FDA Study Data Technical Rejection Criteria (TRC): What you need to know!

For Submissions to CBER and CDER

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Learning Objectives

- **Review the background of the Technical Rejection Criteria (TRC) and updates**
- **List and review the most common TRC errors**
- **Describe the importance of Standardized Study Data**

TRC Background & Updates

Electronic Submission 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:
  - ❖ CDER & CBER Clinical Studies
    - NDA, BLA, ANDA studies that started after December 17th, 2016
  - ❖ CDER Non-clinical Studies
    - NDA, BLA, ANDA studies that started after December 17th, 2016
    - Commercial IND studies that started after December 17th, 2017
  - ❖ CBER Non-clinical studies
    - NDA, BLA, ANDA, and Commercial IND studies that started after March 15, 2023
- **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 Specification for eCTD Validation Criteria.

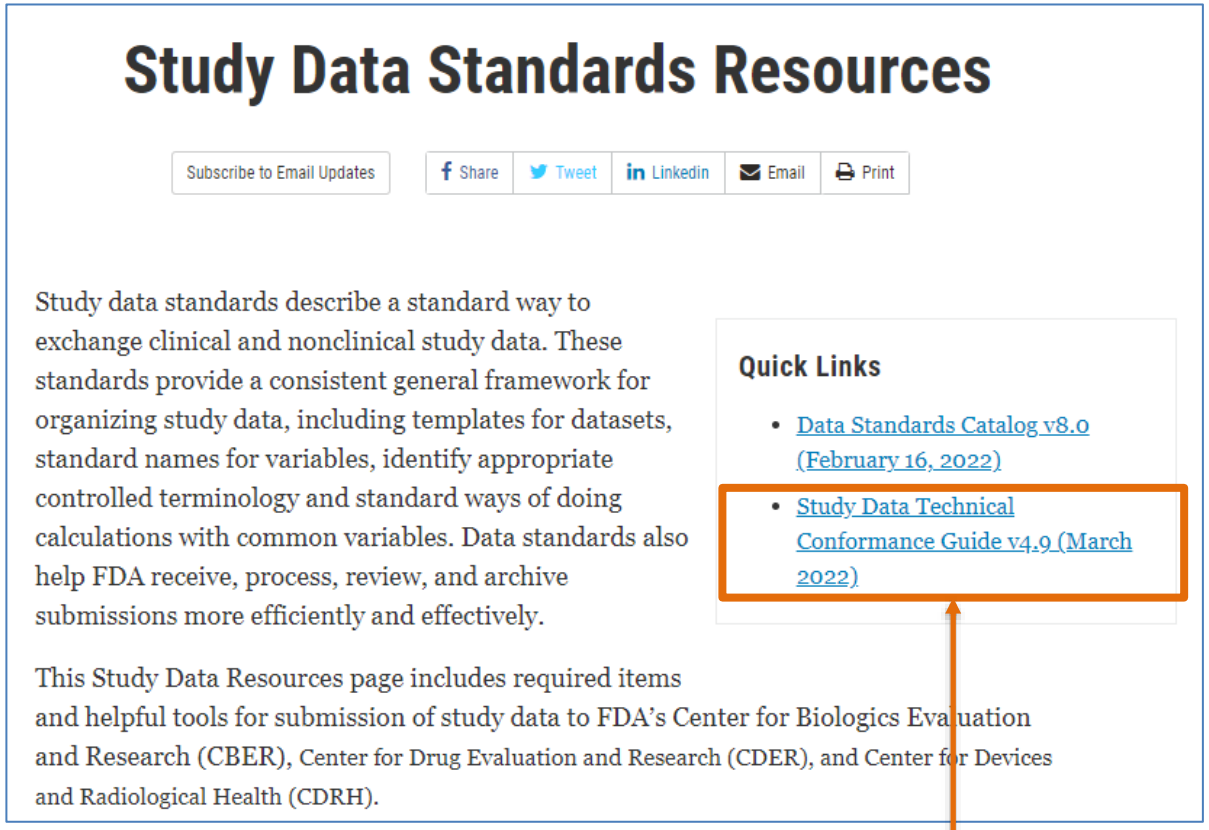
For more information on how to submit and what will be validated, see the documents below:

- Study Data Technical Conformance Guide – Latest update March 2022
- Study Data for Submission to CDER and CBER website

Study Data Technical Conformance Guide

- The Study Data Technical Conformance Guide is available on the Study Data Standards Resources web page

