Paper DS08

Technical Rejection Criteria for Study Data (TRC) and Beyond

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ABSTRACT

Study data is the most import part of the drug application submission. The submitting standardized study data could accelerate the drug review process and make the drug review more efficient.

In order to comply with FDA Study Data Guidance and enforce the CDISC standards data submission, FDA developed Technical Rejection Criteria for Study Data (TRC) to help industry understand how FDA is using eCTD validations to check conformance. Starting Sept 15th, 2021 eCTD validations for study data in TRC took effective. if a submission fails eCTD validations for study data in TRC, the submissions will be rejected. This paper contains the TRC background, the update of the rejection trend for eCTD validations for study data, TRC rejections & top error reasons. Beyond TRC, Frequently Ask Questions related study data submissions and study data standards from eData mailbox will be included.

INTRODUCTION

This paper introduce TRC Background & What's New, Overview of the Technical Rejection Criteria (TRC), TRC Rejections & Top Error Reason, Importance of Standardized Study Data, Frequently Asked Questions. It will help sponsors or applicants to understand Technical Rejection Criteria for Study Data and how to prepare the study data submission to comply with Technical Rejection Criteria.

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

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

WHAT'S NEW for TRC (Effective after 3/15/2023):

- ❖ 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`

Overview of the Technical Rejection Criteria (TRC)

TRC Important Dates

- ❖ **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

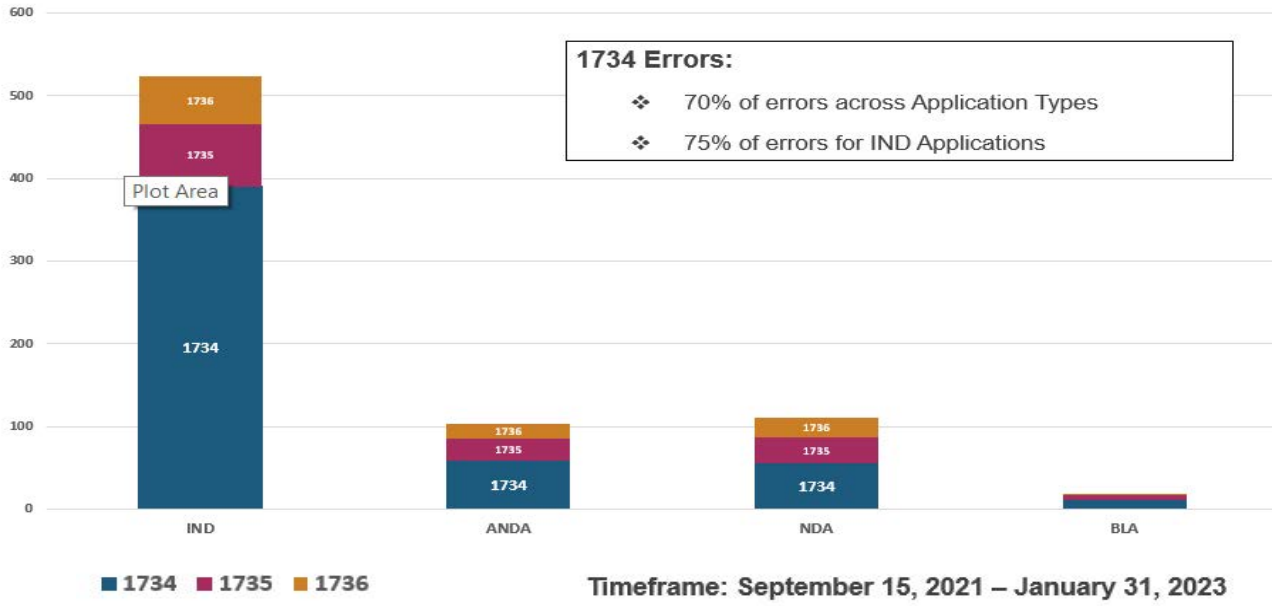
- ❖ **09/15/2021 – TRC rejections began**
- ❖ **03/16/2023 – CBER Non-Clinical requirements begin**

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**

CDER TRC Rejections



ADDRESSING TOP ERROR: 1734

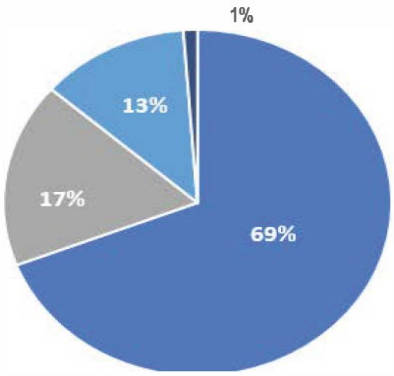
- **75% of all 1734 errors are from studies in IND Applications**

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

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)

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

For questions please contact:

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