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

For submissions to CBER and CDER

Jiang Xu | Lina Cong

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

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AGENDA

- TRC Background & What's New
- Overview of the Technical Rejection Criteria (TRC)
- CDER & CBER SEND Requirements & TRC
- TRC Rejections & Top Error Reasons
- Importance of Standardized Study Data

TRC BACKGROUND & WHAT'S NEW

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

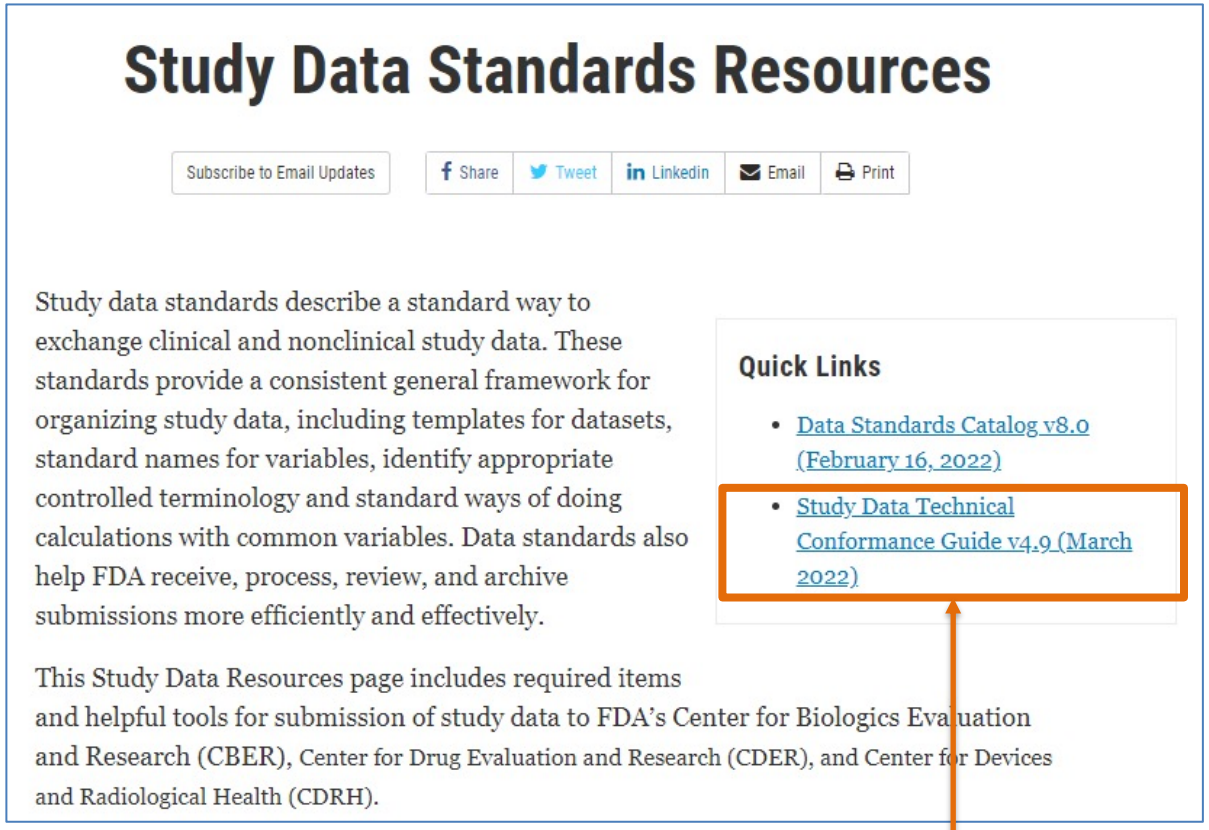
WHAT'S NEW

- CDER and CBER began rejecting submissions that fail eCTD study data validations on September 15, 2021
- FDA Data Standards Catalog was updated (February 2022)
  - Added SENDIG v3.1.1 with the Date Support begins and the Date Requirement begins
- CBER Non-clinical studies requirements will start after March 15, 2023
- Technical Rejection Criteria for Study Data (TRC) document was incorporated into the Study Data Technical Conformance Guide (March 2022)

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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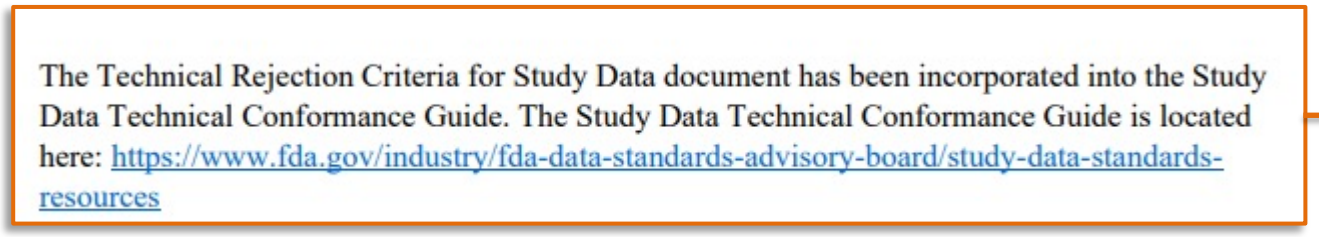
Study data standards describe a standard way to exchange clinical and nonclinical study data. These standards provide a consistent general framework for organizing study data, including templates for datasets, standard names for variables, identify appropriate controlled terminology and standard ways 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

OVERVIEW OF THE TECHNICAL REJECTION CRITERIA (TRC)

TRC IMPORTANT DATES

Data Standard Requirements

12/17/2016 – CDER & CBER Clinical Studies that start after require standardized data for NDAs, ANDAs, and certain BLAs

12/17/2017 – CDER Non-clinical Studies that start after require standardized data for commercial INDs.

