U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Study Data Rejections in eCTD Submissions

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Agenda

- What's New in eCTD v3.2.2?
- Common Errors
- Common Questions
- eCTD v4.0

What's New in eCTD v3.2.2?

What's New in eCTD v3.2.2?

- File format spec
  - Updated .docx permissible uses
  - Updated .xml accepted locations and permissible uses
  - Removed "CDER Only" from permissible uses for
    - .cas, .csv, .dat, .r, .rmd
  - Updated file format added
    - Modeling & Simulation file types
      - .datxplore, .jmd, .json, .mbp3, .mlxtran, .mlxproperties, .pkml, .pksim5, .pkx, .pkxproperties, .pumascp, .smlx, .smlxproperties, .syc, .qmd

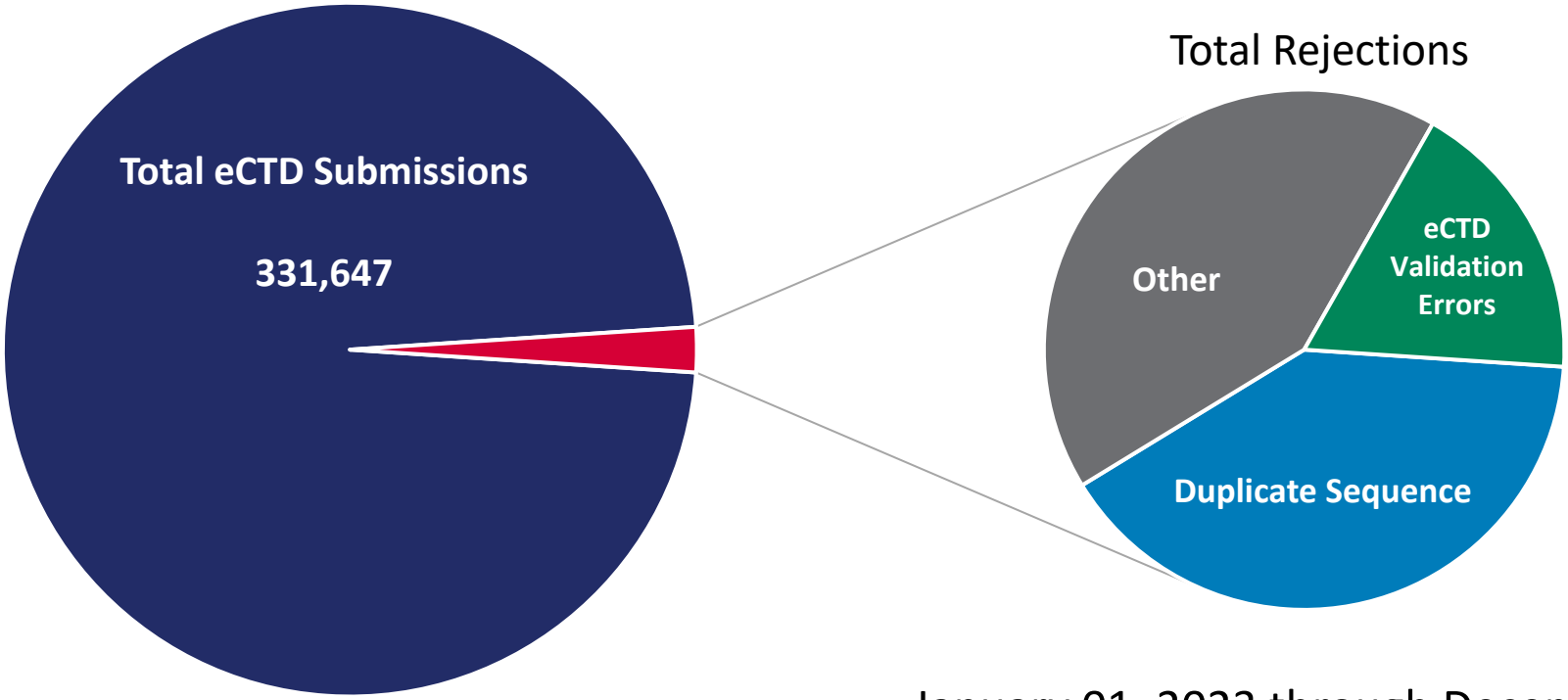
Specifications for File Format Types Using eCTD Specifications