- All links to the TRC now redirect to this web page



Study Data Standards Resources

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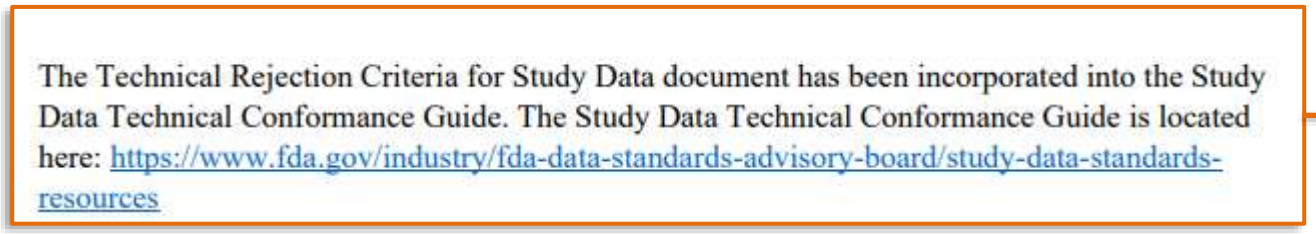
Study data standards describe a standard way to exchange clinical and nonclinical study data. These standards provide a consistent general framework for organizing study data, including templates for datasets, standard names for variables, identify appropriate controlled terminology and standard ways of doing calculations with common variables. Data standards also help FDA receive, process, review, and archive submissions more efficiently and effectively.

Quick Links

- Data Standards Catalog v8.0 (February 16, 2022)
- Study Data Technical Conformance Guide v4.9 (March 2022)

This Study Data Resources page includes required items and helpful tools for submission of study data to FDA's Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH).



The Technical Rejection Criteria for Study Data document has been incorporated into the Study Data Technical Conformance Guide. The Study Data Technical Conformance Guide is located here: https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources

eCTD Validation Updates

- Study Data Validation Effective Date updated:

  9/15/2021 (CBER module 4 sections, 03/16/2023)

Error	Description
1734	A dataset named ts.xpt with information on study start date must be present for each study in required sections*
1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*
1736	For SEND data, DM dataset and define.xml must be submitted in Module 4 required sections* For SDTM data, DM dataset and define.xml must be submitted in Module 5 required sections* For ADaM data, ADSL dataset and define.xml must be submitted in Module 5 required sections*
1737	For each study in required sections, no more than one dataset of the same name should be submitted as new*

** Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4*
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

Please review eCTD Validation Specification all details are not included in this presentation

eCTD Validation Updates

eCTD validation rule 1789 has different expectations than 1734, 1735, and 1736.

Error	Description
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

- 1789 applies to all subsections of modules 4 and 5 except:

  Sections 4.3, 5.2, 5.4, and 5.3.6

- An STF must be provided for all applications and data types for both CDER and CBER regardless of study start date

Challenge Question #1

When does CBER's SEND requirement begin?

A. Studies started after December 17th, 2017

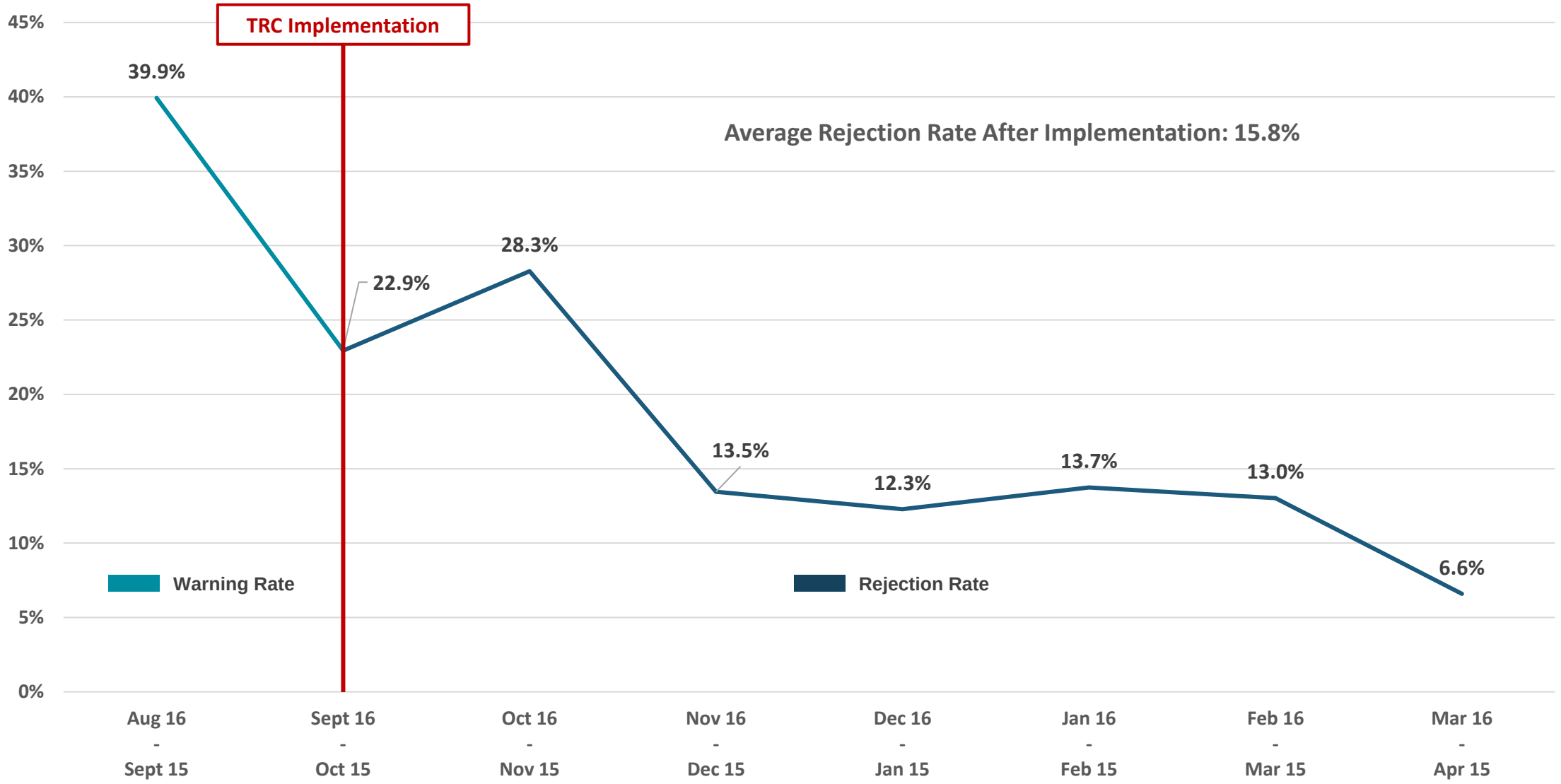
B. Studies started after December 17th, 2016

