Technical Rejection Criteria for Study Data (TRC) and Beyond

PHUSE US Connect 2023

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CDER | US FDA

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PRESENTER

Lina Cong

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Office of Business Informatics, EDATA Team

CDER | US FDA

Lina Cong has a medical and computer background with over ten years of experience on study data standards and study data submissions in FDA. She also has ten years of experience on clinical trial data analysis and clinical data management within the pharmaceutical industry.

AGENDA

- TRC Background & What's New
- Overview of the Technical Rejection Criteria (TRC)
- TRC Rejections & Top Error Reason
- Importance of Standardized Study Data
- Tools to Help Industry Pass TRC Validation
- Frequently Asked Questions

TRC BACKGROUND & WHAT'S NEW

PURPOSE OF ECTD AND STUDY DATA REQUIREMENTS

- Reviewing study data in a timely manner is critical for FDA's review process (e.g. Reviewers have 30 days to review an IND application)
- When sponsors submit data to the FDA in a reliable and accessible format, it improves efficiency and consistency of review decisions
- CDISC Standards enable FDA to streamline the review process:
  - Reduce time for reviewers to locate and identify study data
  - Reduce the burden on sponsors and reviewers from IRs (Information Requests)
  - Reduce review time by enabling the use of COTS reviewer's tools such as JMP, JMP Clinical, etc. to automate review analyses
  - Support data driven decisions by applying data mining and data analytic techniques

"The agreement to assemble all the Quality, Safety and Efficacy information in a common format (called CTD - Common Technical Document) has revolutionized the regulatory review processes, led to harmonized electronic submission that, in turn, enabled implementation of good review practices. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities."

Source: https://www.ich.org/products/ctd.html

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:**
  - 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
- Electronic Common Technical Document (eCTD) website
- Study Data for Submission to CDER and CBER website
- SBIA Webinar, FDA Study Data Technical Rejection Criteria (TRC): What you need to know!

WHAT'S NEW

- CBER Non-clinical study requirements will start after March 15, 2023
- Rule 1734 will no longer check for study ID matching

- Changes to other study data validations:
  - New Validation Rule 1738 for study ID matching
  - Change of scope for Validation Rule 1737

WHAT'S NEW (EFFECTIVE AFTER 3/15/2023)

TRC Updates

1. **CBER SEND Date Requirements**
   - CBER now requires SEND datasets for non-clinical studies with a Study Start Date after 3/15/2023
   - Date applies to all application types
2. **1734 – Remove Study ID Matching**
   - 1734 no longer validates for STUDYID mismatch between ts.xpt and STF file
   - New validation rule 1738 now validates STUDYID matching
3. **1735 – Allow define.xml Files to be Tagged as "data-listing-data-definition"**
   - A Define.xml file tagged as "data-listing-data-definition" no longer triggers a 1735 error

Other Study Data Validation Updates

1. **1737 – Apply Rule to All Sections Except 4.3, 5.2, 5.4, & 5.3.6 Postmarketing reports**
   - 1737 now applies to same sections as validation rule 1789
   - Medium severity error
   - 1737 is not currently included in the Self-Check Worksheet
2. **1738 – New Study ID Matching Rule**
   - 1738 is not currently included in the Self-Check Worksheet
   - 1738 now validates for STUDYID mismatch between ts.xpt and STF file
   - Medium severity error
   - Applies to all sections except 4.3, 5.2, 5.4, & 5.3.6 Postmarketing reports

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

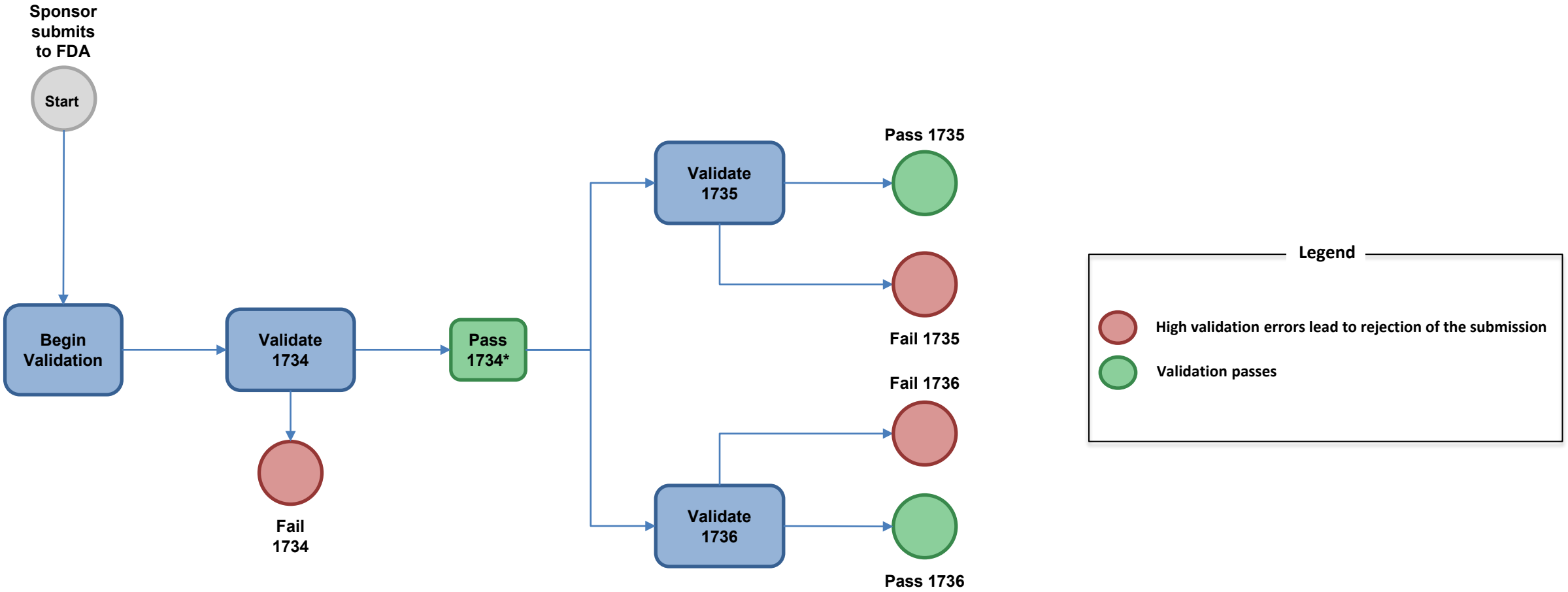
For more information, please reference the Study Data Technical Conformance Guide v5.0 (October 2022)