File Type	File Format	Format Name	Accepted location in eCTD	Archive Format Copy	Permissible Uses
	.xml	Extensible Markup Language	M1.14, 1.16, M4 - M5		Labeling, REMS, Data
	.xsd	XML Schema Definition	M1, M4 - M5		
	.xsl	Extensible Stylesheet Language	M1, M4 - M5		\util\style folder, data
Data					
	.csv	Comma Separated Values file	M5.3.3.5		
	.svg	Scalable Vector Graphics	M3 – M5	TXT	
	.xpt	SAS Transport file	M3 – M5		
	.zip	Zip file	M5.3		For grouping large sets of aECG xml files CDER Only
Modeling and Simulation					
	.cmp, .cmpx, .cmpz	SimCYP drug model files	M5		CDER Only
	.wks, .wksx, .wksz	SimCYP workspace files	M5		CDER Only
	.lbr , .lbrx, .lbrz	SimCYP population files	M5		CDER Only
	.mdb	GastroPlus model compound file	M5		CDER Only
	.pbk	GastroPlus whole body physiology files	M5		CDER Only
	.opd	GastroPlus Tissue and/or plasma concentration vs time data file for other	M5		CDER Only

Common Errors for eCTD submissions

Total eCTD Submissions to CDER

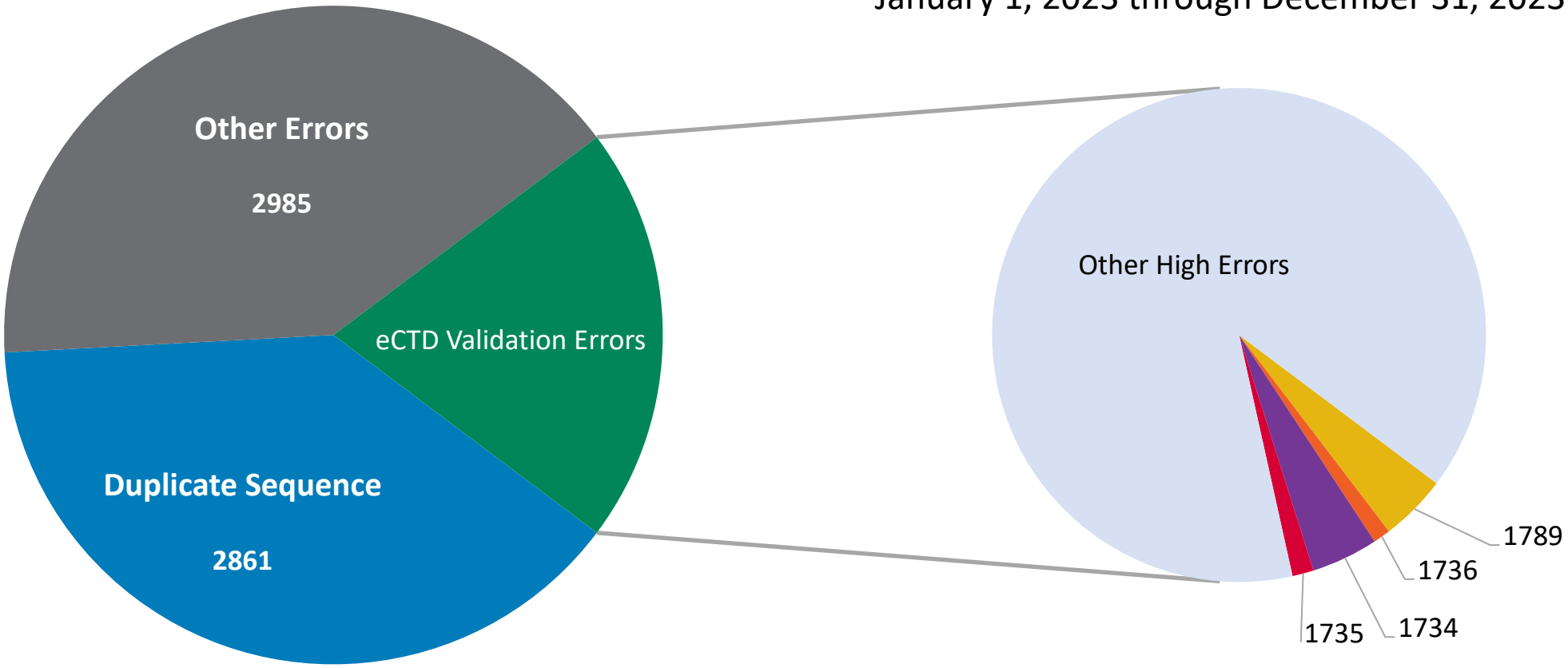
Roughly only 1% of eCTD submissions are rejected



