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Submitting in eCTD: Most Common Submission Issues and FDA Plans for eCTD v4.0

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Agenda

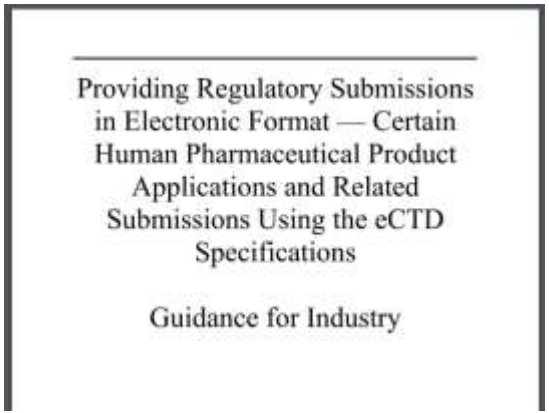
- eCTD Guidance
- Most Common Reasons for Technical Rejection Notice
- eCTD Validations and Study Data
- Frequently Asked Questions to eSub
- FDA Plans for Implementation of eCTD v4.0
- Summary

eCTD Guidance

Electronic Submission Requirements

Industry must follow FDA guidance when submitting an ANDA:

Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using eCTD Specifications – Guidance for Industry
https://www.fda.gov/media/135373/download

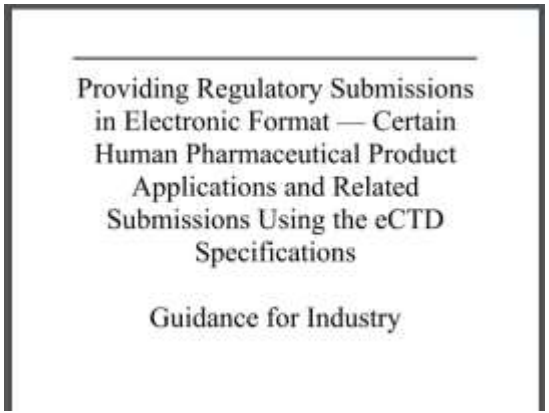


Electronic Submission Requirements

Two key requirements stated in the guidance:

1. Submissions **must** be in eCTD format
2. Submissions sized 10 GB or less **must** be submitted through the FDA Electronic Submission Gateway (ESG)

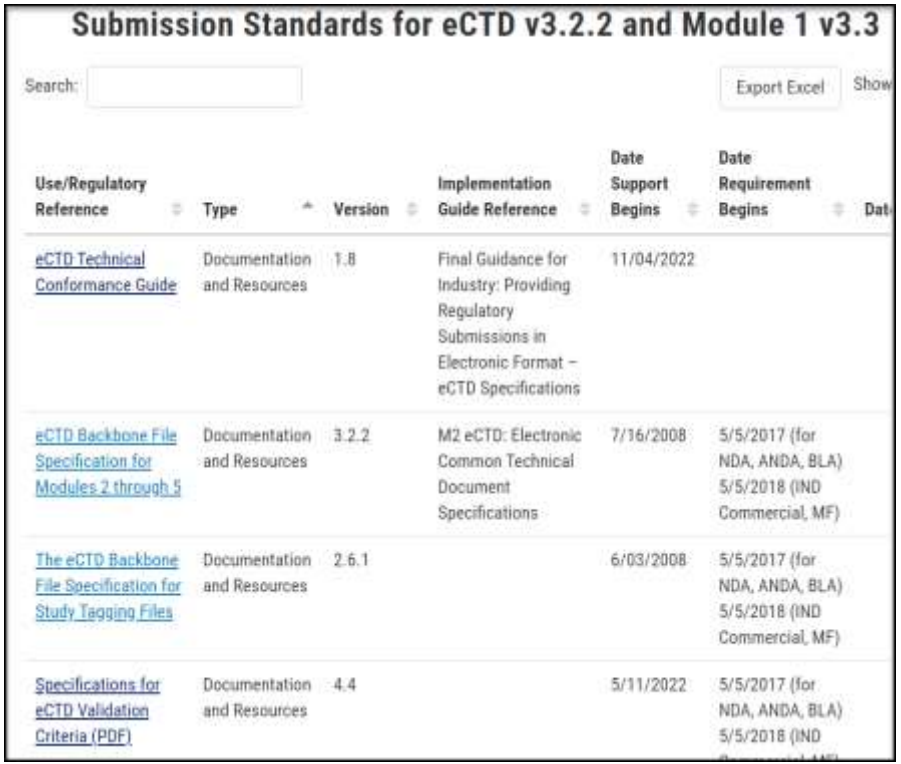
If the above requirements are not followed, the submission will be rejected.