03/15/2023 – CBER Non-clinical Studies that start after require standardized data for NDAs, ANDAs, BLAs, and Commercial INDs

TRC Implementation

09/15/2021 – TRC rejections began

03/16/2023 – CBER Non-Clinical requirements begin

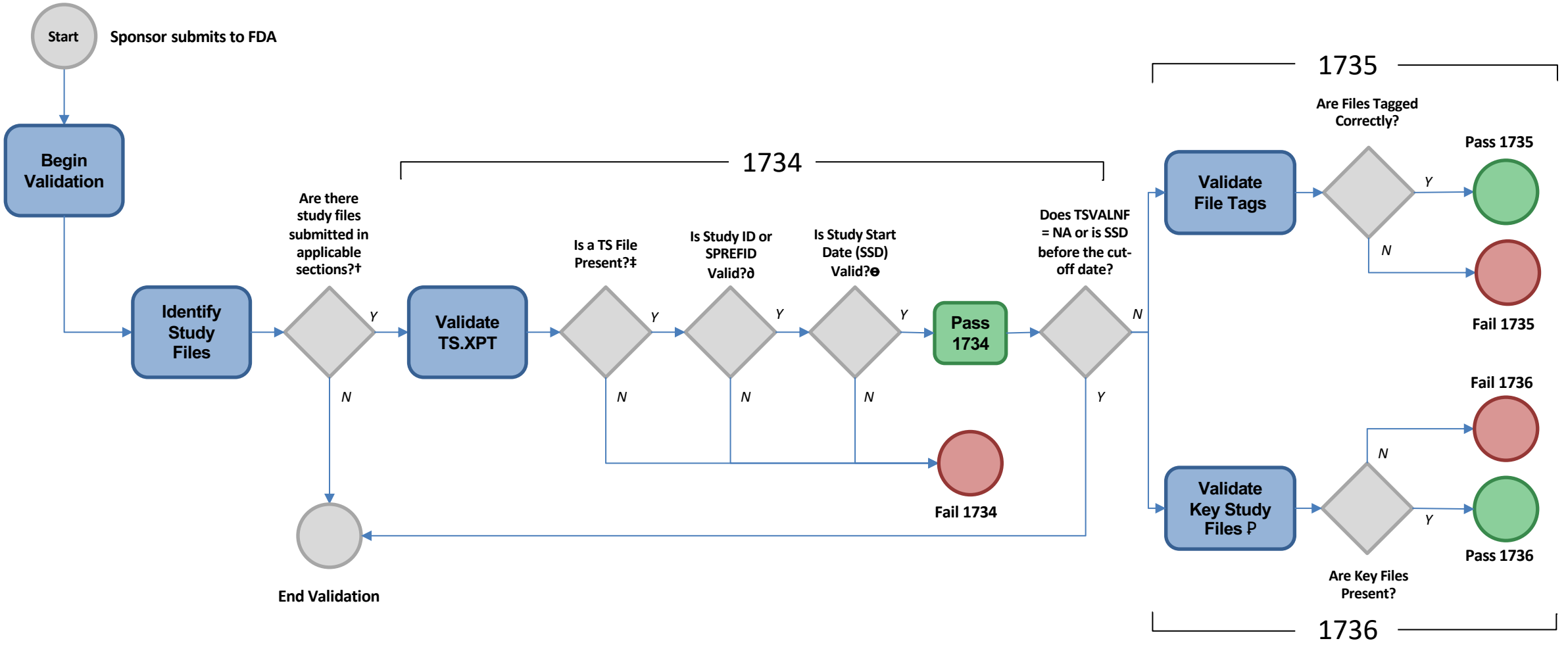
For more information, please reference the Study Data Technical Conformance Guide

FDA TECHNICAL REJECTION CRITERIA FOR STUDY DATA

Error	Description (Reference to Specifications for eCTD Validation Criteria)	Severity Level	Effective Date
1734	A dataset named ts.xpt with information on study start date must be present for each study in required sections*	High	9/15/2021 (CBER module 4 sections, 03/16/2023)
1735	The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*	High	9/15/2021 (CBER module 4 sections, 03/16/2023)
1736	For Standard for Exchange of Nonclinical Data (SEND) data, a Demographic (DM) dataset and define.xml must be submitted in Module 4 required sections* For Study Data Tabulation Model (SDTM) data, a DM dataset and define.xml must be submitted in Module 5 required sections* For Analysis Data Model (ADaM) data, an ADaM Subject level analysis dataset (ADSL) dataset and define.xml must be submitted in Module 5 required sections*	High	9/15/2021 (CBER module 4 sections, 03/16/2023)

** 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

TRC VALIDATION RULE FLOW



† XPT file type submitted in M5 or any file type submitted in M4 that has a file tag of "pre-clinical-study-report," "legacy-clinical-study-report," or "study-report-body"
‡ TS file does not need to be in the current sequence if it has been previously submitted and referenced by the STF
∂ Study ID or SPREFID should match the STF Study ID
ɵ Valid Study Start Date in ISO 8601 format (i.e. YYYY-MM-DD)
Ᵽ Key Files are dm.xpt or adsl.xpt and corresponding define.xml

CDER & CBER SEND REQUIREMENTS & TRC

ELECTRONIC STUDY DATA REQUIREMENTS

The following nonclinical study types are required to have SEND datasets as defined by study initiation date:

SEND Requirement Dates for Nonclinical Studies Modeled in SEND (Studies started after these dates require SEND datasets)		
Study Types Modeled in SEND	**NDAs/BLAs**	**Commercial INDs**
Single Dose Toxicity, Repeat Dose Toxicity, and Carcinogenicity Studies	December 17, 2016 (SENDIG v3.0) March 15, 2019 (SENDIG v3.1)	December 17, 2017 (SENDIG v3.0) March 15, 2020 (SENDIG v3.1)
Cardiovascular and Respiratory Safety Pharmacology Studies	March 15, 2019 (SENDIG v3.1)	March 15, 2020 (SENDIG v3.1)
Animal Rule (Natural History and Efficacy Studies)	March 15, 2022 (SENDIG AR v1.0)	March 15, 2023 (SENDIG AR v1.0)

SEND REQUIREMENTS, ECTD STRUCTURE, AND THE TRC

Module 4
Nonclinical Study Reports

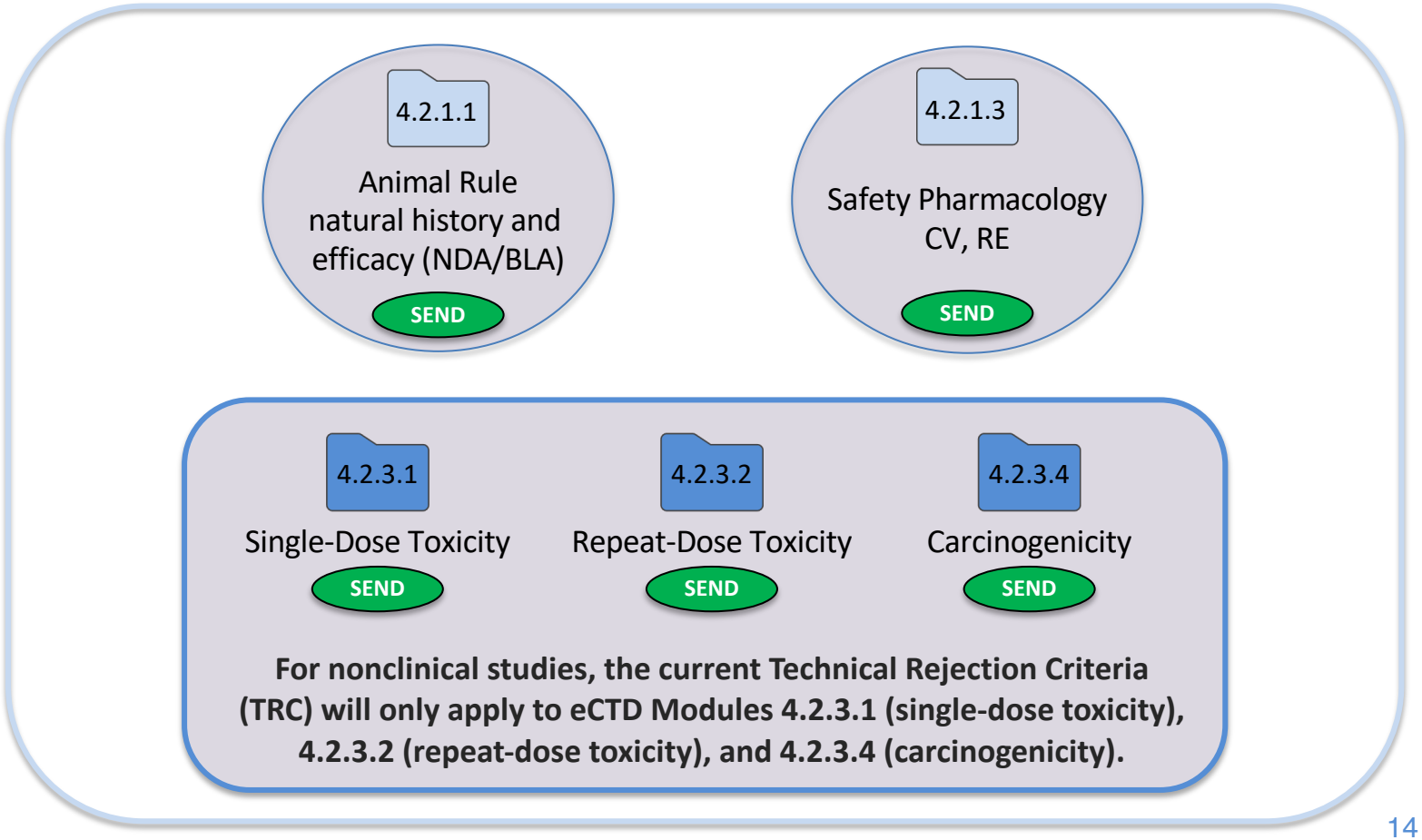
4.2.1 Pharmacology

4.2.2 Pharmacokinetics

4.2.3 Toxicology

4.3 Literature References

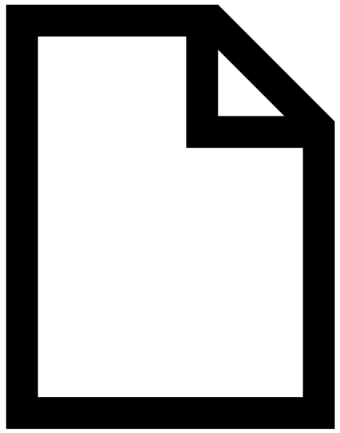
SEND is currently required for single-dose toxicity, repeat-dose toxicity, carcinogenicity, CV and RE safety pharmacology studies, and Animal Rule natural history and efficacy studies (NDA/BLA)



SEND OR SIMPLIFIED TS.XPT (TRIAL SUMMARY)

TRC Applied

- 4.2.3.1 Single-Dose Toxicity
- 4.2.3.2 Repeat-Dose Toxicity
- 4.2.3.4 Carcinogenicity



Nonclinical Study Report

Automated Process

SEND (Full ts.xpt)

SEND Requirement based on Study Type (supported SENDIG) and Study Initiation Date (see FDA Data Standards Catalog)

