eCTD Backbone Files Specification for Module 1
- Specifications for File Format Types
- FDA's eCTD v4 implementation page

U.S. FOOD & DRUG ADMINISTRATION

Questions?

Heather Crandall
Division of Data Management Services and Solutions
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CDER | US FDA

Have questions after the conference? Please send to esub@fda.hhs.gov


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