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, 3/16/2023)
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, 3/16/2023)
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, 3/16/2023)

** 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



** Not every submission will proceed beyond 1734 to 1735 and 1736, depending on the Study Start Date (SSD)*

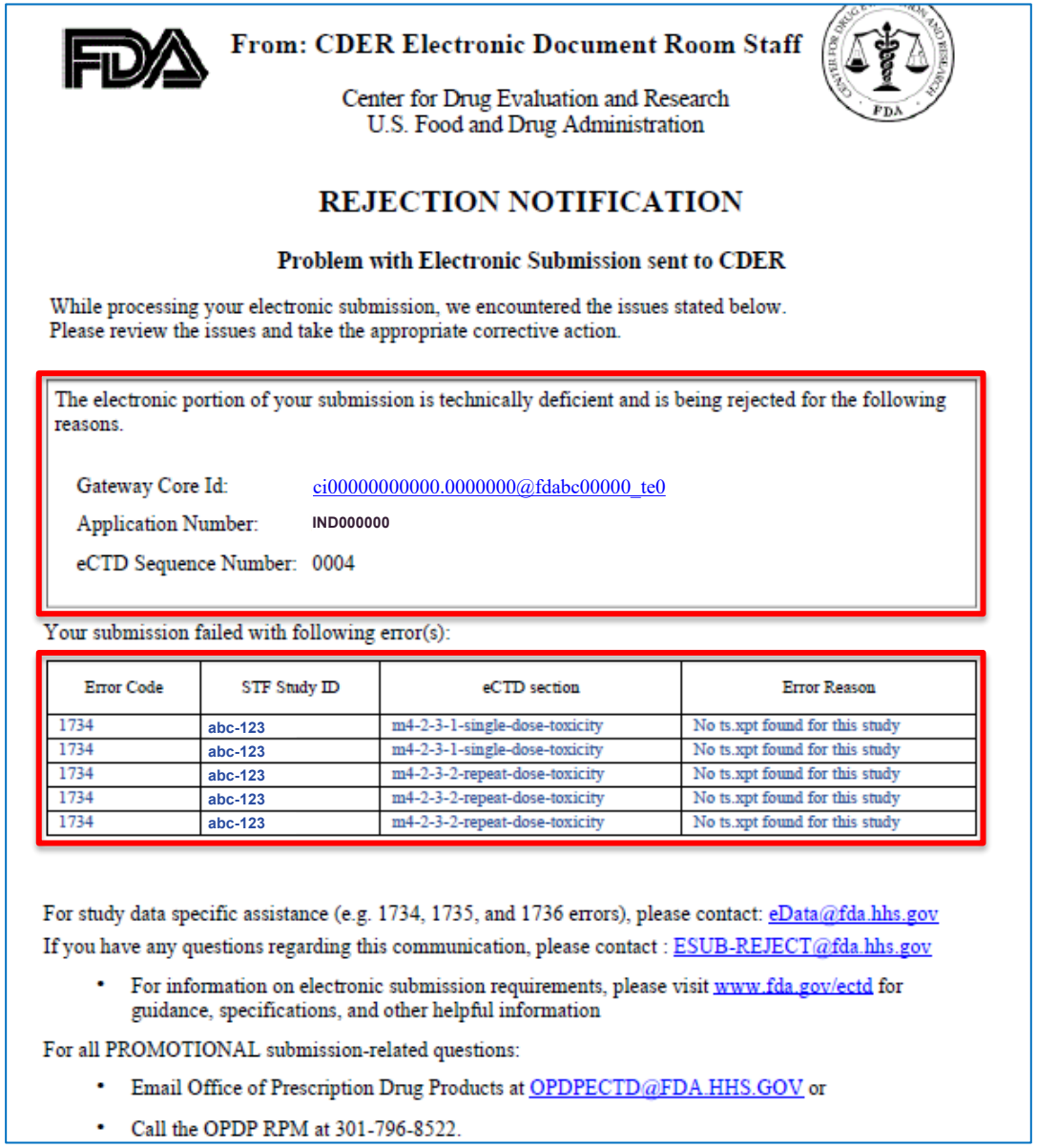
TRC REJECTIONS & TOP ERROR REASONS

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

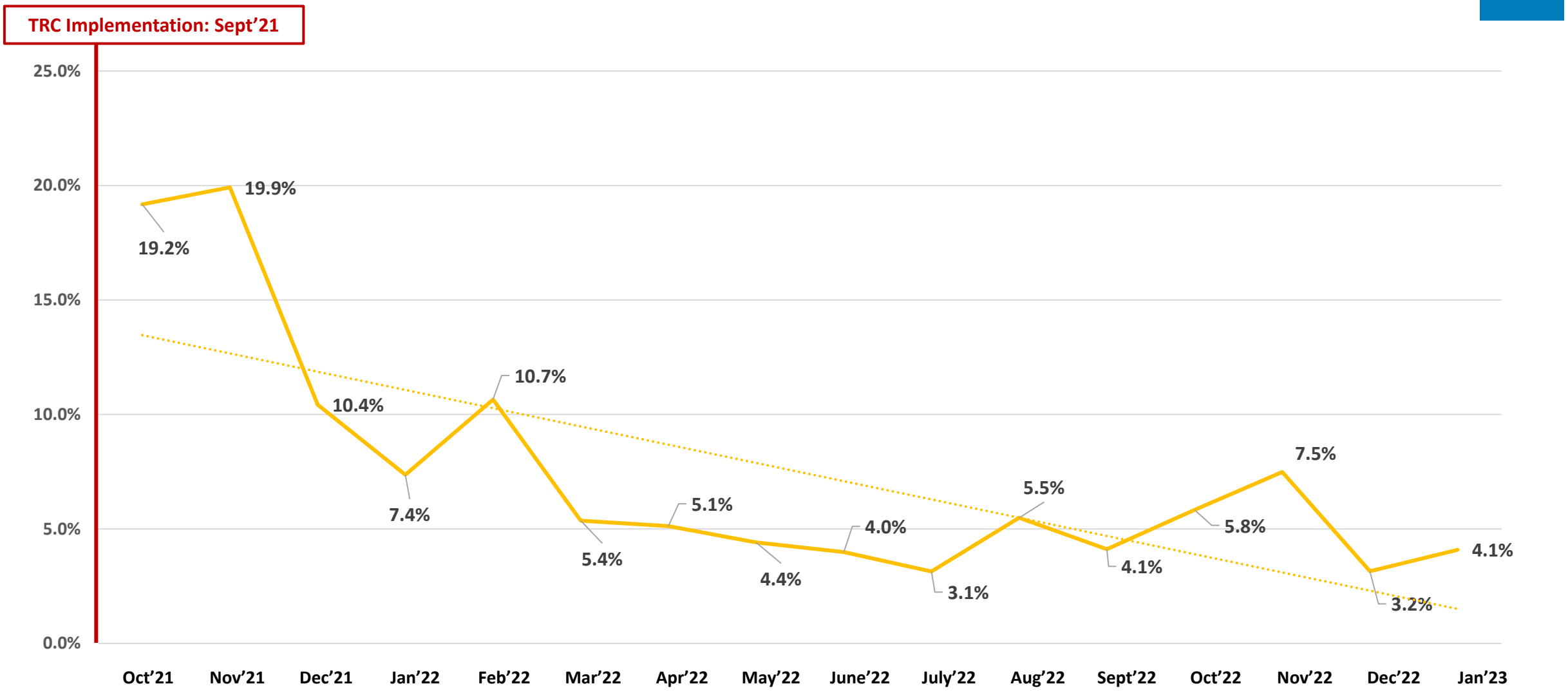
For study data specific assistance (e.g. 1734, 1735, and 1736 errors), please contact: eData@fda.hhs.gov
If you have any questions regarding this communication, please contact : ESUB-REJECT@fda.hhs.gov