Electronic Submission Requirements

See the following resources for more information:

1. eCTD Guidance (Revision 7)
2. eCTD Technical Conformance Guide
3. eCTD Submission Standards
4. eCTD Website



Submission Standards for eCTD v3.2.2 and Module 1 v3.3

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Use/Regulatory Reference	Type	Version	Implementation Guide Reference	Date Support Begins	Date Requirement Begins	Dat
eCTD Technical Conformance Guide	Documentation and Resources	1.8	Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format – eCTD Specifications	11/04/2022		
eCTD Backbone File Specification for Modules 2 through 5	Documentation and Resources	3.2.2	M2 eCTD: Electronic Common Technical Document Specifications	7/16/2008	5/5/2017 (for NDA, ANDA, BLA) 5/5/2018 (IND Commercial, MF)	
The eCTD Backbone File Specification for Study Tagging Files	Documentation and Resources	2.6.1		6/03/2008	5/5/2017 (for NDA, ANDA, BLA) 5/5/2018 (IND Commercial, MF)	
Specifications for eCTD Validation Criteria (PDF)	Documentation and Resources	4.4		5/11/2022	5/5/2017 (for NDA, ANDA, BLA) 5/5/2018 (IND	

Most Common Reasons for Technical Rejection Notice

Most Common Reasons for Technical Rejection Notice

Basic check performed prior to eCTD validation

Number of Rejection (FY2022)	Top Errors that result in auto-rejection of a submission
2815	Duplicate eCTD sequence
690	A submission contains only a single file
536	Backbone files are not provided in an eCTD submission

Most Common Reasons for Technical Rejection Notice

eCTD validations

Number of Rejection (FY2022)*	Top eCTD Errors that result in auto-rejection	eCTD Error Code
337	All submitted files are not referenced in the backbone files	Error Code 1306
269	Submission file(s) are referenced in the backbone files, but they are not provided within a submission	Error Code 1323
246	An unsupported DTD version is used in us-regional.xml	Error Code 1463
198	ts.xpt with information on the study start data for each study is not present	Error Code 1734
164	All files provided in a study section must be referenced by an STF file	Error Code 1789

Number of Submissions (FY2022)	Top high eCTD errors that are subject to manual review and possible rejection	eCTD Error Code
276	A submission type is invalid for an application type	Error Code 2034
141	A submission sub-type is invalid for submission type or/and application type	Error Code 2022

*In 2022, FDA rejects less than 2% of all eCTD submissions
See Specifications for eCTD Validation Criteria for more details

eCTD Validations and Study Data

eCTD Study Data Validations: What's New (effective March 16, 2023)

Study Data Technical Rejection Criteria (TRC) Updates	Other Study Data Validation Updates (medium severity)
1. 1734 – A dataset named ts.xpt with information on study start date must be present for each study ▪ No longer validates for STUDYID mismatch between ts.xpt and STF file (moved to 1738) New	**1. 1737 – For each study referenced by an STF, no more than one dataset of the same file name and leaf title should be submitted using the lifecycle operator "new"** ▪ Applies to all sections except 4.3, 5.2, 5.4, & 5.3.6 New
2. 1735 – The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files ▪ A Define.xml file tagged as "data-listing-data-definition" no longer triggers a 1735 error New	**2. 1738 – STF Study ID should match STUDYID or SPREFID listed in the referenced Trial Summary (ts.xpt) file** New ▪ Validates for STUDYID mismatch between ts.xpt and STF file ▪ Applies to all sections except 4.3, 5.2, 5.4, & 5.3.6

Electronic Study Data Guidance

"**Study Data Guidance**" - *Providing Regulatory Submissions in Electronic Format -- Standardized Study Data (last updated June 2021)*