-OR-

Simplified ts.xpt

Needed when SEND is not required:

1. Study Initiation Date is prior to requirement date
2. A Study Initiation Date is Not Applicable (see Section 8.2.2 of the Study Data Technical Conformance Guide)

Neither SEND (TS) nor simplified ts.xpt = TRC Rejection

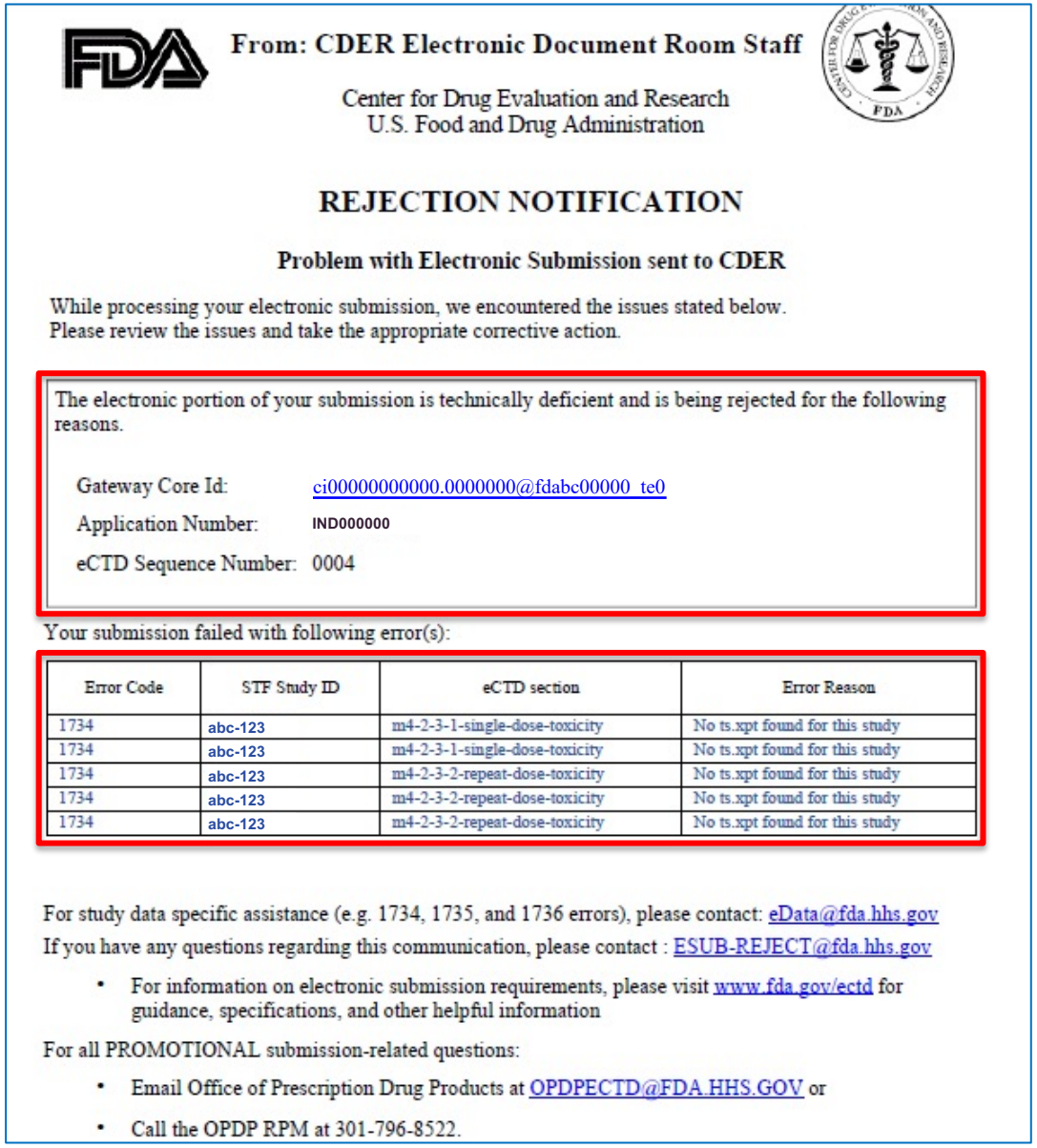
TRC REJECTIONS & TOP ERROR REASONS

REJECTION NOTIFICATIONS

Sponsors receive a rejection notice from FDA when an eCTD validation error is identified.

Rejection notifications specify each error and provide:

- Error Code
- Error Reason
- STF Study ID (if applicable)
- eCTD Section



From: CDER Electronic Document Room Staff

Center for Drug Evaluation and Research
U.S. Food and Drug Administration

REJECTION NOTIFICATION

Problem with Electronic Submission sent to CDER

While processing your electronic submission, we encountered the issues stated below.
Please review the issues and take the appropriate corrective action.

The electronic portion of your submission is technically deficient and is being rejected for the following reasons.