C. Studies started after March 15th, 2023

D. CBER will not require SEND standardized data

Most Common Errors

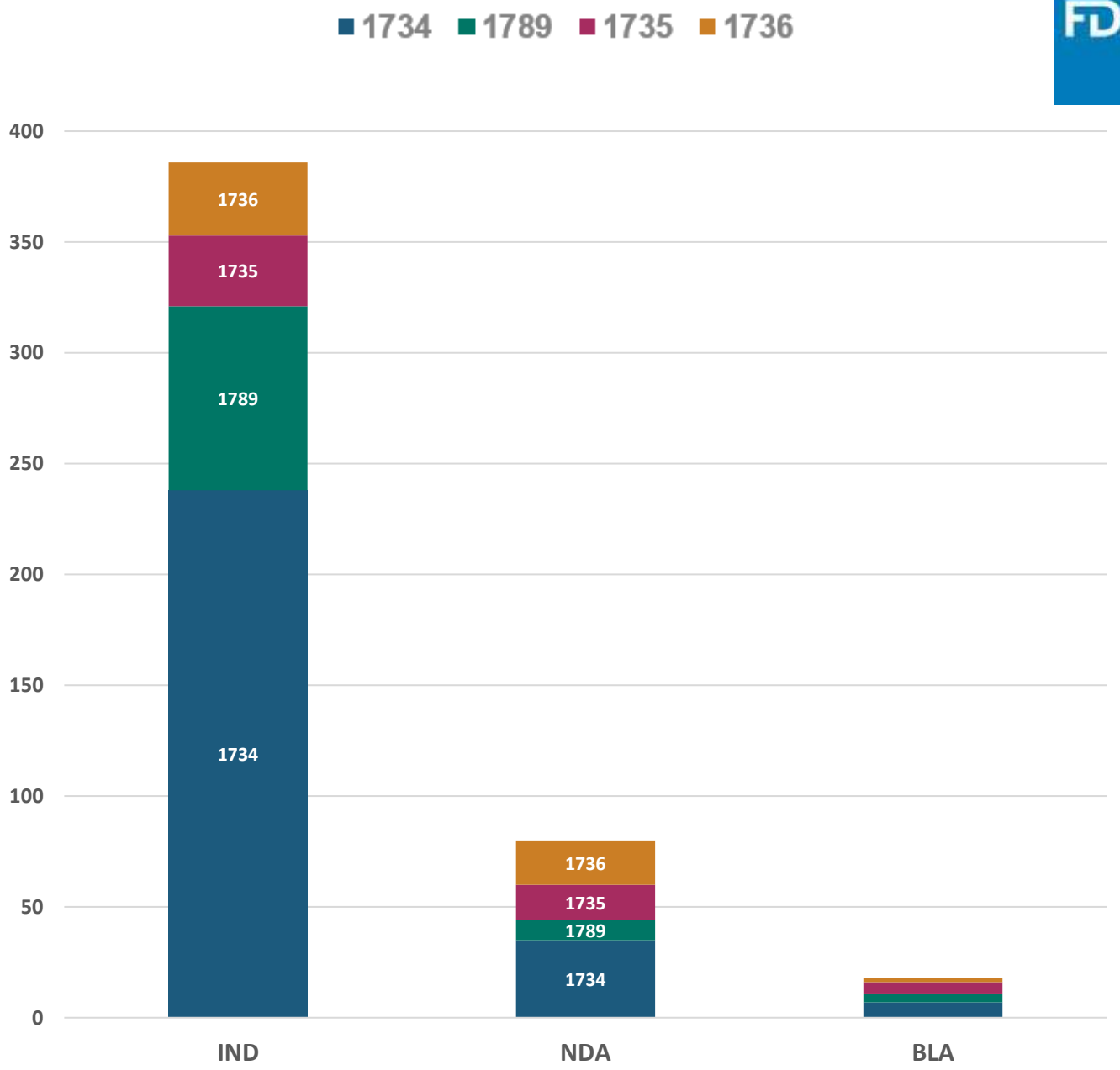
Monthly TRC Warning & Rejection Trend (CDER)