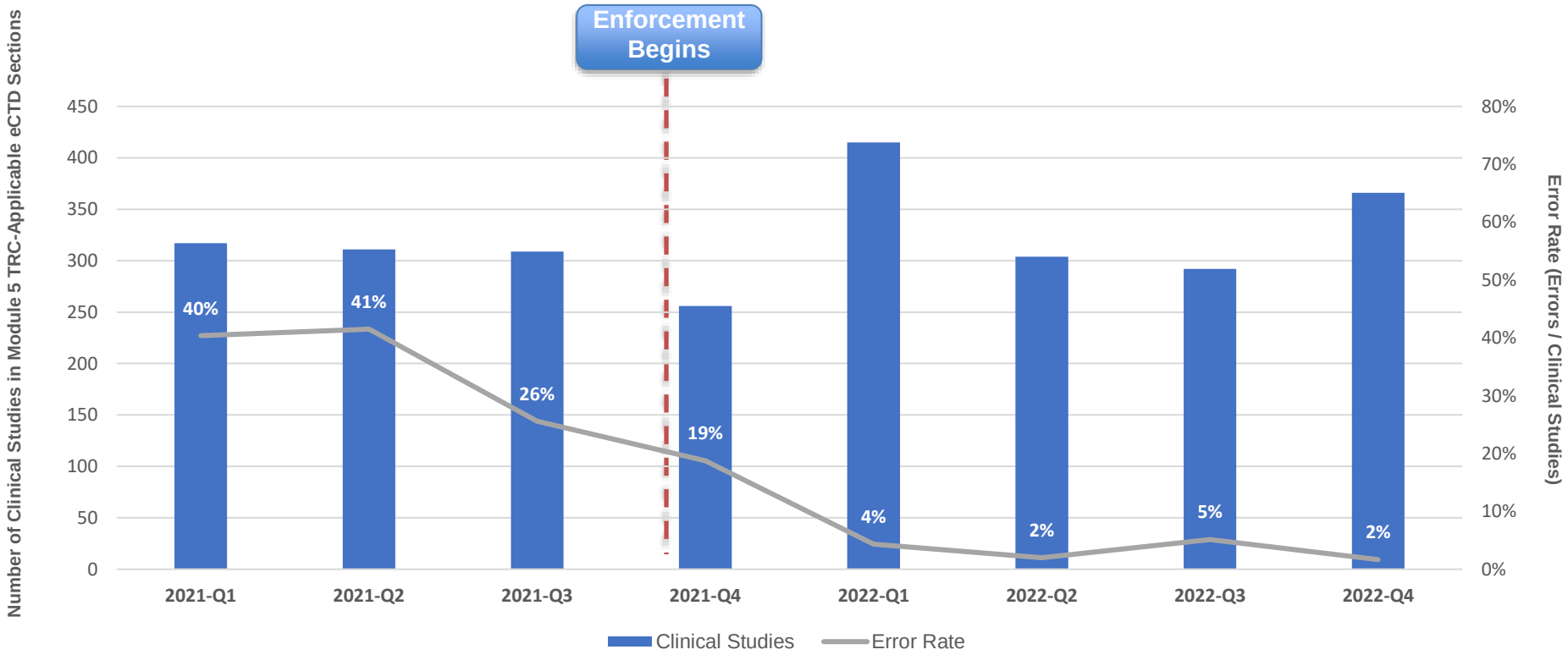
- **Sponsors must conform to standards in the FDA Data Standards Catalog:**
  - NDA, BLA, ANDA studies that started after December 17th, 2016
  - Commercial IND studies started after December 17th, 2017
- **FDA uses eCTD validations (1734, 1735, 1736)** to confirm Sponsors are conforming to the FDA Data Standards Catalog. This subset of eCTD validations are described in detail in the Technical Rejection Criteria for Study Data (TRC)*.