Gateway Core Id: ci00000000000.0000000@fdabc00000_te0
Application Number: IND000000
eCTD Sequence Number: 0004

Your submission failed with following error(s):

Error Code	STF Study ID	eCTD section	Error Reason
1734	abc-123	m4-2-3-1-single-dose-toxicity	No ts.xpt found for this study
1734	abc-123	m4-2-3-1-single-dose-toxicity	No ts.xpt found for this study
1734	abc-123	m4-2-3-2-repeat-dose-toxicity	No ts.xpt found for this study
1734	abc-123	m4-2-3-2-repeat-dose-toxicity	No ts.xpt found for this study
1734	abc-123	m4-2-3-2-repeat-dose-toxicity	No ts.xpt found for this study

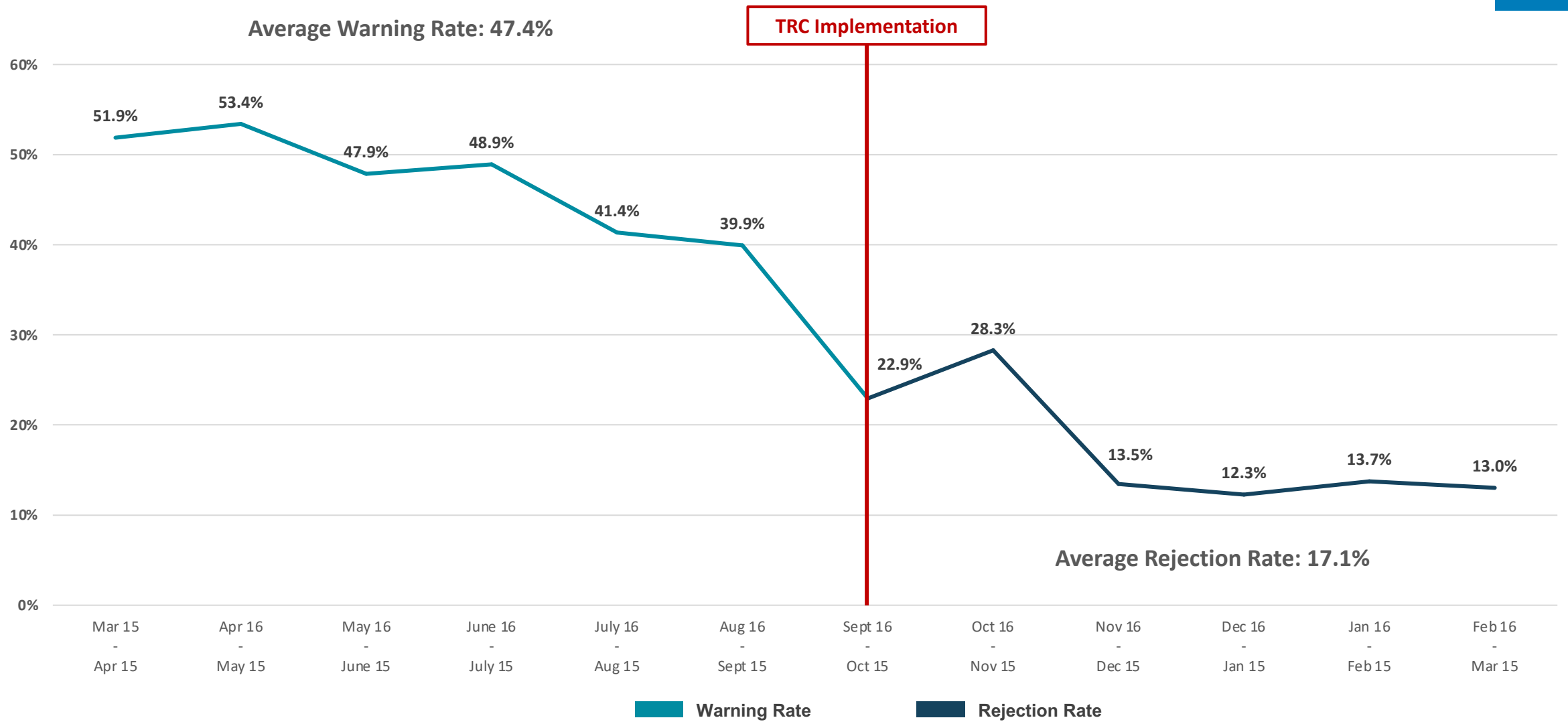
For study data specific assistance (e.g. 1734, 1735, and 1736 errors), please contact: eData@fda.hhs.gov
If you have any questions regarding this communication, please contact : ESUB-REJECT@fda.hhs.gov

- For information on electronic submission requirements, please visit www.fda.gov/ectd for guidance, specifications, and other helpful information

For all PROMOTIONAL submission-related questions:

- Email Office of Prescription Drug Products at OPDPECTD@FDA.HHS.GOV or
- Call the OPDP RPM at 301-796-8522.