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

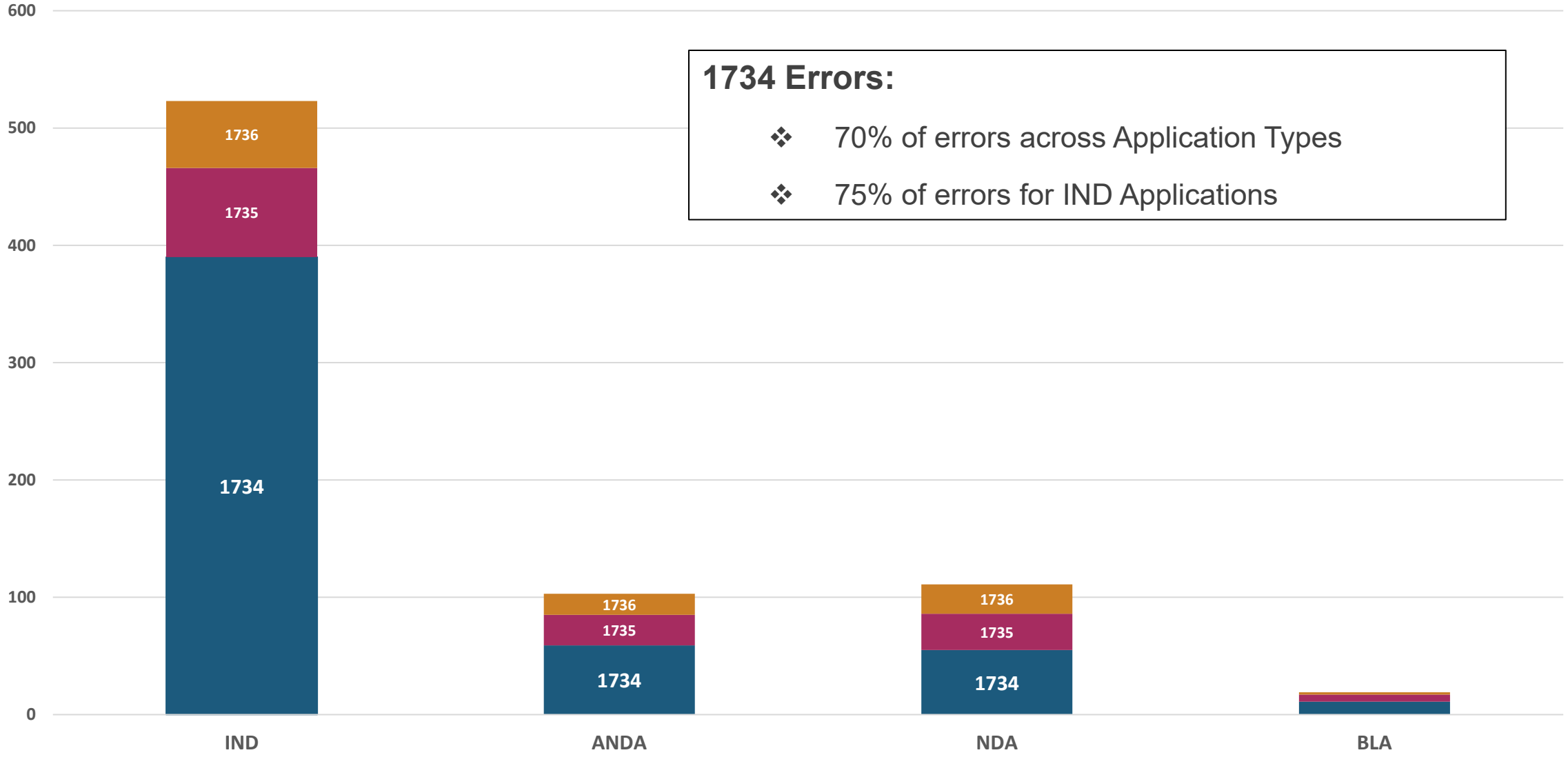
For all PROMOTIONAL submission-related questions:

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

MONTHLY TRC REJECTION TREND (CDER)



CDER TRC REJECTIONS



1734 Errors:

- 70% of errors across Application Types
- 75% of errors for IND Applications

Timeframe: September 15, 2021 – January 31, 2023

ADDRESSING TOP ERROR: 1734

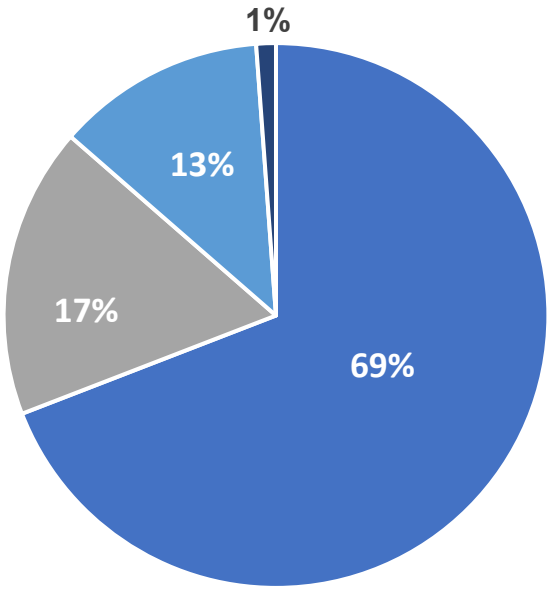
- **75% of all 1734 errors are from studies in IND Applications**

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

*moving to rule 1738, effective after 3/15/2023



69% due to Missing ts.xpt

87% 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: 506 1734 Study Errors between Sept. 15, 2022 – Jan. 31, 2023