Notes: *Metrics generated from data between Aug. 15, 2021 and April 15, 2022.*
Error 1789 applies to all application types.
Warning and rejection rates calculated as total warnings/rejections as a percentage of submissions with study data in TRC-applicable sections

CDER TRC Rejections

- 1734 is the most common error and failure reason for all application types for a missing ts.xpt
- 1789 is the second most common error and failure reason
- Commercial IND submissions the have highest number of failures overall and have particularly high numbers of 1734 and 1789 errors



Notes: *Metrics generated from data between September 15, 2021 and April 30, 2022.*

1789 severity elevated to high 9/15/21 but not specific to standardized study data requirements.

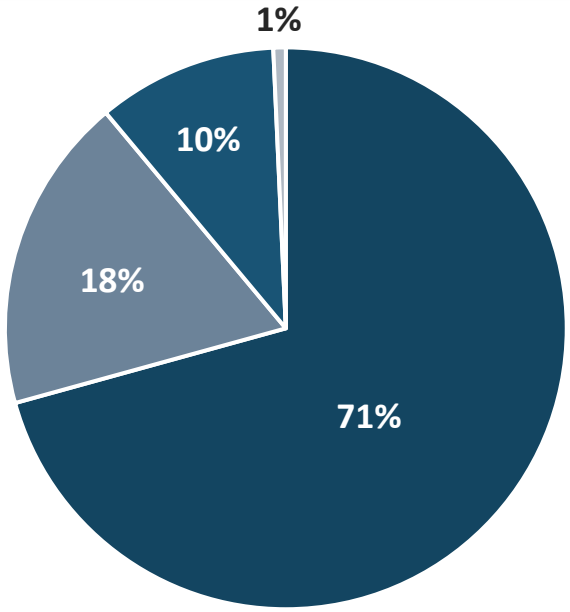
Addressing Top Errors: 1734

- **58% of errors across Application Types**
- **62% of errors for IND Applications**

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 ID (or SPREFID) matches STF Study ID
- ✓ Study start date is provided (or TSVALNF = NA)
- ✓ Study start date is in a valid format



71% due to Missing ts.xpt

90% of Missing ts.xpt 1734 Errors are for Non-Clinical Studies in M4

- No ts.xpt found for this study
- Study ID in ts.xpt does not match study ID from STF
- No ts.xpt with value for SSD found (and no null flavor value)
- Study start date is incorrectly formatted and TSVALNF has no null flavor value

Note: 280 1734 Study Errors for IND, NDA, BLA submissions between Sept. 15 – Apr. 30, 2022

Addressing 1734 Errors: Missing TS File

CDER and CBER expectations for standardized data:

The Study Data Technical Conformance Guide can be found here:

https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources

Application Type	Data Type	Modules & Sub-Modules	Expectation by CDER	Expectation by CBER
NDA, BLA, ANDA	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	*Study Start Date: On or prior to 2016-12-17* Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	***Study Start Date: On or prior to 2023-03-15*** **Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)**
NDA, BLA, ANDA	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	*Study Start Date: On or prior to 2016-12-17* Rejection criteria will be applied; submit a simplified TS if the study contains an xpt dataset (other than the ts.xpt)	
Comm. INDs	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	*Study Start Date: On or prior to 2017-12-17* Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	***Study Start Date: On or prior to 2023-03-15*** **Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)**
Comm. INDs	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	*Study Start Date: On or prior to 2017-12-17* Rejection criteria will not be applied	
NDA, BLA, ANDA	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	*Study Start Date: After 2016-12-17* Rejection criteria will be applied; submit a full TS	***Study Start Date: After 2023-03-15*** **Rejection criteria will be applied; submit a full TS**
NDA, BLA, ANDA	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	*Study Start Date: After 2016-12-17* Rejection criteria will be applied; submit a full TS with standardized data	
Comm. INDs	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	*Study Start Date: After 2017-12-17* Rejection criteria will be applied; submit a full TS	***Study Start Date: After 2023-03-15*** **Rejection criteria will be applied; submit a full TS**
Comm. INDs	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	*Study Start Date: After 2017-12-17* Rejection criteria will not be applied	