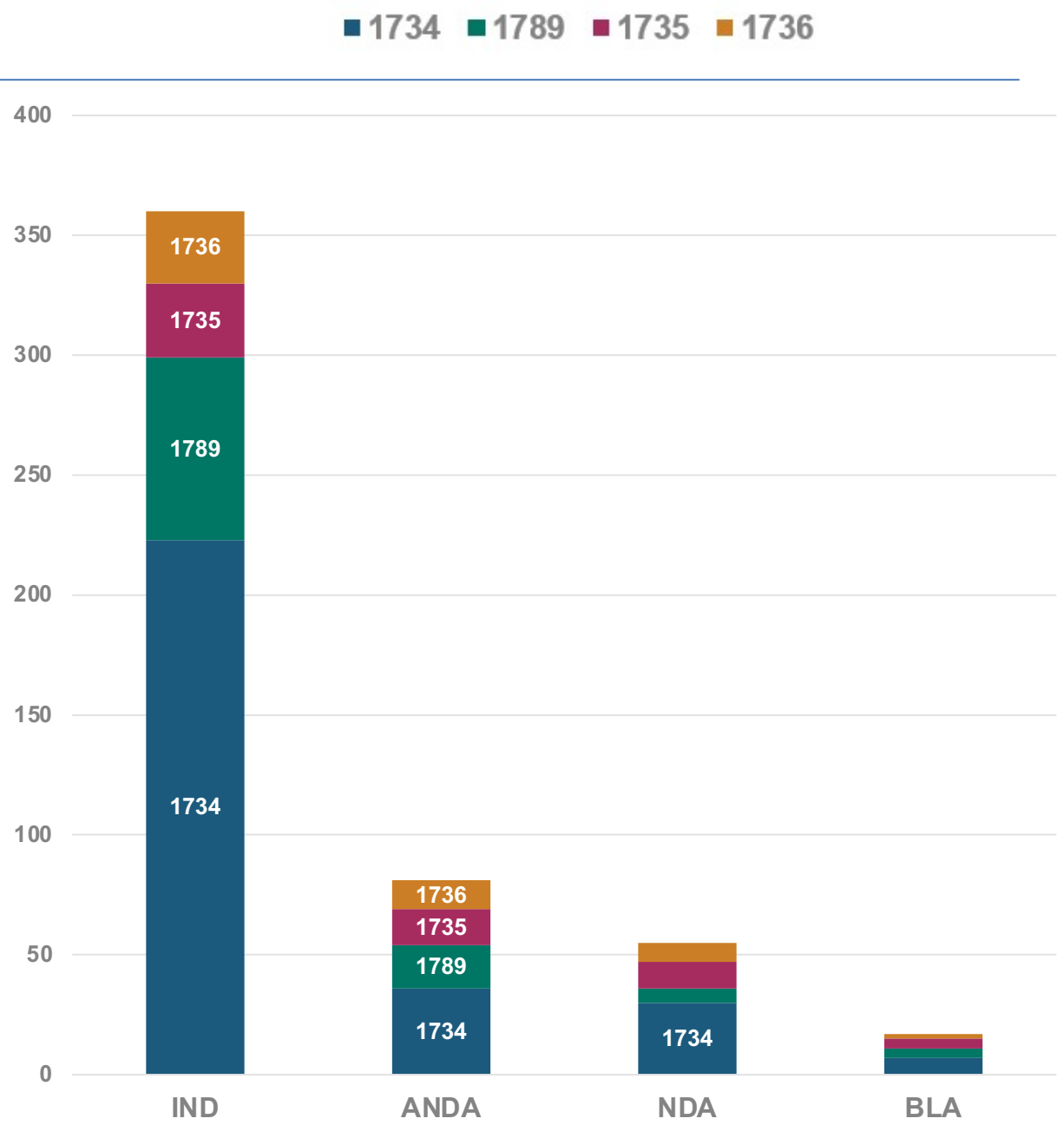
MONTHLY TRC WARNING & REJECTION TREND (CDER)



Notes: *Metrics generated from data between March 15, 2021 and March 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
- Commercial IND submissions have highest number of failures overall and have particularly high numbers of 1734 errors



