FDA Disclaimer

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Update on eCTD Submissions

Heather Crandall
Operations Research Analyst
CDER/OSP/OBI

February 4, 2025

Agenda

- What's New?

- Common Errors for eCTD submissions

What's New?

What's New?

eCTD Submission Standards for eCTD v3.2.2 and Regional M1

- 03/20/2024 – Updates to File Format Specification
    - **Removed recommendation to include PDF archive format copy** when submitting .doc/.docx, .xls/.xlsx
    - Updated file format added:
        - Modeling & Simulation file types: .pumascp, .jmd, .qmd

- 09/09/2024 – Updates to
    - Version of Lorenz tool
    - eCTD Technical Conformance Guide
        - As of April 1, 2024, FDA published final guidance "Providing Regulatory Submissions in Electronic Format: IND Safety Reports Guidance for Industry", which provides a new method to submit these reports
    - Comprehensive Table of Contents Headings and Hierarchy
        - adding Valid-Values.xml v6.0 (support date TBD)

Module 5 Clinical Study Reports

5.2 Tabular listing of all clinical studies
5.3 Clinical study reports and related information

...

Pharmacogenomics
Pharmacokinetics
Quality of life
Hepatic Impairment Study (TBD)
Renal Impairment Study (TBD)
Drug-drug Interaction Study (TBD)
Mass Balance Study (TBD)
Population PK Report (TBD)

What's New?

Submit a Standardized Data Sample to FDA

Formerly "Submit **an eCTD** or Standardized Data Sample to FDA"

- FDA now encourages all eCTD samples to be in v4.0 format

- Standardized data samples can be submitted for sample evaluation and feedback utilizing **either** v3.2.2 or v4.0 format

---

4. Send a Sample Submission to FDA ⌃

Submitting a sample eCTD or standardized data sample is optional and can provide valuable feedback. This is separate from the test submissions made as part of the ESG account signup process.

Please refer to the following pages:

- Submitting standardized study data
- Submitting eCTD v4.0 (may include standardized study data sample)

Tip: Submit the sample early to allow time to make adjustments prior to final submission.
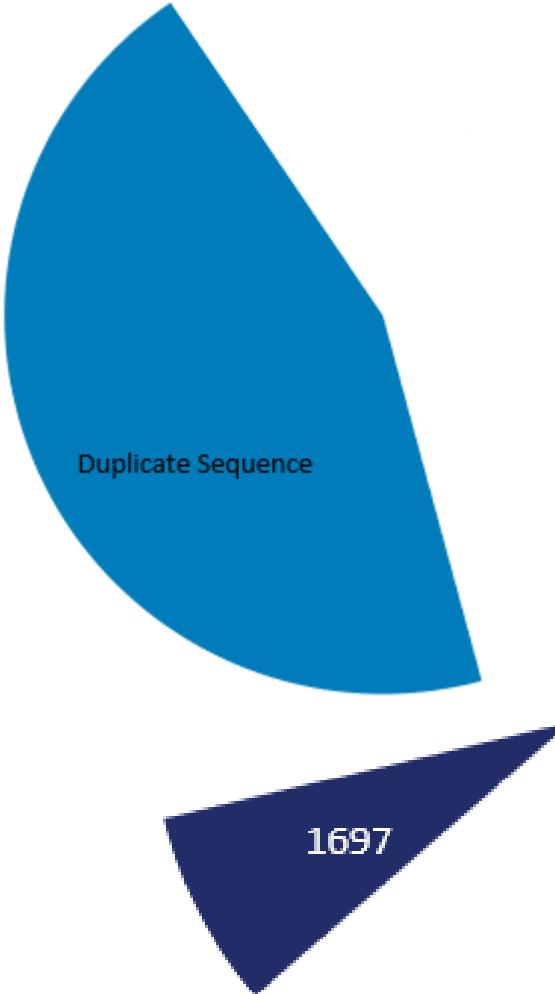
Common Errors for eCTD submissions