January 01, 2023 through December 31, 2023

Top Reasons for eCTD Rejection

January 1, 2023 through December 31, 2023

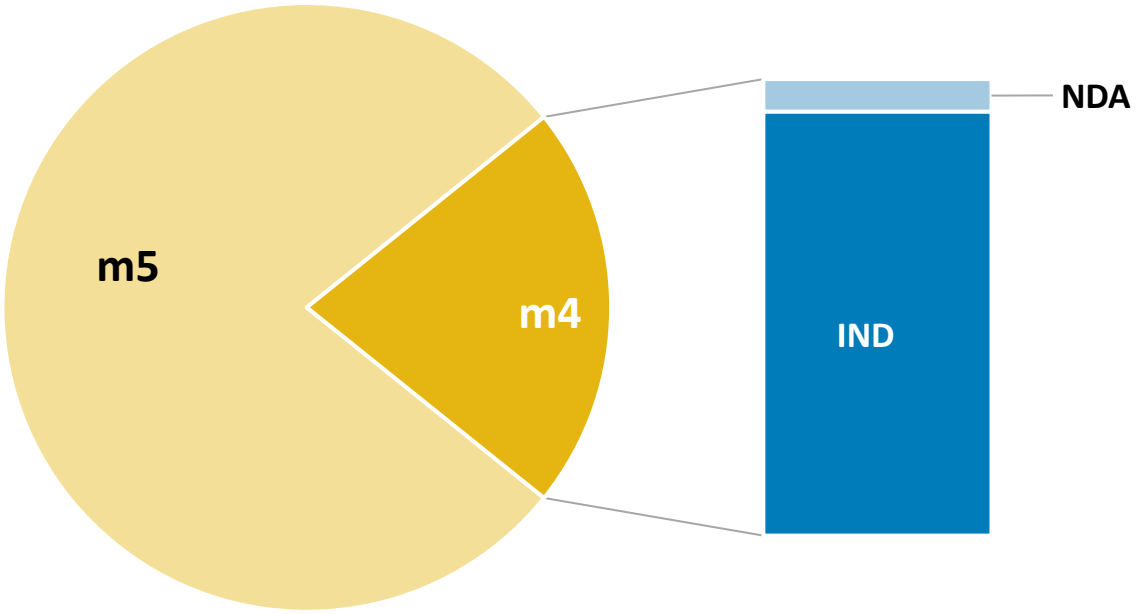


1789 Error

A file has been submitted in a study section without providing an STF file

- 65 Submissions failed for error 1789
  - 22% of these submissions were for SEND data (m4)
  - Majority of errors in IND nonclinical sections (m4)

1789 Errors by Module

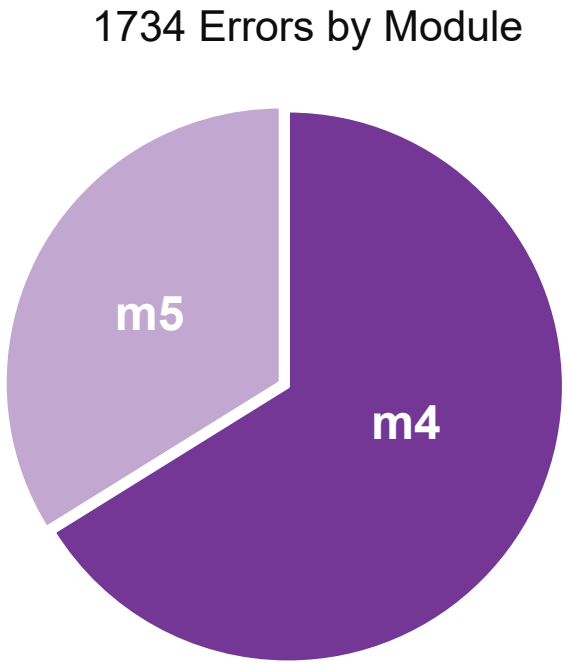


January 1, 2023 through December 31, 2023

1734 Error

A dataset named ts.xpt with information on study start date must be present for each study in a TRC-applicable section