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

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

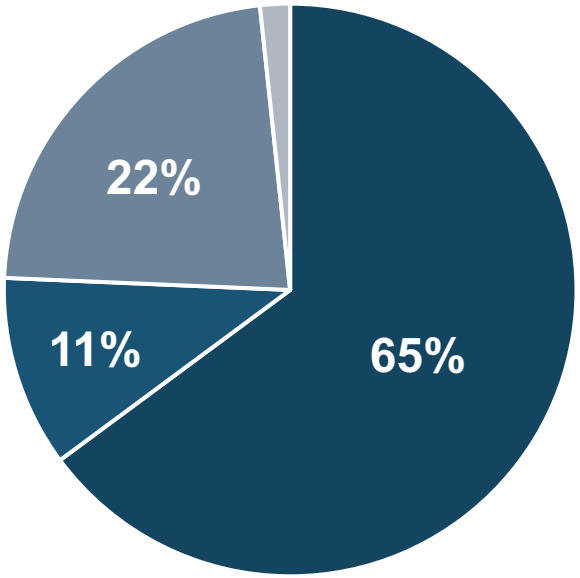
ADDRESSING TOP ERRORS: 1734

- **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



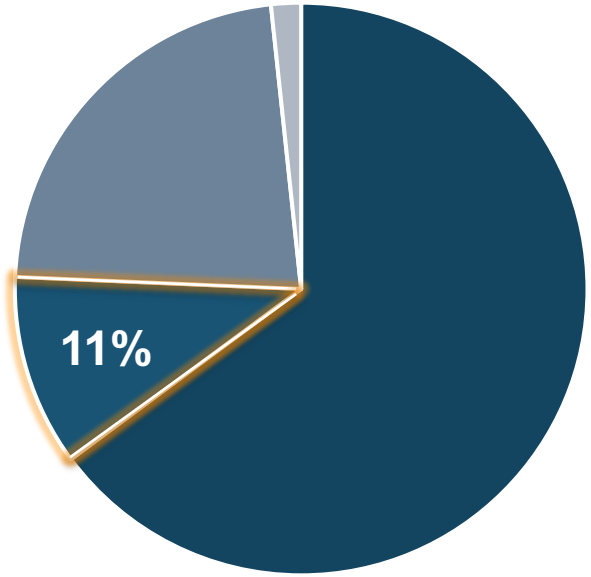
65% due to Missing ts.xpt

86% 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

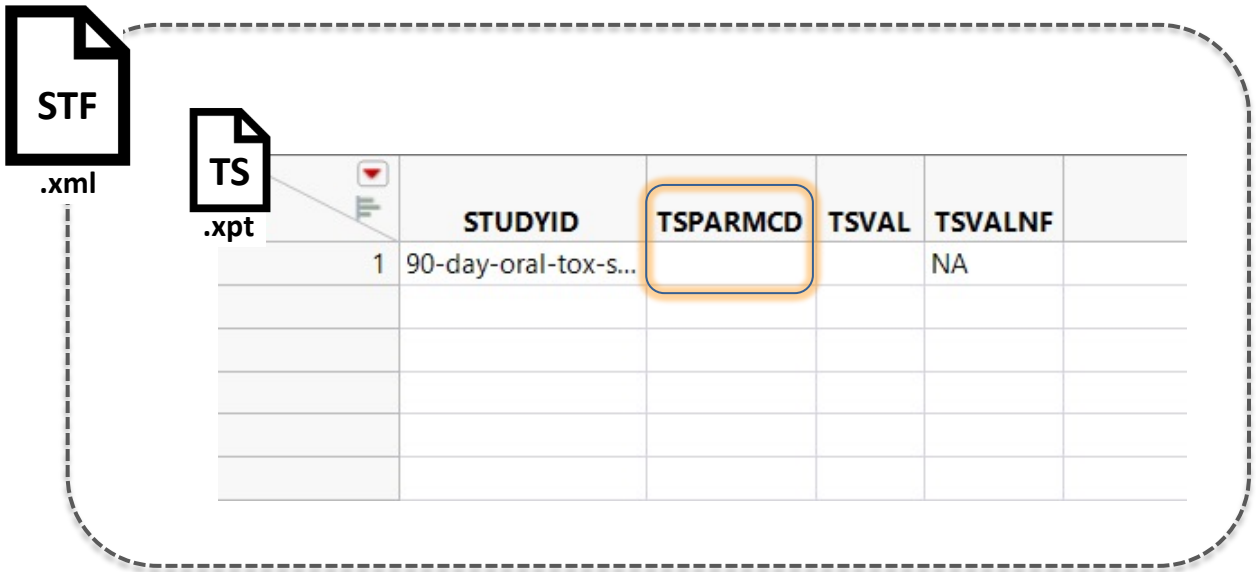
Note: 296 1734 Study Errors between Sept. 15 – Mar. 15, 2022

ADDRESSING TOP ERRORS: 1734



- 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

Simplified ts.xpt referenced by the study causes a 1734 failure for missing study start date:



	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	90-day-oral-tox-s...			NA

Causes of 1734 Missing Study Start Date:

- Missing Value for SSD
- Missing Parameter Code
- Incorrect Parameter Code

Note: 296 1734 Study Errors between Sept. 15 – Mar. 15, 2022

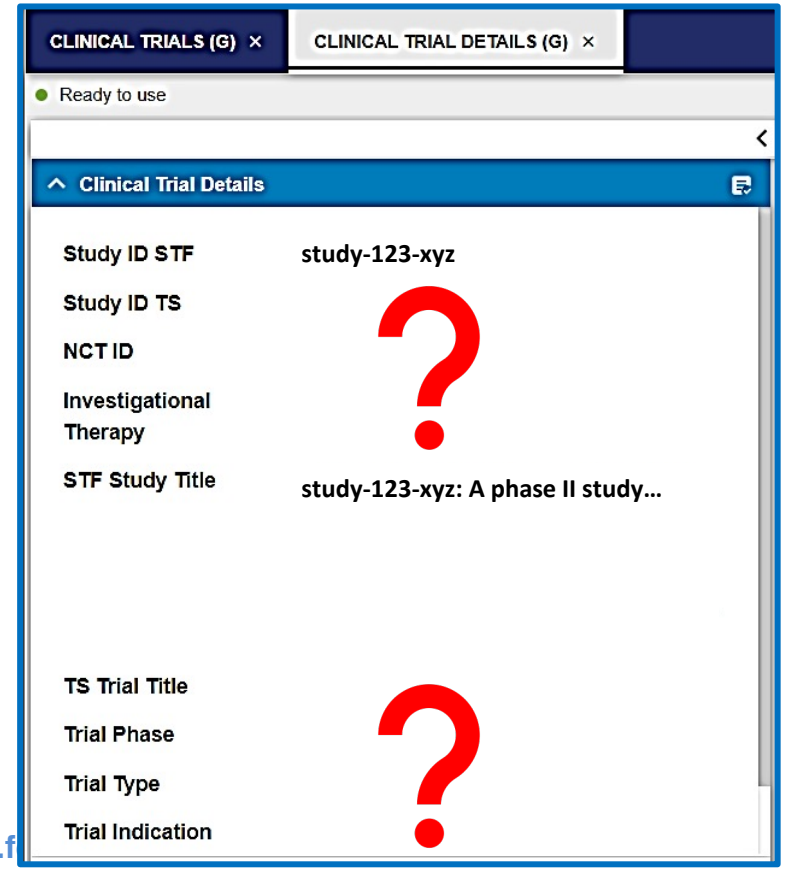
IMPORTANCE OF STANDARDIZED STUDY DATA

WHY IS 1734 IMPORTANT?

Missing ts.xpt:

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

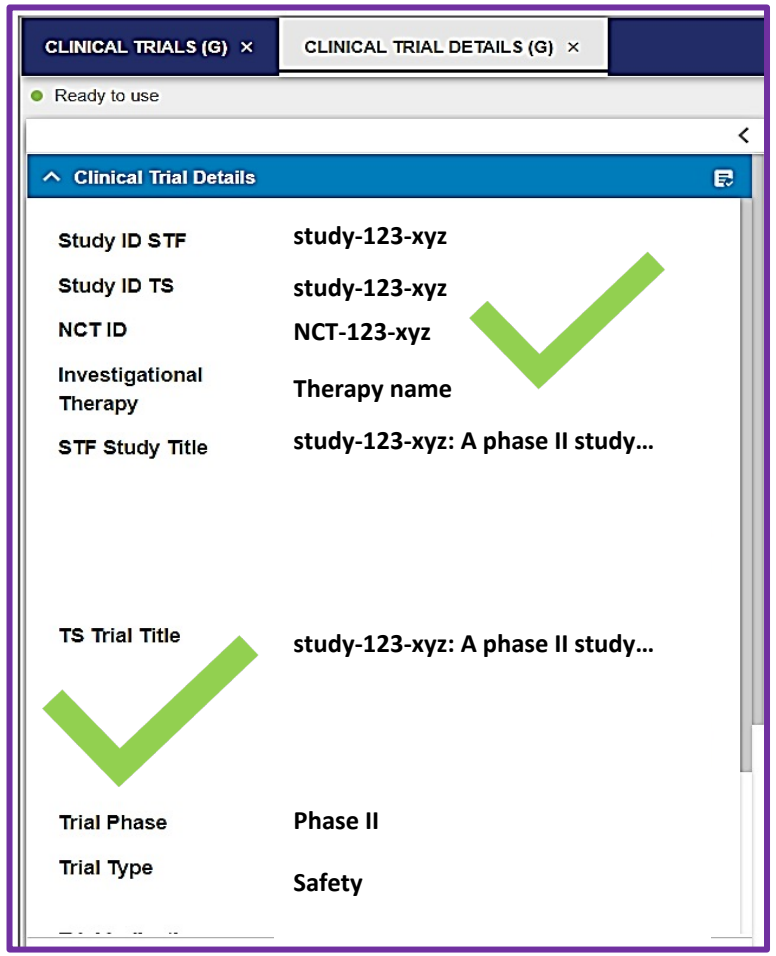
X Cannot connect to other clinical trial data and limits details available to reviewers