Top Reasons for eCTD Rejection
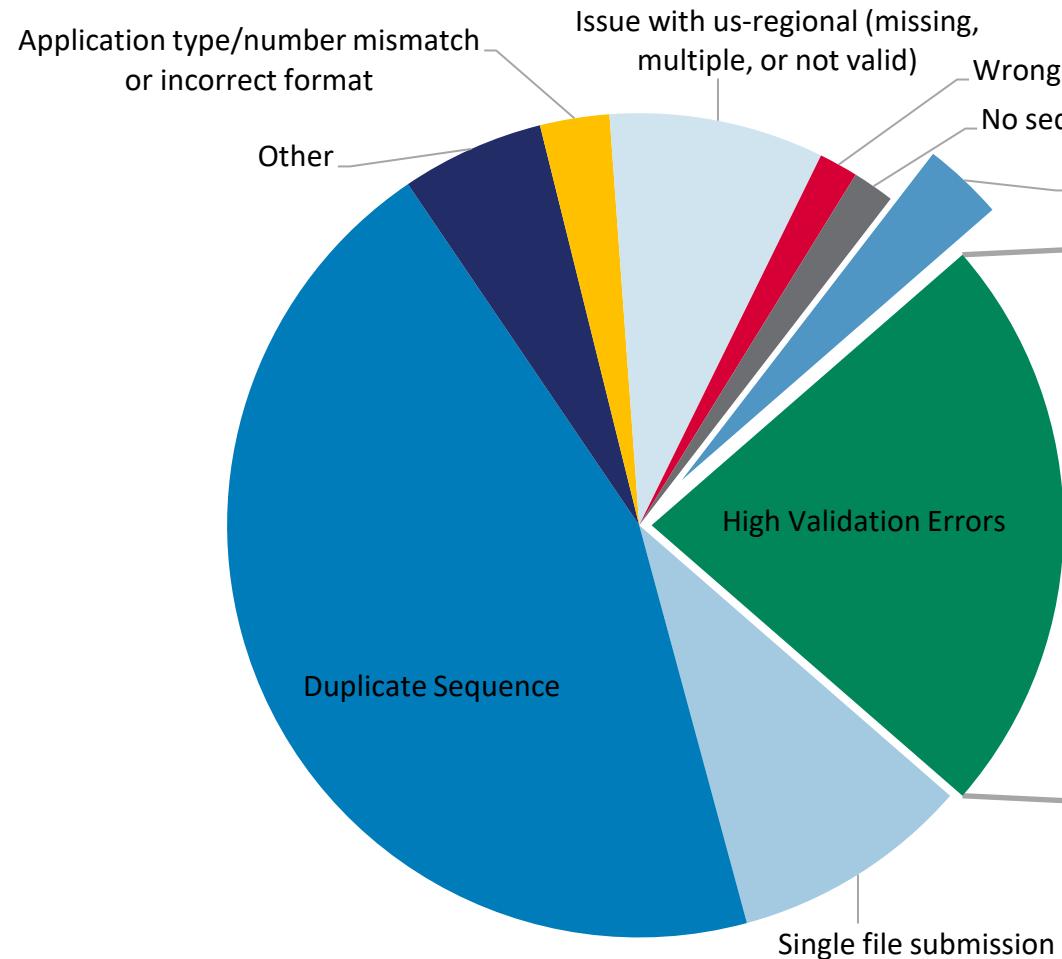
**January 1, 2023 through December 31, 2023**
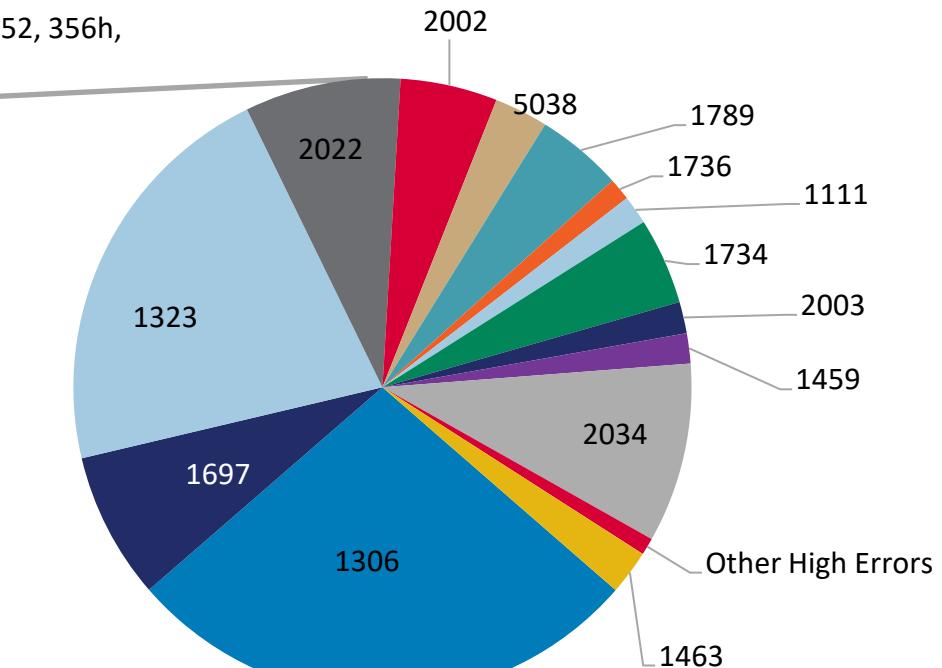
Duplicate Sequence Numbers