- 65 Submissions failed for error 1734
  - 66% of these submissions were for SEND data (m4)
  - Only IND applications had errors in nonclinical sections (m4)

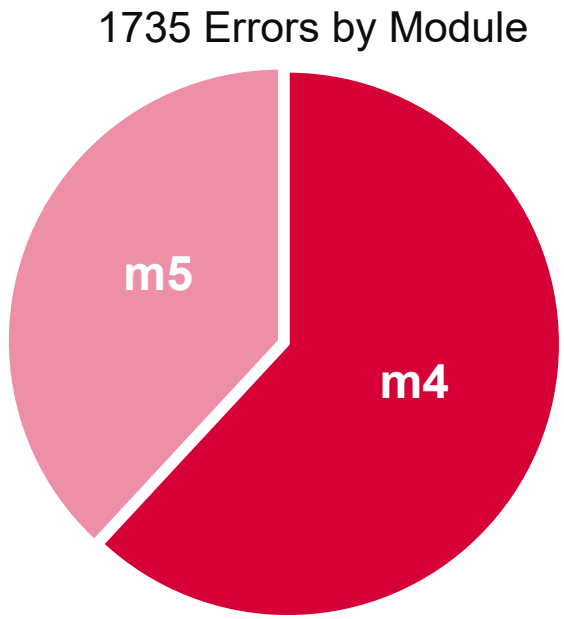


January 1, 2023 through December 31, 2023

1735 Error

The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in a TRC-applicable section

- 21 Submissions failed for error 1735
  - 62% of these submissions were for SEND data (m4)
  - Only IND applications had errors in nonclinical sections (m4)

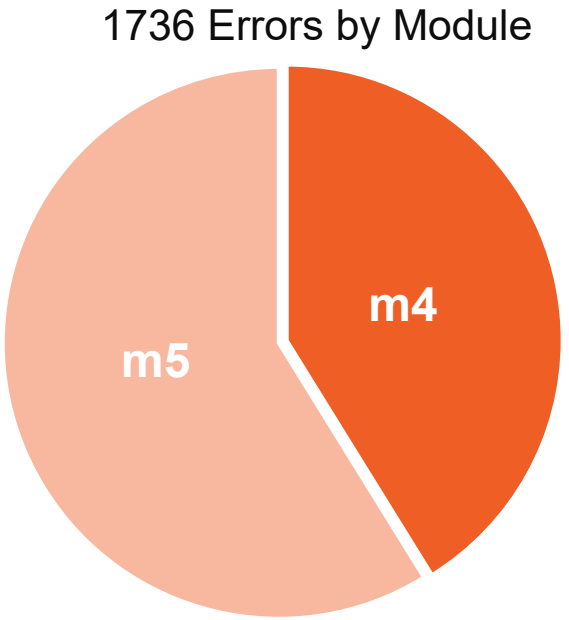


January 1, 2023 through December 31, 2023

1736 Error

For SEND data, a Demographic (DM) dataset and define.xml must be submitted for studies in TRC-applicable Module 4 sections

- 17 Submissions failed for error 1736
  - 41% of these submissions were for SEND data (m4)
  - Only IND applications had errors in nonclinical sections (m4)