For more information on how to submit and what will be validated, see the documents below:

- Study Data Standards Resources
  - Data Standards Catalog
  - Study Data Technical Conformance Guide
- Electronic Common Technical Document (eCTD) website
- Study Data for Submission to CDER and CBER website

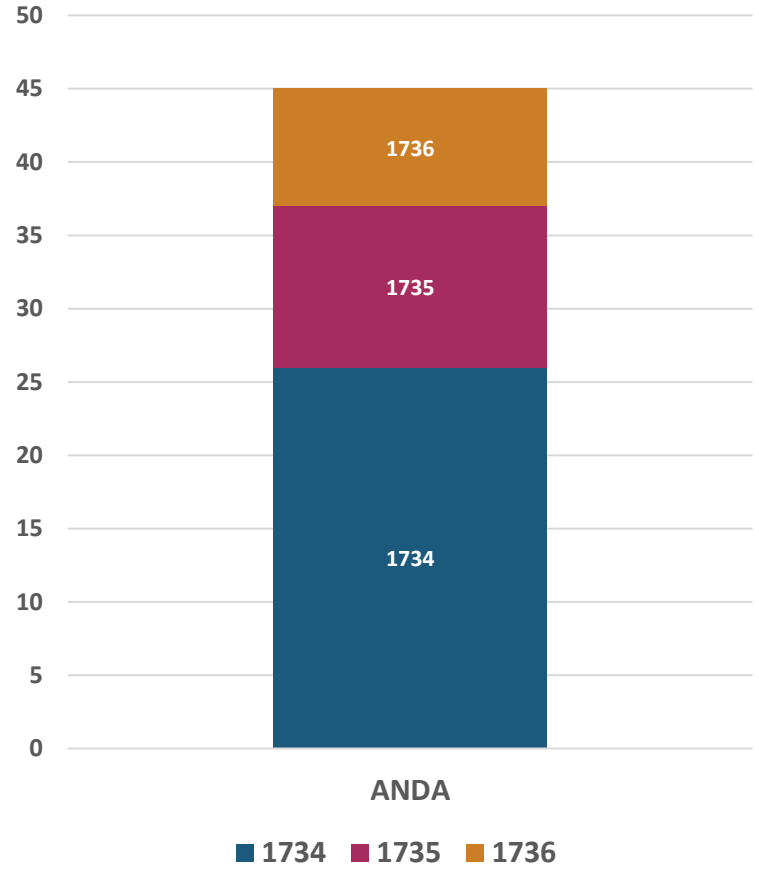
*The TRC is located in the Study Data Technical Conformance Guide

ANDA Study Data Technical Rejection Criteria (TRC) Conformance Trend: 2021-2022



Rejected Submissions: February 15, 2022 – February 15, 2023

- 1734 (58%) is the most common error and rejection reason for a missing ts.xpt



Notes: *Metrics generated from data between February 15, 2022 and February 15, 2023.*

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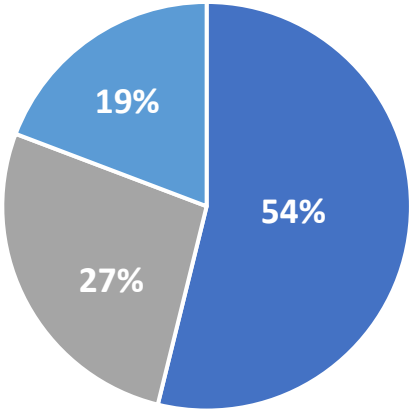
Addressing Top Error: 1734

1734 Validation

A dataset named ts.xpt with information on study start date must be present for each study in required sections*

- ✓ Trial Summary Dataset (ts.xpt) is present
- ✓ Study start date is provided (or TSVALNF = NA)
- ✓ Study start date is in a valid format
- ✓ Study ID (or SPREFID) matches STF Study ID*

*Moved to validation 1738, effective as of 3/16/2023



54% of 1734 errors in ANDA applications due to Missing ts.xpt

- No ts.xpt found for this study
- No ts.xpt with value for SSD found (and no null flavor value)
- Study ID in ts.xpt does not match study ID from STF

Note: 1734 Study Errors between Feb. 15, 2022 – Feb. 15, 2023

Frequently Asked Questions to eSub

- Where should my document go within the eCTD structure?
  - The following documents will be helpful in organizing submissions
    - eCTD Technical Conformance Guide
    - Comprehensive Table of Contents Headings and Hierarchy (CTOC)
    - M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use Guidance for Industry
    - M4: The CTD -- Quality Questions and Answers /Location Issues

- Why did my submission fail eCTD validation 1734?
  - Study data was submitted to M4 or M5 and there is no valid ts.xpt referenced under the STF for the study. See “8.2.2.1 – eCTD Technical Rejection Criteria for Study Data” in the Study Data Technical Conformance Guide for details