Addressing Top Errors: 1789

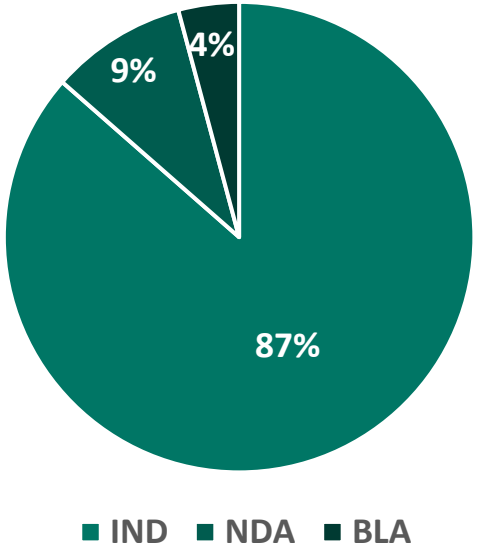
- **20% of errors across Application Types**
- **22% of errors for IND Applications**

1789 Validation:

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).

✓ All study files are included in a Study Tagging File (STF)

9% of all 1789 Errors for NDA Applications

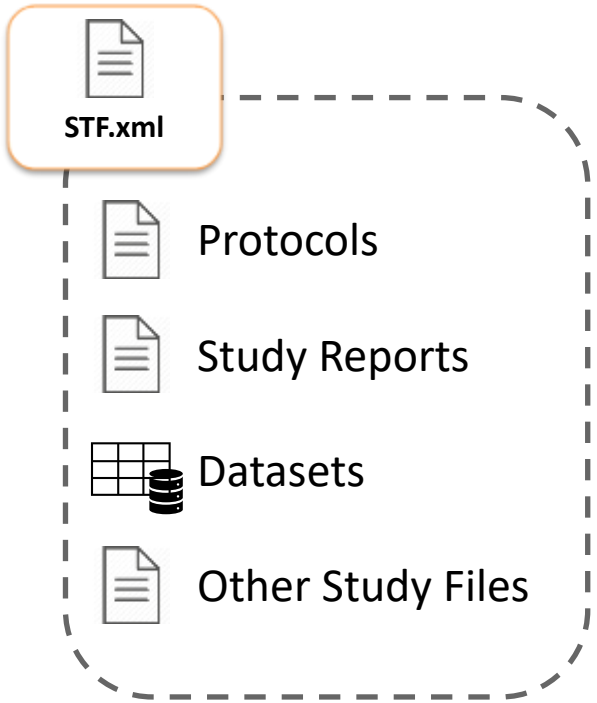


87% of all 1789 Errors for IND Applications

When placing files in applicable sections within Modules 4 and 5, they should also be referenced within an STF for the study to which they belong.

Note: 96 1789 Submission Errors for IND, NDA, BLA submissions between Sept. 15 – Apr. 30, 2022

1789 & STF Files



Study Tagging Files:

- Identify and link together all files associated with a study
- index.xml and us-regional.xml do not contain enough information on the subject matter of several documents (e.g., study report documents) to support certain regulatory uses
- An STF must be provided with the submission of any file or group of files belonging to a study in Modules 4 and 5.
- The STF provides for additional heading elements, *file-tags*, and heading attributes not currently provided by the eCTD DTD

ICH Study Tagging File Specification

Challenge Question #2

What is the most common reason for a 1734 error?

A. No ts.xpt found for the study

B. Study ID in ts.xpt does not match study ID from STF

C. No ts.xpt with value for SSD found

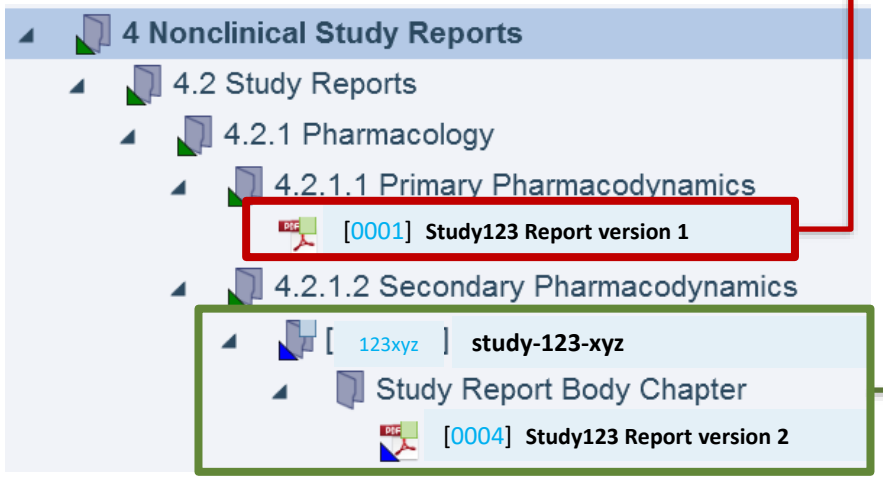
D. Study start date is incorrectly formatted

Importance of Standardized Study Data

Why is 1789 important?