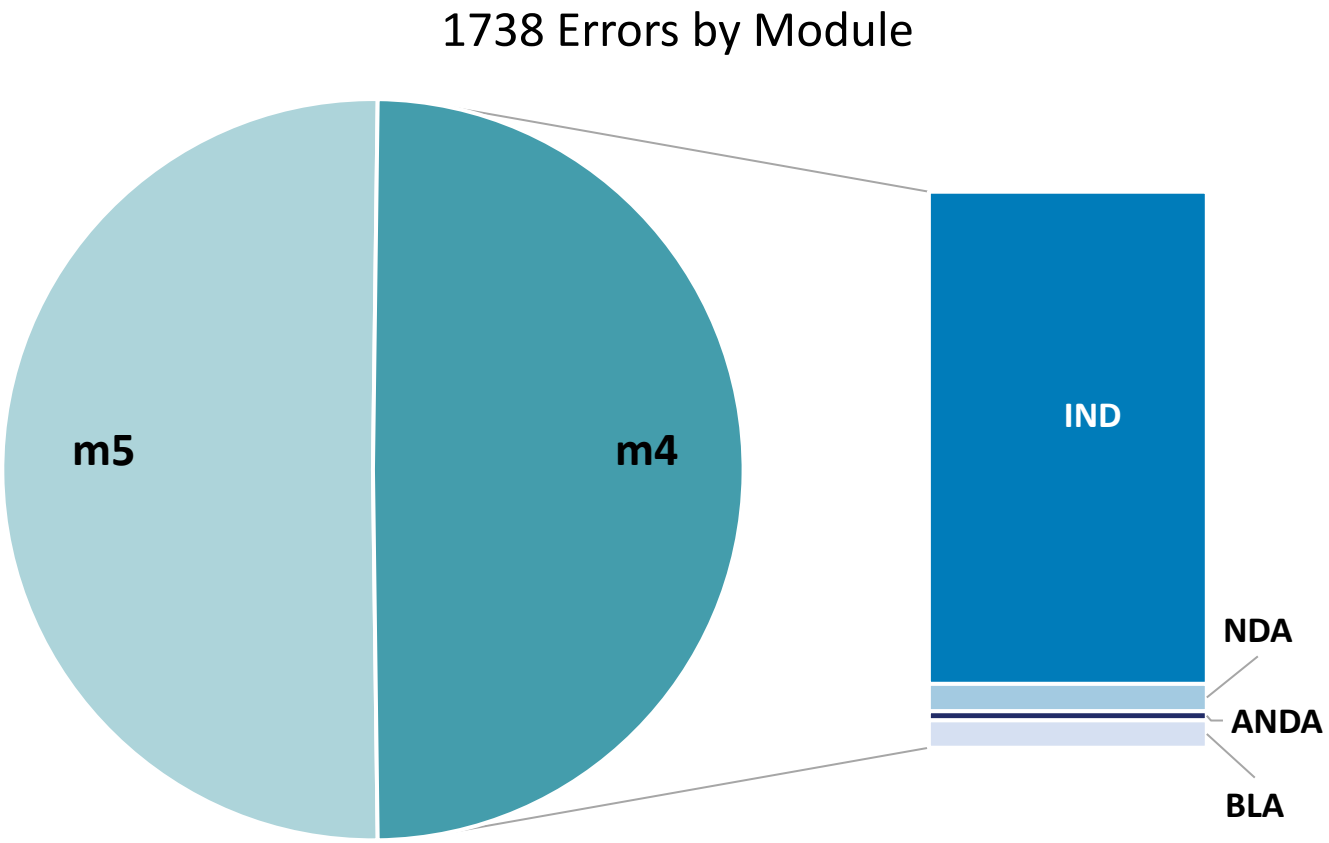


January 1, 2023 through December 31, 2023

1738 Error

STF Study ID should match STUDYID or SPREFID listed in the referenced Trial Summary (ts.xpt) file

- 123 Submissions received a 1738 error
  - 61 of these submissions were for nonclinical data (m4)
  - Majority of errors in IND nonclinical sections (m4)
- Top m4 sub-sections:
  - 4.2.1.3 Safety pharmacology
  - 4.2.3.1 Single dose toxicity
  - 4.2.3.2 Repeat dose toxicity