Frequently Asked Questions to eSub

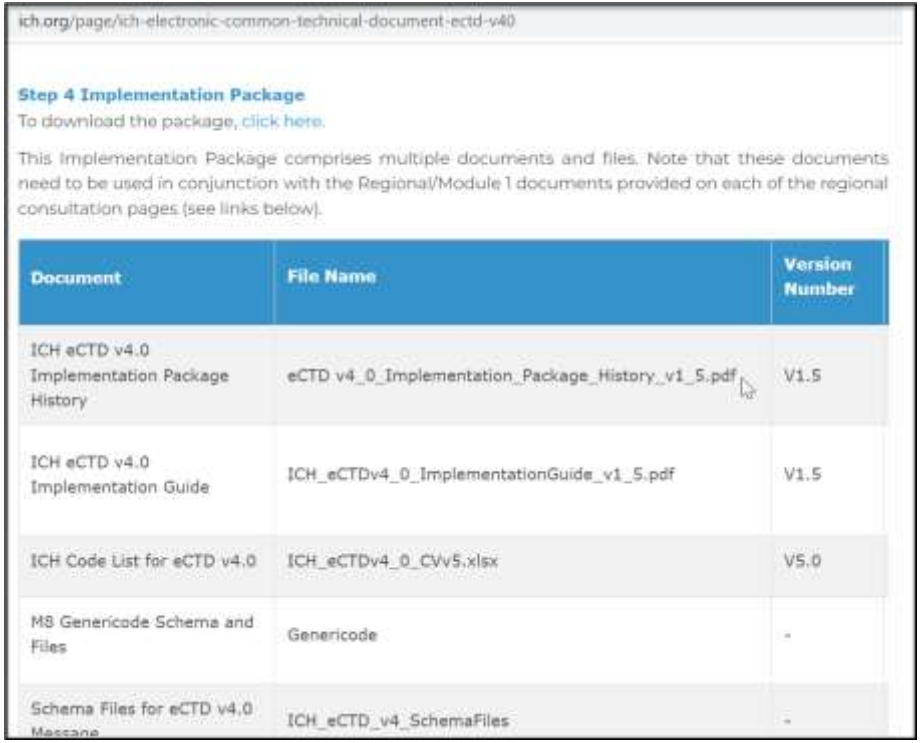
- Will a validation error cause a rejection?
  - Specifications for eCTD Validation Criteria contains the latest list of validations
  - Each validation has a severity description and those marked “high” cause rejections

Number:	1306
Group:	File checks
Description:	No leaf element for file
Severity Description:	High
US DTD Version	3.3
Effective Date:	3/1/2022
Problem:	You have submitted the file(s) listed in the validation report without a corresponding reference in the backbone.
Corrective Action:	Resubmit, corrective action is based on the underlying reason for the error. If the error is the result of a simple omission of a leaf element, then you should ensure the leaf element file is included in the submission before resubmitting. If the error occurred due to a difference between the name of the file in a leaf reference and the actual name of the file, then you should correct the leaf element before resubmitting.
Guidance Source:	ICH Q&A 36 #13; ICH eCTD Specification V3.2.2; eCTD Comprehensive Table of Contents Headings and Hierarchy

FDA Plans for Implementation of eCTD v4.0

FDA Plans for Implementation of eCTD v4.0: – ICH Activities

- ICH eCTD v4.0 Implementation Package
  - V1.5 May 2022
- Q&A Change Requests
  - V1.7 June 2022
- Regional Implementation Information posted on ICH eCTD v4.0 webpage
  - Regional planned Technical Pilots & Implementation Dates
  - Links to regional Implementation Documents



ich.org/page/ich-electronic-common-technical-document-ectd-v40

Step 4 Implementation Package

To download the package, click here.

This Implementation Package comprises multiple documents and files. Note that these documents need to be used in conjunction with the Regional/Module 1 documents provided on each of the regional consultation pages (see links below).