Each study has its own stf.xml file with a unique study id and study title. When files are not referenced in a study tagging file they will not be connected to a specific study and may lead to reviewers not being able to find or review the data.

eCTD Viewer:

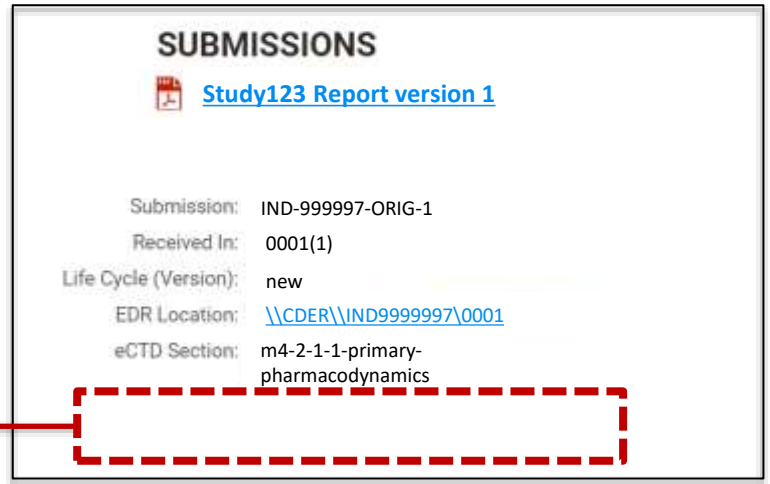


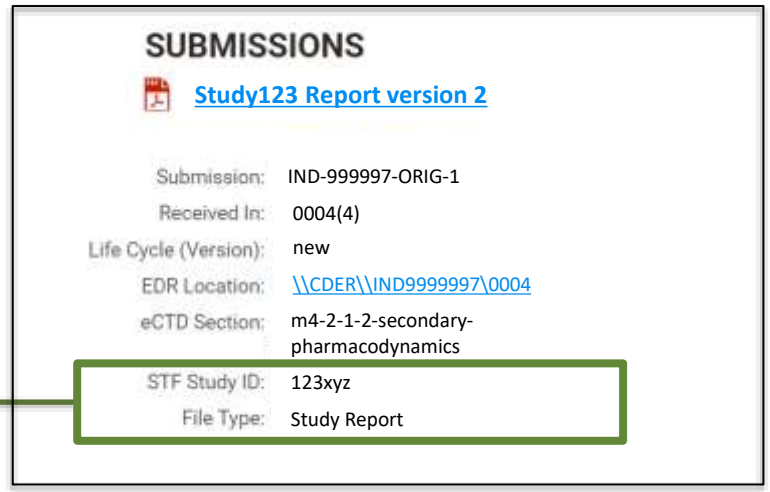
Unorganized and not connected to a study

Organized by Study Title and ID

File Tags indicate file types

Search:



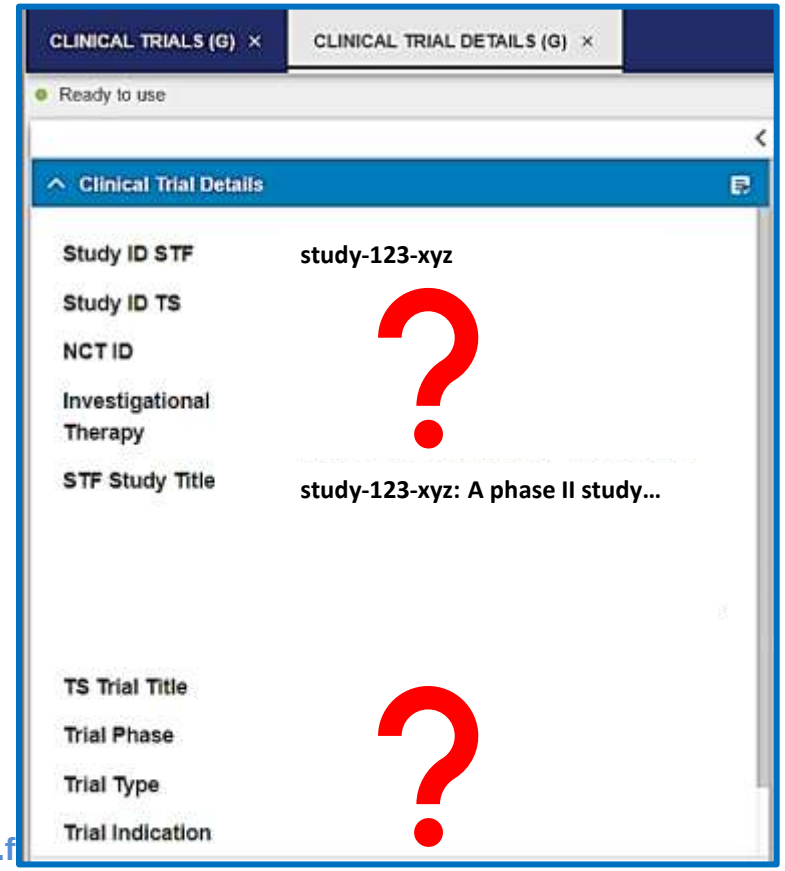


Why is 1734 important?

Missing ts.xpt:

X Can't determine the study start date, if TRC applies and whether standardized datasets are required

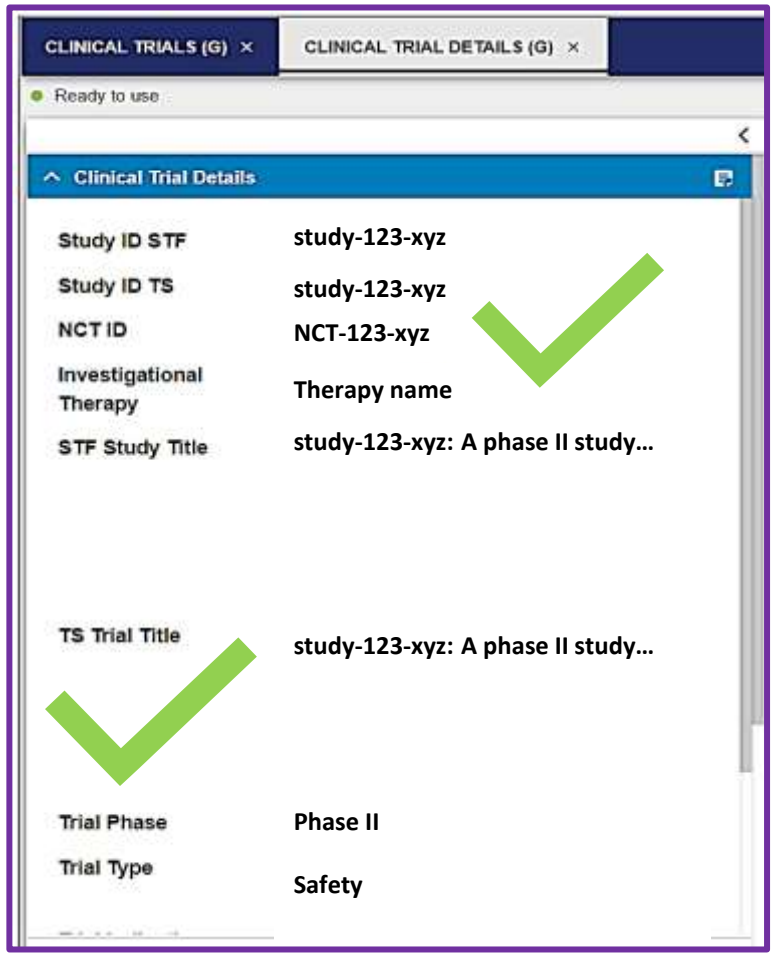
X Cannot connect to other clinical trial data and limits details available to reviewers



When a ts.xpt is included:

✓ Enables detailed searches

✓ Enables connections between data sources, such as ClinicalTrials.gov using NCT number



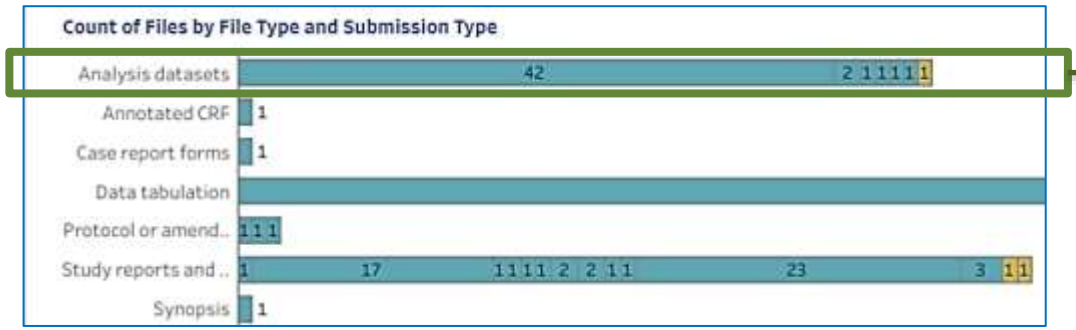
Why are 1735 & 1736 important?