- From January 1 through August 1, 2023, **2973 applications were rejected** for duplicate sequence numbers
  - All sequence numbers, including sequence numbers for child applications in a grouped submission must be unique

- Sequence numbers for a given application **must** be unique
  - The sequence-number element is used to uniquely identify each individual submission to an application. It must be a unique number with a maximum of four (4)-numeric digits – The eCTD Backbone Files Specification for Module 1

Duplicate Sequence

1697

Leaf element errors

1323

1306
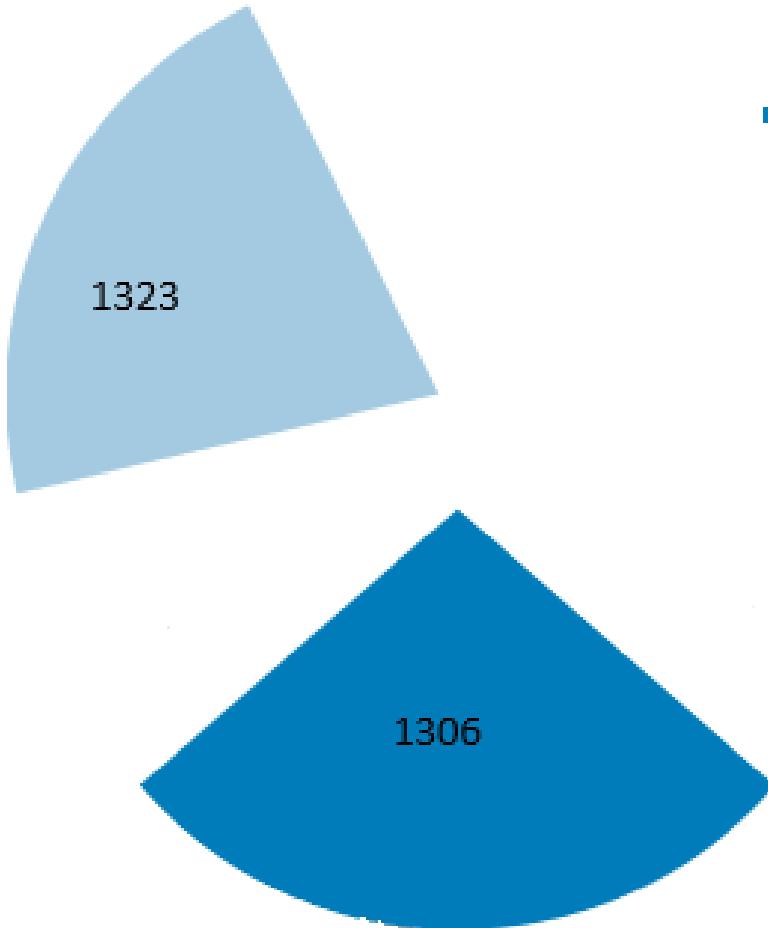
- From January 1 through August 1, 2023, **710 applications were rejected** for leaf element errors
  - A leaf element is "Information for an individual document is contained in the leaf element, its attributes, and its title element." – The eCTD Backbone Files Specification for Module 1

  - Validation Code 1306 - No leaf element for file

  - Validation Code 1323 – No file for leaf element

us-regional.xml errors

Issue with us-regional (missing, multiple, or not valid)