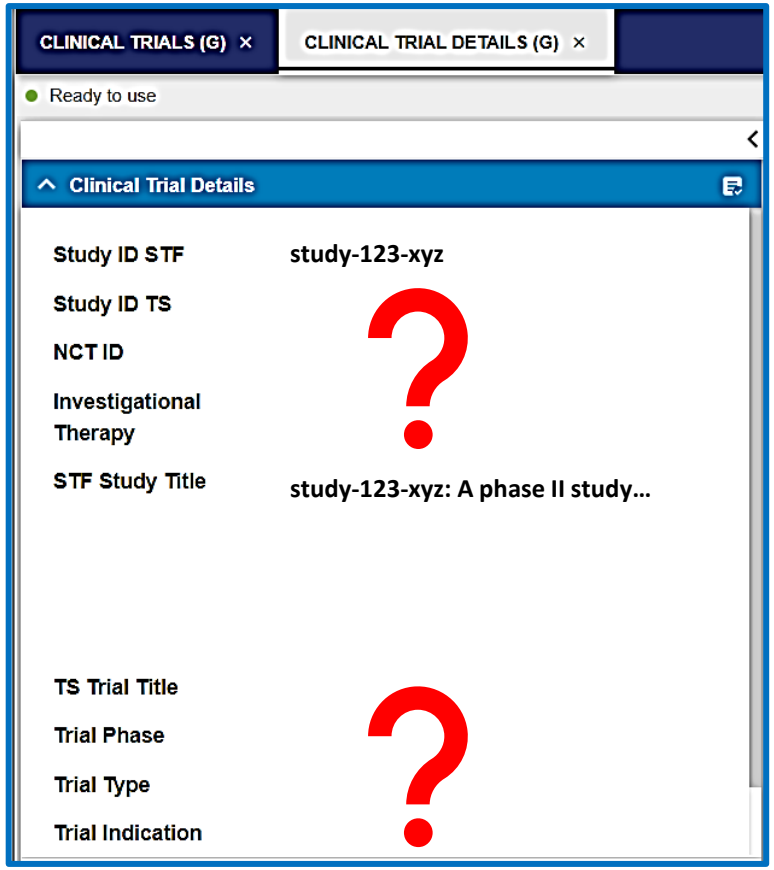
IMPORTANCE OF STANDARDIZED STUDY DATA

WHY IS 1734 IMPORTANT?

Missing ts.xpt:

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

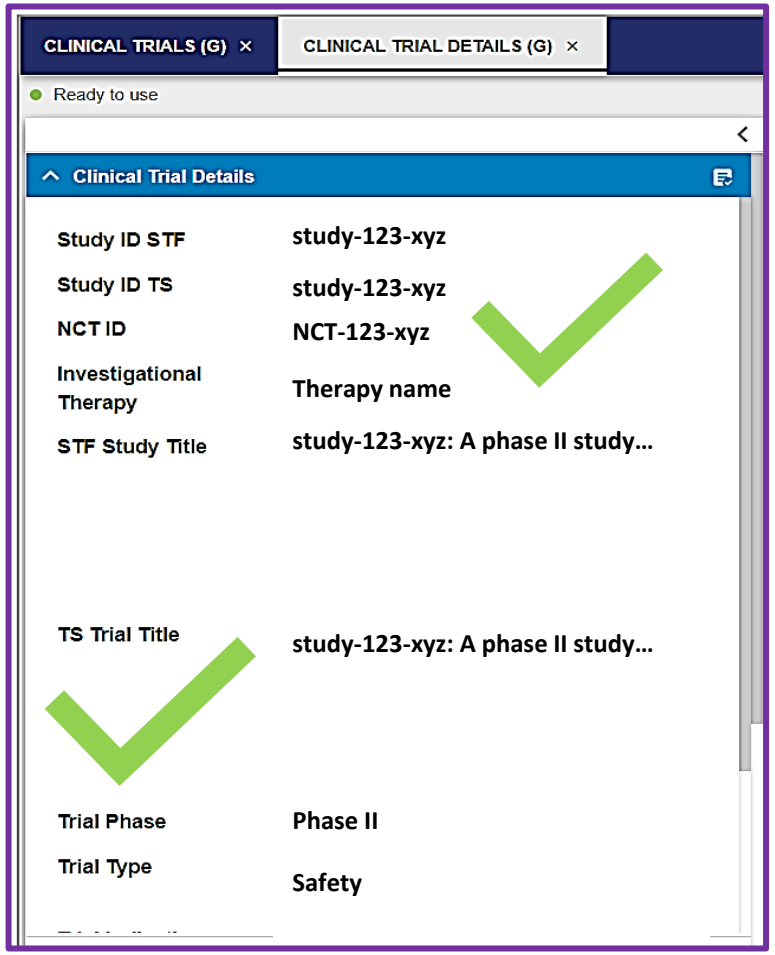
X Cannot connect to other clinical trial data and limits details available to reviewers



When a ts.xpt is included:

✓ Enables detailed searches

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



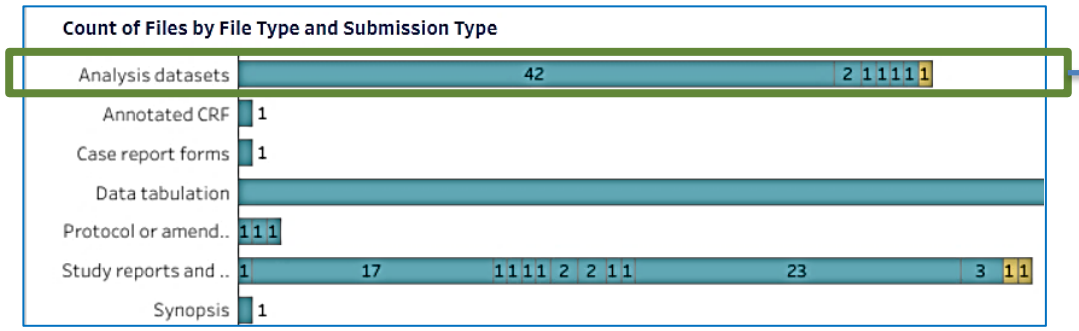
WHY ARE 1735 & 1736 IMPORTANT?