When a ts.xpt is included:

✓ Enables detailed searches

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



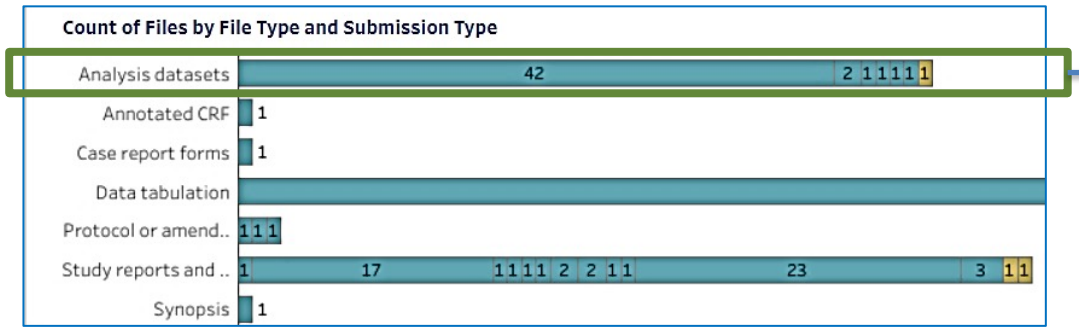
WHY ARE 1735 & 1736 IMPORTANT?

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:

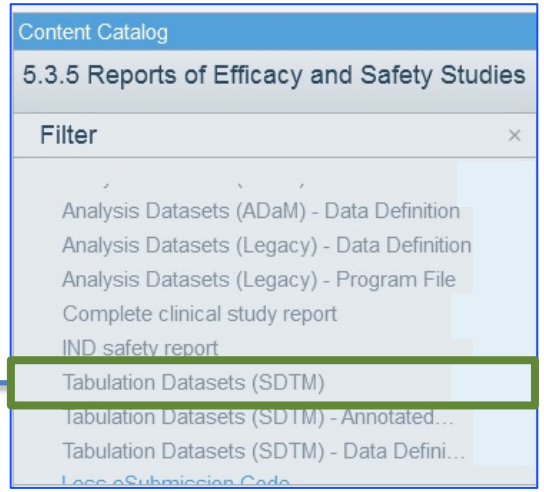
- ✓ Enables detailed searches by file type
- ✓ Enables filtering by file type
- ✓ Enables locating essential study files, including dm.xpt, adsl.xpt, and define.xml
- ✓ Enables automated loading into analysis applications

Reports & Filtering:

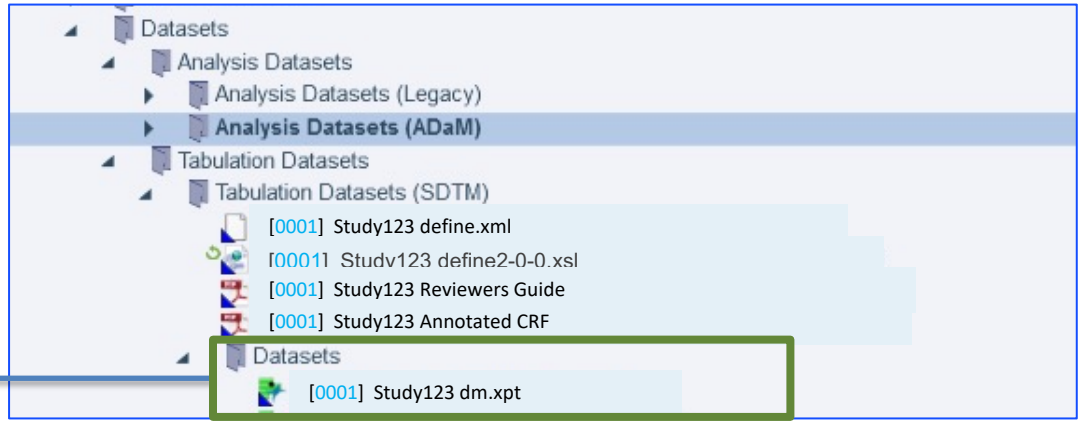


ADaM Datasets Grouped

eCTD Viewer:



SDTM Datasets Grouped



REFERENCES

- **Study Data Standards Resources**
  - Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [June 2021]
  - FDA Data Standards Catalog [February 2022]
  - Study Data Technical Conformance Guide [March 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
- **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

ADDITIONAL QUESTIONS

For questions please contact:

Study Data Questions:
edata@fda.hhs.gov

eCTD Questions:
esub@fda.hhs.gov

Questions for CBER:
cber-edata@fda.hhs.gov