- From January 1 through December 31, 2023, **595 applications were rejected** for errors with the us-regional.xml backbone file

  - 469 submissions had no us-regional.xml file

  - 58 submissions had more than one us-regional.xml file

  - 58 submissions had an invalid or unsupported version of the us-regional.xml file

The eCTD Backbone Files Specification for Module 1

INTRODUCTION

This document provides specifications for creating the electronic common technical document (eCTD) backbone file for Module 1 for submission to the FDA. It should be used in conjunction with the guidance to industry: *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*

Font formatting conventions are used in this document to enhance its readability and emphasize items such as heading elements, attributes, titles, and file names:

- ***Bold italic*** font is used for elements and attributes.
- *Italic* font is used for links, leaf titles, publication titles, file names, and folder names.

The Module 1 eCTD Backbone File (*us-regional.xml*) includes administrative information and information for each file submitted in Module 1. The backbone file contains an XML element named ***fda-regional:fda-regional***, which contains both the ***admin*** and ***m1-regional*** elements. The individual file information is provided within an XML element called the ***leaf*** element. The ***leaf*** elements are organized using the Module 1 section headings. The Module 1 section headings are named and organized according to the subject matter of the information contained in the files. Section headings are provided as XML elements in the ***m1-regional*** element of the backbone file. Administrative information about each submission is provided in the ***admin*** element of the backbone file.

The Module 1 eCTD Backbone File may be used in a wide range of applications and related submission types; therefore, a specific submission may not use all of the possible section heading elements. Only include the section headings that reference files in the submission. Empty section headings should not be included. The ***admin*** element should always be included, and it contains two elements named: ***applicant-info*** and ***application-set***. These elements should be included in order as listed in *section III Admin Elements.*

The *us-regional-v3-3.dtd* file (refer to *Appendix 1*) provides the organization for each element used in the *us-regional.xml* file.

I.   USE OF ATTRIBUTES

Certain ***admin*** and ***m1-regional*** heading elements require an attribute to provide information that is pertinent to the application and submission. The attribute lists are maintained as separate XML files, and each contains a standard set of codes and display names for each defined attribute type. The attribute files contain a version number, version date and coded values and display names for each value. Each coded value has a status of "active" or "inactive" to accommodate future changes; only coded values with a status of "active" should be submitted. Only the code should be provided as the attribute value in the appropriate element in the *us-regional.xml* file. The display name is shown to the reviewers in the review tool.

The following table contains the names of the attribute type lists and their respective file names.

Version 2.5   1

Submission-type errors

2022

2034

- From January 1 through December 31, 2023, **256 applications were rejected** for errors with submission-type attributes

  - Validation Code 2034 – Submission-type is invalid for application-type

  - Validation Code 2022 – Submission-sub-type is invalid for submission-type

The eCTD Backbone Files Specification for Module 1

Table 2: Submission Types and Descriptions of Use

Submission Type	Submission Sub-Type	Supplement Effective Date Type (if applicable and *submission-sub-type* = "application")	Valid For Application Types
Original Application	Presubmission Application Amendment Resubmission		IND, NDA, ANDA, BLA, DMF, EUA
Efficacy Supplement	Presubmission		NDA, BLA
	Application	Prior Approval Supplement (PAS)	
	Amendment Resubmission		
Chemistry Manufacturing Controls Supplement	Presubmission		NDA, ANDA, BLA
	Application	Prior Approval Supplement (PAS), Changes Being Effected (CBE-0), or Changes Being Effected 30 (CBE-30)	
	Amendment Resubmission		
Labeling Supplement	Presubmission		NDA, ANDA, BLA
	Application	Prior Approval Supplement (PAS) or Changes Being Effected (CBE-0)	
	Amendment Resubmission		
REMS Supplement	Application	Prior Approval Supplement (PAS) or Changes Being Effected (CBE-30)	NDA, ANDA, BLA
	Amendment Resubmission		
Annual Report	Report Amendment		IND, NDA, ANDA, BLA, DMF
Product Correspondence	Correspondence Amendment		IND, NDA, ANDA, BLA, DMF
Postmarketing Requirements or Postmarketing Commitments	Original Amendment		NDA, BLA
Promotional Labeling Advertising	Original Resubmission Amendment		NDA, ANDA, BLA
IND Safety Reports	Report Amendment		IND
Periodic Safety Reports (Periodic Adverse Drug Experience Report	Report Amendment		NDA, ANDA, BLA