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

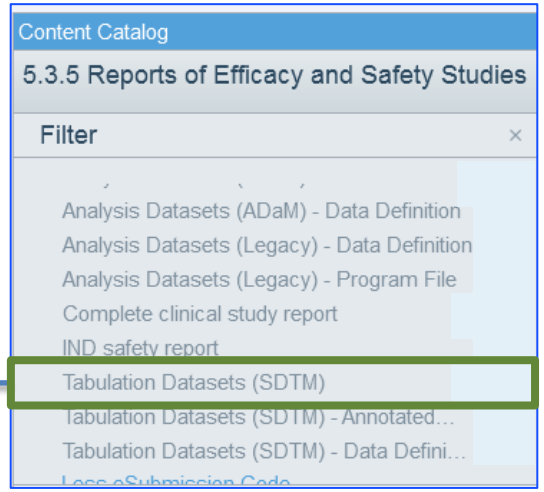
Reports & Filtering:

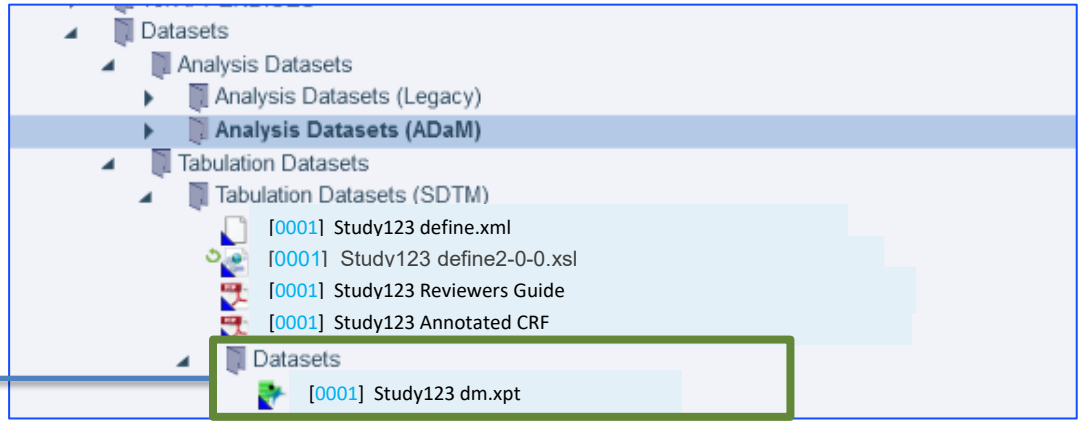


ADaM Datasets Grouped

SDTM Datasets Grouped

eCTD Viewer:





TOOLS TO HELP INDUSTRY PASS TRC VALIDATION

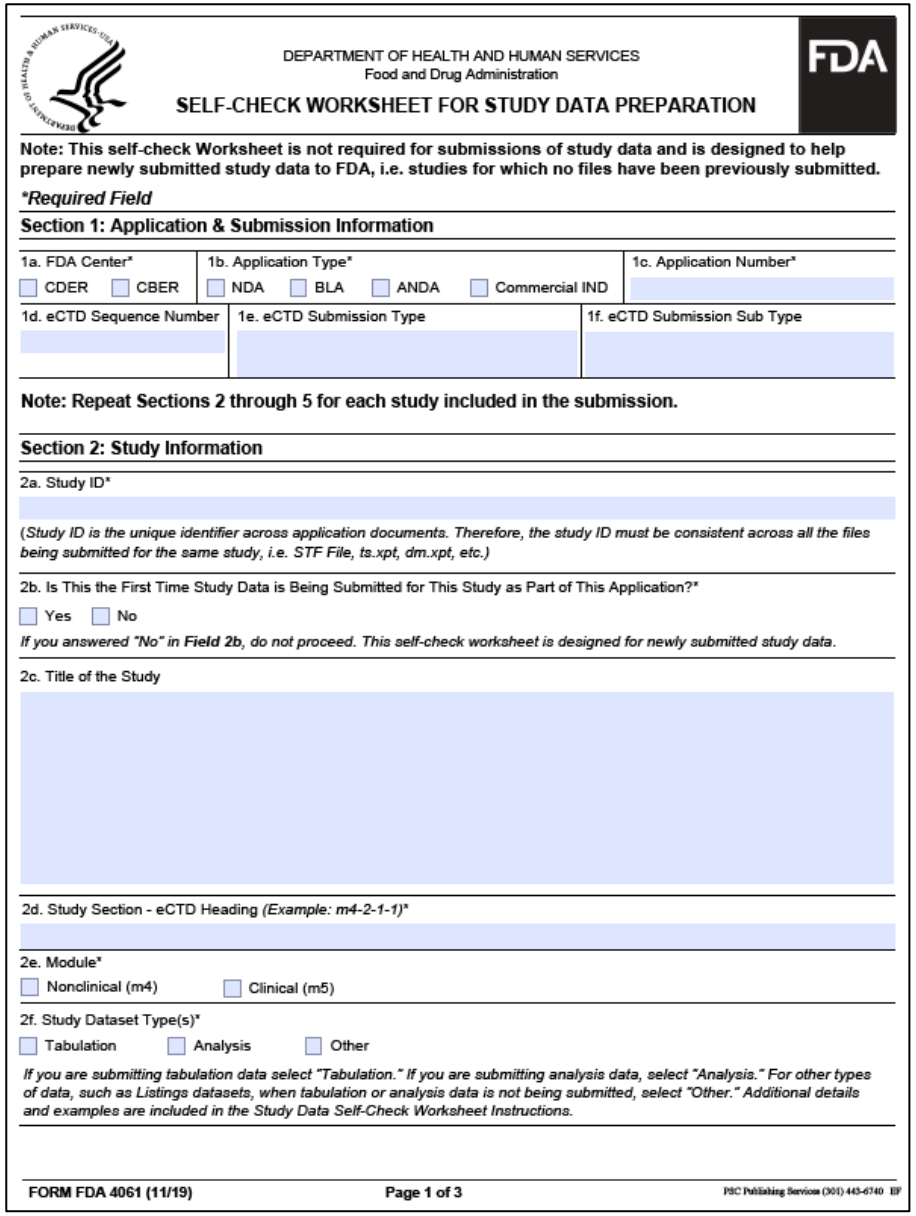
THE SELF-CHECK WORKSHEET

- Designed to walk sponsors through each step of the TRC validation process
- Dynamically guides sponsors through study data requirements based on study information entered
- Helps sponsors prepare study data to submit to the FDA for the first time

[Demonstration Videos & Other Supporting Material]

[Technical Rejection Criteria Self-Check Worksheet]

[Self-Check Worksheet Instructions]



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

SELF-CHECK WORKSHEET FOR STUDY DATA PREPARATION

Note: This self-check Worksheet is not required for submissions of study data and is designed to help prepare newly submitted study data to FDA, i.e. studies for which no files have been previously submitted.

**Required Field*

Section 1: Application & Submission Information

1a. FDA Center*	1b. Application Type*	1c. Application Number*
☐ CDER ☐ CBER	☐ NDA ☐ BLA ☐ ANDA ☐ Commercial IND	

1d. eCTD Sequence Number	1e. eCTD Submission Type	1f. eCTD Submission Sub Type