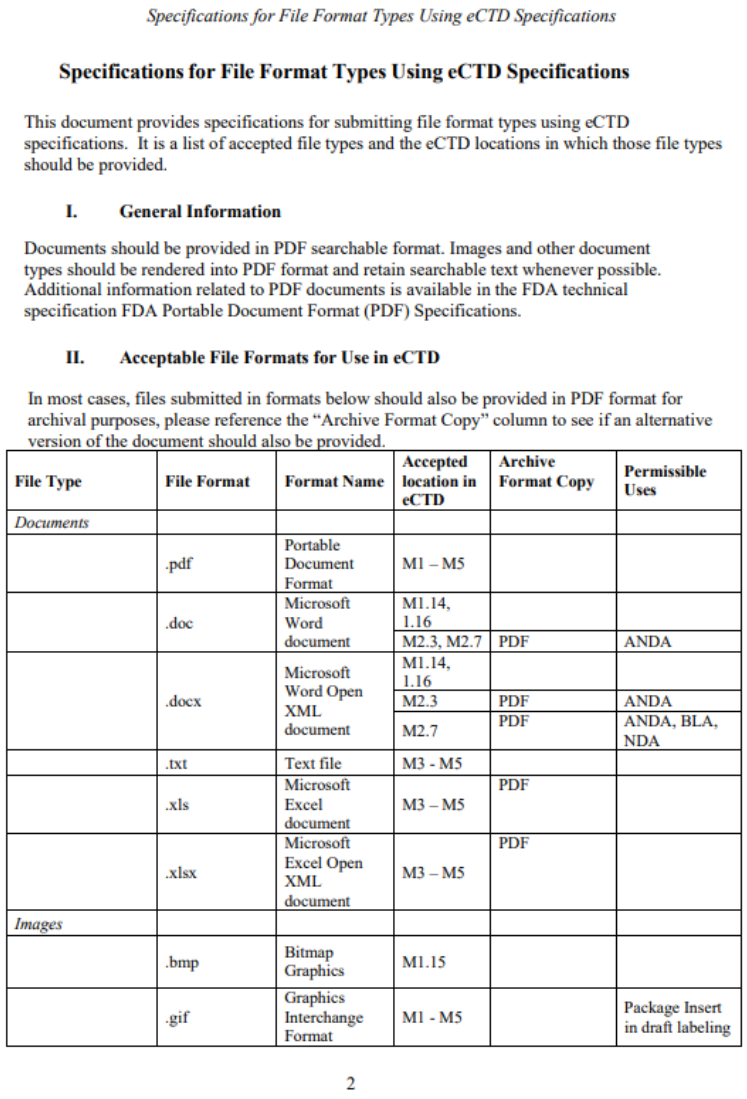


Common Questions for eSub

What file types can I submit?

Resources:

- ✓Specifications for File Format Types Using eCTD Specifications
- ✓eCTD Technical Conformance Guide
- ✓FDA Regulatory Project Manager
- ✓esub@fda.hhs.gov



Specifications for File Format Types Using eCTD Specifications

Specifications for File Format Types Using eCTD Specifications

This document provides specifications for submitting file format types using eCTD specifications. It is a list of accepted file types and the eCTD locations in which those file types should be provided.

I. General Information

Documents should be provided in PDF searchable format. Images and other document types should be rendered into PDF format and retain searchable text whenever possible. Additional information related to PDF documents is available in the FDA technical specification FDA Portable Document Format (PDF) Specifications.

II. Acceptable File Formats for Use in eCTD

In most cases, files submitted in formats below should also be provided in PDF format for archival purposes, please reference the "Archive Format Copy" column to see if an alternative version of the document should also be provided.

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	PDF	ANDA
			M2.7	PDF	ANDA, BLA, NDA
	.txt	Text file	M3 - M5		
	.xls	Microsoft Excel document	M3 – M5	PDF	
	.xlsx	Microsoft Excel Open XML document	M3 – M5	PDF	
Images					
	.bmp	Bitmap Graphics	M1.15		
	.gif	Graphics Interchange Format	M1 - M5		Package Insert in draft labeling

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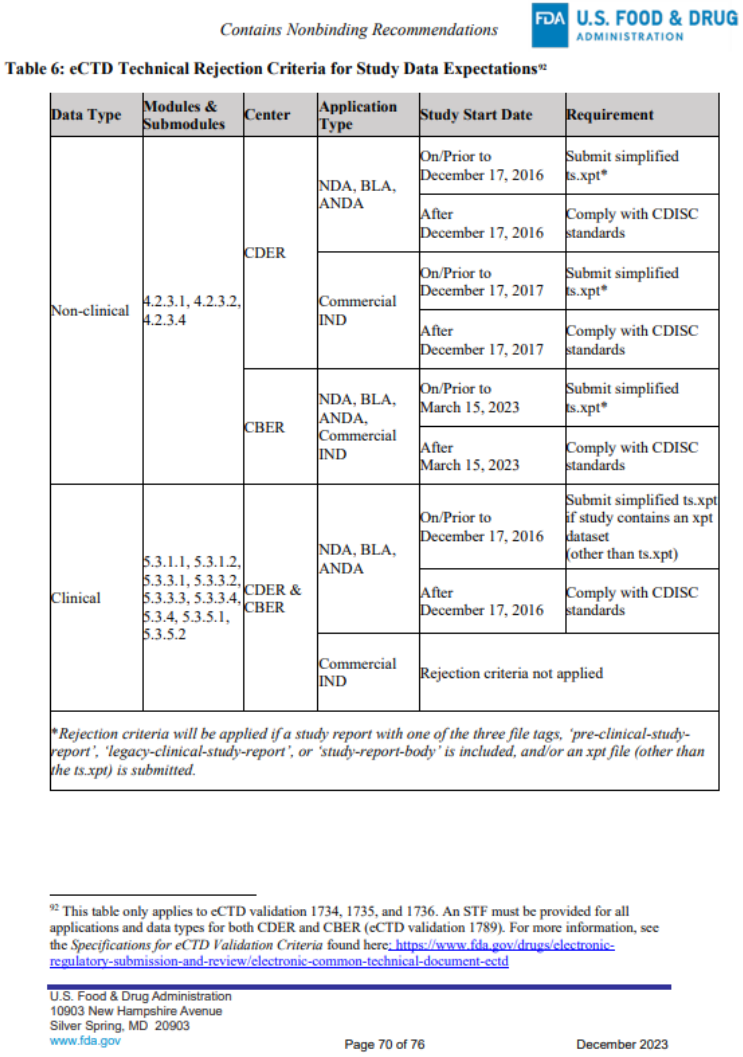
I received a 1734 error. How can I make sure I pass validation?