Version 2.5   9

FDA

No fillable form

- From January 1 through December 31, 2023, **243 applications were rejected** for fillable form errors

  - Annual Report submissions <u>must</u> have a fillable 2252 form

  - All other NDA, ANDA, and BLA submissions <u>must</u> have a fillable 356h form

  - All other IND submissions <u>must</u> have a fillable 1571 form

Fillable Form Expiration Dates

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2026
See PRA Statement on page 4

- Recommend using latest version of forms to include new information

- Should not use forms past their expiration date
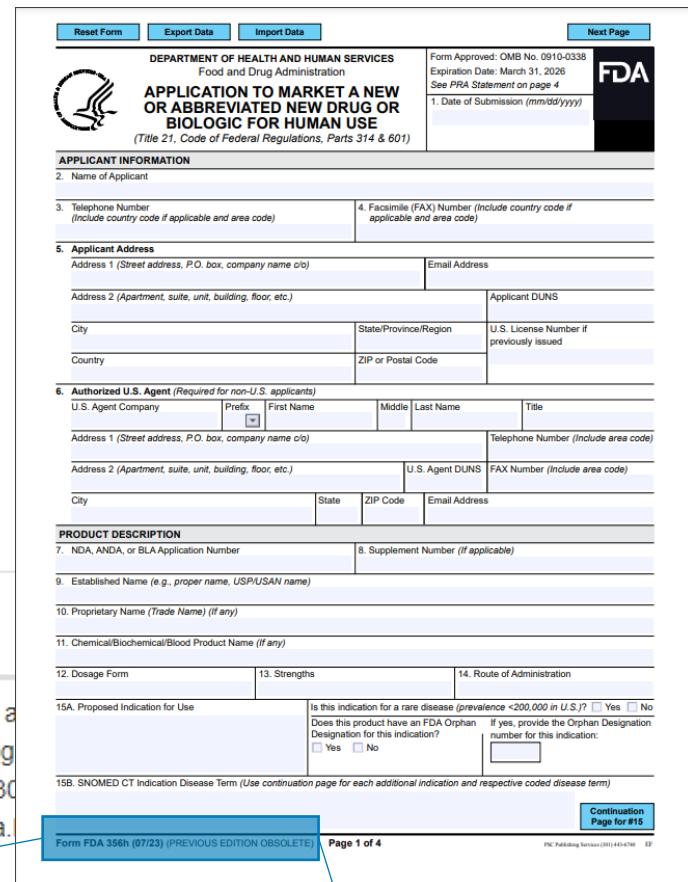
Common Questions for eSub

FDA

How do I confirm the latest version of the form?

Resources:

- ✓ [FDA Forms webpage](#)

- ✓ druginfo@fda.hhs.gov

- ✓ esub@fda.hhs.gov

Form Number	Title	Edition Date	Format	Contact
0356h	Application to Market a New or Abbreviated New Drug or Biologic for Human Use (PDF)	07/2023	FDA-356h_AcroForm_Sec_07-07-2023_0.pdf3.37 MB	CBER MATT a industry.biolog Drug Info at 3(druginfo@fda.|

Form FDA 356h (07/23) (PREVIOUS EDITION OBSOLETE)

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 for 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 license**
  - 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

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

2

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

FDA U.S. FOOD & DRUG ADMINISTRATION

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.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

Page 70 of 76

December 2023

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

Resources

- eCTD
  - [Web page for latest version of eCTD guidance, specifications, and validations](#)
  - [eCTD Comprehensive Table of Contents Headings and Hierarchy](#)
  - [eCTD Technical Conformance Guide](#)
  - [The eCTD Backbone Files Specification for Module 1](#)
  - [Specifications for File Format Types](#)

- Standards
  - [M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use Guidance for Industry](#)
  - [Interdisciplinary Review Team for Cardiac Safety Studies (formerly QT-IRT)](#)

- eCTD 4
  - [FDA's eCTD v4 implementation page](#)