Note: Repeat Sections 2 through 5 for each study included in the submission.

Section 2: Study Information

2a. Study ID*

(Study ID is the unique identifier across application documents. Therefore, the study ID must be consistent across all the files being submitted for the same study, i.e. STF File, ts.xpt, dm.xpt, etc.)

2b. Is This the First Time Study Data is Being Submitted for This Study as Part of This Application?*

☐ Yes ☐ No

*If you answered "No" in **Field 2b**, do not proceed. This self-check worksheet is designed for newly submitted study data.*

2c. Title of the Study

2d. Study Section - eCTD Heading *(Example: m4-2-1-1)**

2e. Module*

☐ Nonclinical (m4) ☐ Clinical (m5)

2f. Study Dataset Type(s)*

☐ Tabulation ☐ Analysis ☐ Other

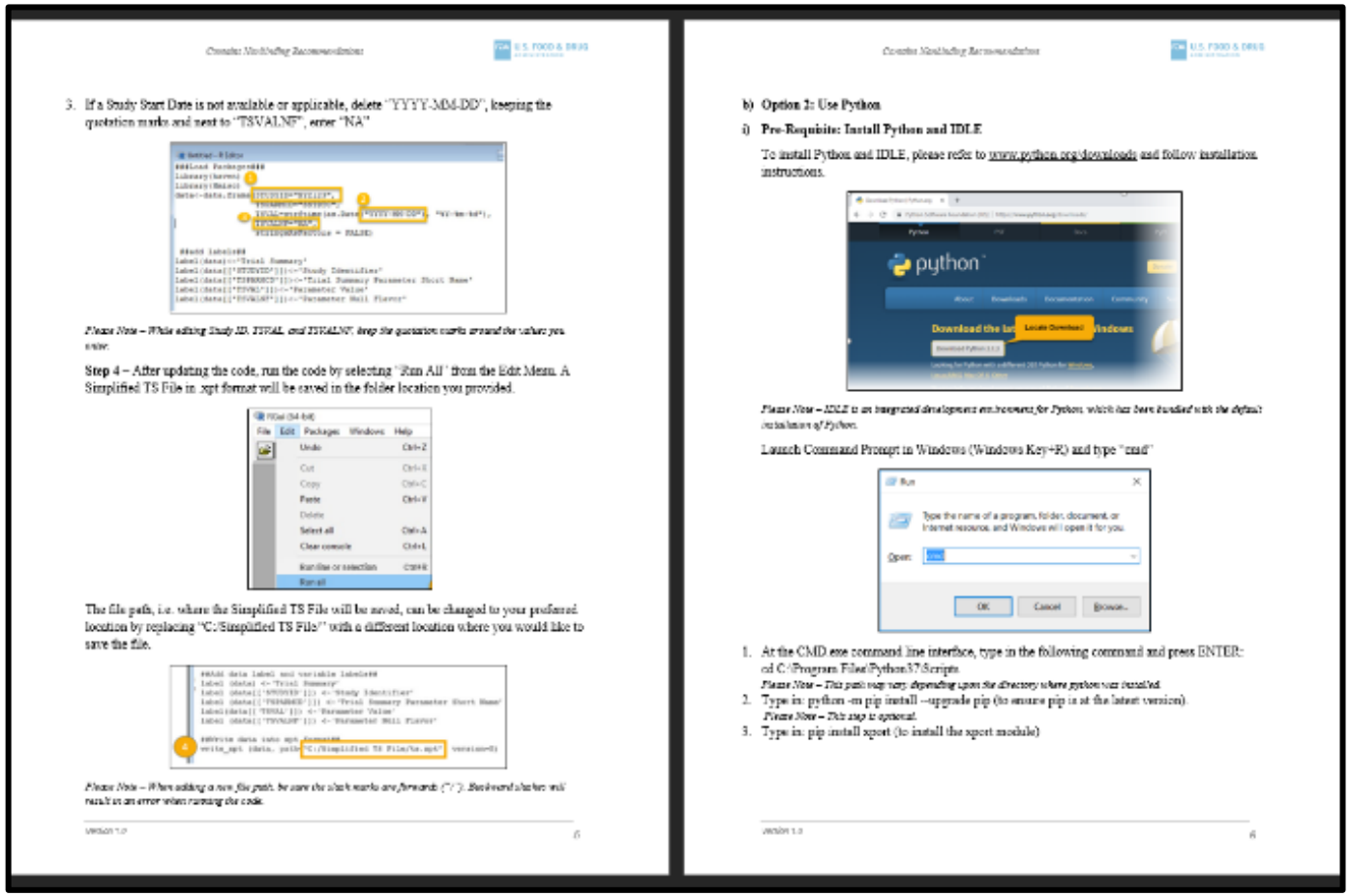
If you are submitting tabulation data select "Tabulation." If you are submitting analysis data, select "Analysis." For other types of data, such as Listings datasets, when tabulation or analysis data is not being submitted, select "Other." Additional details and examples are included in the Study Data Self-Check Worksheet Instructions.