Document	File Name	Version Number
ICH eCTD v4.0 Implementation Package History	eCTD v4_0_Implementation_Package_History_v1_5.pdf	V1.5
ICH eCTD v4.0 Implementation Guide	ICH_eCTDv4_0_ImplementationGuide_v1_5.pdf	V1.5
ICH Code List for eCTD v4.0	ICH_eCTDv4_0_CVv5.xlsx	V5.0
M8 Genericode Schema and Files	Genericode	-
Schema Files for eCTD v4.0 Message	ICH_eCTD_v4_SchemaFiles	-

FDA Plans for Implementation of eCTD v4.0: – FDA Activities

- eCTD v4.0 Technical Conformance Guide and FDA eCTD v4.0 Module 1 Implementation Package
  - Posted February 2020 for public comment
  - Posted updates on September 2022
- Specifications for eCTD v4.0 Validation Criteria (October 2022)
- eCTD v4.0 Comprehensive Table of Contents Headings and Hierarchy (June 2021)
- Software updates and testing
  - Currently testing eCTD v4.0 vendor software
  - eCTD v4.0 Technical Pilot

Electronic Common Technical Document (eCTD) v4.0

The documents and files referenced on this web page are: FOR IMPLEMENTATION PLANNING ONLY

The documentation and links on this webpage provide information on how to submit eCTD v4.0-based electronic submissions to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER).

FDA eCTD v4.0 Implementation Status

CDER and CBER are in the process of testing our eCTD v4.0 software and coordinating with our industry technical pilot participants to perform eCTD v4.0 submission testing in 2022.

CDER and CBER plan to accept new applications in eCTD v4.0 format in 2023. Future implementation phases will address existing v3.2.2 applications and two-way communication.

FDA Plans for Implementation of eCTD v4.0: – FDA Implementation Strategy

- Initial release/acceptance for new applications in eCTD v4.0
  - Technical Pilot
    - Small group (ending April)
  - Accept sample submissions for technical feedback
    - Open to all (planned for late 2023)
  - Begin accepting new applications in eCTD v4.0 in late 2023 or early 2024
- Future phases
  - Transition of current applications
  - Two-way communication

FDA Plans for Implementation of eCTD v4.0: – FDA Technical Pilot

- The objective of the FDA Technical Pilot is to determine if the implementation satisfies the requirements in the technical specification and make any changes prior to accepting eCTD v4.0 submissions in the production environment.
- Testing June 2022 – April 2023

FDA Plans for Implementation of eCTD v4.0: – How to Prepare

- Discuss eCTD v4.0 development plans with your vendor and/or IT organization
  - Understanding the specifications
  - Is there a plan for transitioning to eCTD v4.0?
  - Send questions to ICH or FDA
- Become familiar with eCTD v4.0 concepts and enhancements
  - ICH Supplemental Documents for eCTD v4.0
    - Support Documentation and Orientation Material for eCTD v4.0 Implementation Package
  - FDA eCTD v4.0 Technical Conformance Guide
- Know where to find the eCTD v4.0 information
- Submit an eCTD v4.0 sample submission for technical feedback
  - Information will be posted on the *eCTD Sample Submission Process* webpage later this year (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/submit-ectd-or-standardized-data-sample-fda)

FDA Plans for Implementation of eCTD v4.0: – eCTD v4.0 Websites

- ICH eCTD v4.0 Webpage (https://www.ich.org/page/ich-electronic-common-technical-document-ectd-v40)
  - ICH eCTD v4.0 Implementation Package
  - Supplemental Documents for eCTD v4.0 Implementation Package
  - Regional Implementation Information & Regional Links
  - Change Control
    - Process
    - Change Requests & Questions
    - Q&A document
- FDA eCTD v4.0 Webpage

  (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd-v40)
  - FDA eCTD v4.0 M1 Implementation Package
  - eCTD v4.0 Technical Conformance Guide, CTOC, Validations
  - Link to ICH eCTD v4.0 webpage

Summary

- Common Submission Issues
  - Duplicate eCTD sequence numbers are #1 issue
- Frequently Asked Questions to eSub
  - esub@fda.hhs.gov is a great resource for questions related to electronic submissions
- ANDA Study Data Conformance
  - 95% to 98% Conformance in 2022
  - Most common eCTD error related to study data is 1734
  - Top trigger for 1734 was missing ts.xpt
- FDA Plans for Implementation of eCTD v4.0
  - Specifications published
  - Testing underway
  - FDA expects to accept eCTD v4.0 end of 2023 or early 2024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