File tags act as standardized sub-headings within a study to help distinguish and group files based on content.

When datasets are provided and tagged correctly:

- ✓ Enables detailed searches by file type
- ✓ Enables filtering by file type
- ✓ Enables locating essential study files, including dm.xpt, adsl.xpt, and define.xml
- ✓ Enables automated loading into analysis applications

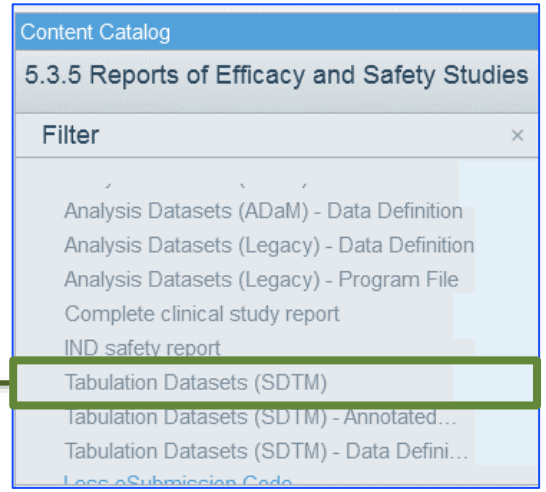
Reports & Filtering:

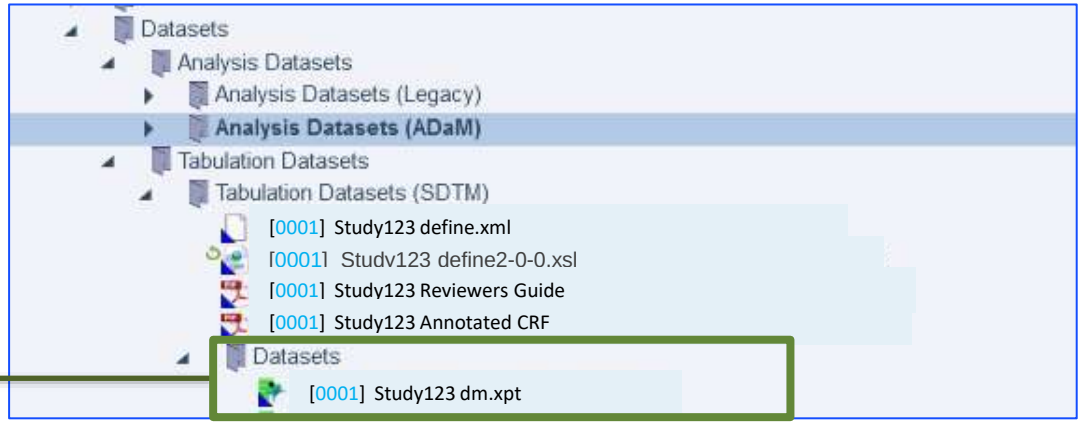


ADaM Datasets Grouped

SDTM Datasets Grouped

eCTD Viewer:





References

- **Study Data Standards Resources**
  - Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [June 2021]
  - Study Data Technical Conformance Guide [March 2022]
  - FDA Data Standards Catalog [February 2022]
  - Link: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

- **Study Data for Submission to CDER and CBER**
  - Technical Rejection Criteria Self-Check Worksheet
  - Technical Rejection Criteria Self-Check Worksheet Instructions
  - Link: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

- **Electronic Common Technical Document (eCTD)**
  - Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications: Guidance for Industry [February 2020]
  - eCTD Submission Standards [May 2022]
  - Specifications for eCTD Validation Criteria [May 2022]
  - Link: https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd

- **Providing Regulatory Submissions In Electronic Format - Submissions Under Section 745a(a) Of The FD&C Act: Guidance For Industry**
  - Link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents

Summary

- FDA uses eCTD validations (1734, 1735, 1736) to confirm Sponsors are conforming to the FDA Data Standards Catalog
- CBER's SEND requirement for module 4 begins March 16, 2023
- Commercial IND submissions have the highest number of failures related to TRC errors
- Missing ts.xpt is the most common error reason for 1734
- 1789 is the second most common error and failure reason
- Standardized data helps FDA to streamline the review process by organizing files and data and enabling search and automation capabilities

QUESTIONS?

For questions please contact:

- CDER
  - Study Data Questions: edata@fda.hhs.gov
  - eCTD Questions: esub@fda.hhs.gov
- CBER
  - Study Data Questions: cber-edata@fda.hhs.gov
  - eCTD Questions: esub-prep@fda.hhs.gov