FORM FDA 4061 (11/19) **Page 1 of 3** PSC Publishing Services (301) 443-6740 EF

THE SIMPLIFIED TS.XPT CREATION GUIDE

- ❖ Helps industry create simplified TS files using free and open-source software, R and Python

- Provides step by step instructions to install the necessary software
- Users can copy and paste code samples from the guide into R or Python
- Available on FDA's web page, *Study Data for Submission to CDER and CBER*
- Demonstration video also available at *Study Data for Submission to CDER and CBER*
- Additionally, a publicly available tool was developed by PHUSE:
  Simplified ts.xpt File Generator (*https://geotiger.shinyapps.io/07_genTS/*)



FREQUENTLY ASKED QUESTIONS (FAQ)

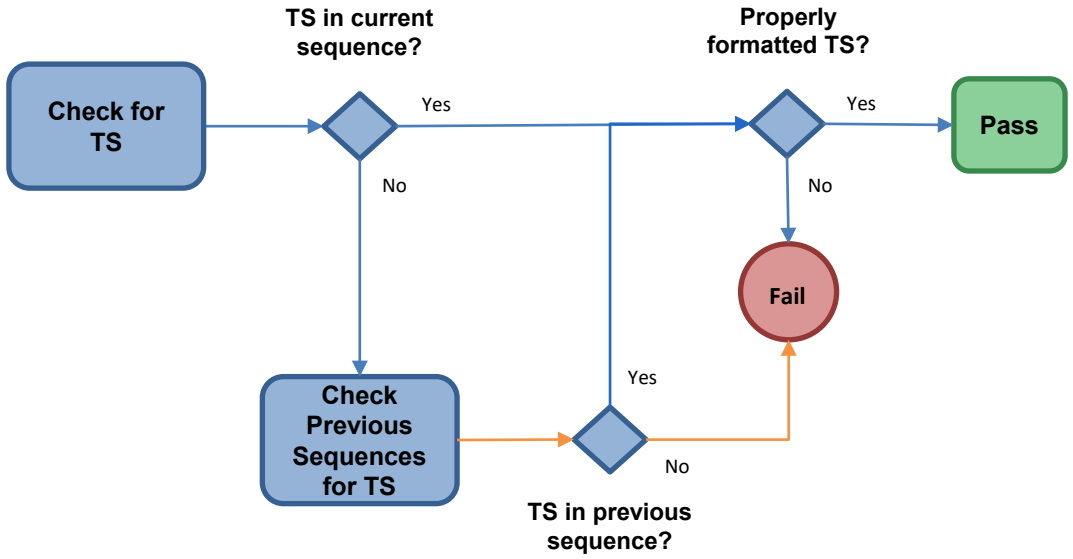
DO I HAVE TO SUBMIT A TS.XPT WITH EVERY SUBMISSION TO MEET TRC REQUIREMENTS?

- It is not required to submit a ts.xpt with every submission
- Previously submitted ts.xpt must be standardized and properly formatted
- Validations check previously submitted files for Rule 1734 (ts.xpt) and Rule 1736 (dm.xpt, adsl.xpt, and define.xml)

Properly Formatted TS:

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

^Moving to Rule 1738, effective 3/16/2023



HOW CAN MULTIPLE SETS OF DATA BE SUBMITTED FOR THE SAME STUDY?

- Option 1: Submitting multiple sets of data under the same STF
  - Creating sub-folders for each set of data
  - Assigning different leaf titles for each set of data
- Option 2: Submitting multiple sets of data under different STFs
  - Using different STFs for each sets of data – treat each set of data as different studies

REFERENCES

- **Study Data Standards Resources**
  - Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [April 2022]
  - Study Data Technical Conformance Guide [October 2022]
  - FDA Data Standards Catalog [August 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 [December 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

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