Resources:

- ✓Study Data Technical Conformance Guide
- ✓Technical Rejection Criteria Self-Check Worksheet
- ✓eCTD Technical Conformance Guide
- ✓esub@fda.hhs.gov



Contains Nonbinding Recommendations

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Table 6: eCTD Technical Rejection Criteria for Study Data Expectations[92]

Data Type	Modules & Submodules	Center	Application Type	Study Start Date	Requirement
Non-clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	CDER	NDA, BLA, ANDA	On/Prior to December 17, 2016	Submit simplified ts.xpt*
				After December 17, 2016	Comply with CDISC standards
			Commercial IND	On/Prior to December 17, 2017	Submit simplified ts.xpt*
				After December 17, 2017	Comply with CDISC standards
		CBER	NDA, BLA, ANDA, Commercial IND	On/Prior to March 15, 2023	Submit simplified ts.xpt*
				After March 15, 2023	Comply with CDISC standards
Clinical	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	CDER & CBER	NDA, BLA, ANDA	On/Prior to December 17, 2016	Submit simplified ts.xpt if study contains an xpt dataset (other than ts.xpt)
				After December 17, 2016	Comply with CDISC standards
			Commercial IND	Rejection criteria not applied	

**Rejection criteria will be applied if a study report with one of the three file tags, 'pre-clinical-study-report', 'legacy-clinical-study-report', or 'study-report-body' is included, and/or an xpt file (other than the ts.xpt) is submitted.*

[92] This table only applies to eCTD validation 1734, 1735, and 1736. An STF must be provided for all applications and data types for both CDER and CBER (eCTD validation 1789). For more information, see the *Specifications for eCTD Validation Criteria* found here: https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd

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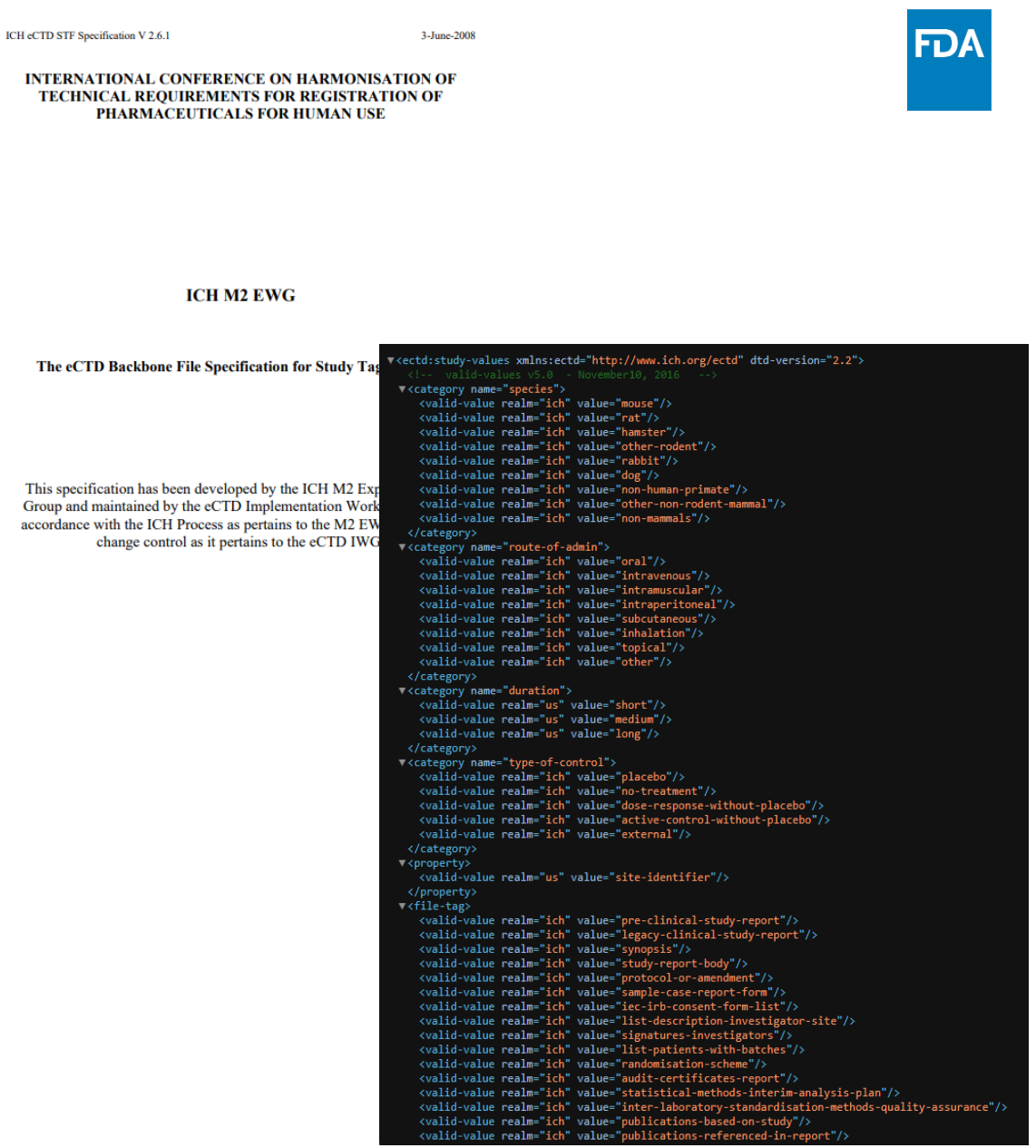
What file-tag should I use?

Resources:

- ✓Valid-Values.xml
- ✓The eCTD Backbone File Specification for Study Tagging Files
- ✓Study Data Technical Conformance Guide
- ✓eCTD Technical Conformance Guide
- ✓esub@fda.hhs.gov



eCTD v4.0

FDA Implementation Strategy

- Initial release/acceptance for new applications in eCTD v4.0
  - Begin accepting new applications in eCTD v4.0 this Summer
    - When FDA is ready to accept, the agency will update the FDA Data Standards Catalog to reflect the date support begins
  - Provide feedback on sample eCTD v4 submissions
    - Exists today for eCTD v3.2.2
    - Plans to expand to include v4.0 when FDA begins accepting voluntary eCTD v4.0 submissions
- Future phases
  - Transition of current v3.2.2 applications (Forward Compatibility)
  - Two-way communication

Region	Technical Pilot[1]	Implementation Dates[2]	Implementation Documents
FDA, United States	2022 - 2Q 2023 (Completed)	2024 (Voluntary) 2029 (Mandatory)	FDA, United States regional implementation page

This information will be updated biannually based on the progress of ongoing implementation activities.

[Updated in January 2024]

v3.2.2 versus v4.0 validation

Specifications for eCTD Validation Criteria

Number:	1734
Group:	General
Description:	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
Severity Description:	High

Number:	1735
Group:	STF
Description:	The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files 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
Severity Description:	High

Specifications for eCTD v4.0 Validation Criteria

Number:	US-eCTD4-516
Group:	Study Data
Category:	Business Rule
Validation Criteria/Description:	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
Severity Description:	High Error

Number:	US-eCTD4-517
Group:	Study Data
Category:	Business Rule
Validation Criteria/Description:	The correct document type must be used for all standardized datasets and corresponding define.xml files 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
Severity Description:	High Error

Resources

- eCTD v3.2.2
  - Web page for latest version of eCTD guidance, specifications, and validations
  - eCTD Submission Standards for eCTD v3.2.2 and Regional M1
  - eCTD Sample Submissions

- Study Data Standards
  - Study Data Standards Resources

- eCTD 4
  - FDA's eCTD v4 implementation page