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

For submissions to CBER and CDER

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The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.
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
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
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)
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.
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
<table>
<thead>
<tr>
<th>Error</th>
<th>Description (Reference to Specifications for eCTD Validation Criteria)</th>
<th>Severity Level</th>
<th>Effective Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1734</td>
<td>A dataset named ts.xpt with information on study start date must be present for each study in required sections*</td>
<td>High</td>
<td>9/15/2021 (CBER module 4 sections, 03/16/2023)</td>
</tr>
<tr>
<td>1735</td>
<td>The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*</td>
<td>High</td>
<td>9/15/2021 (CBER module 4 sections, 03/16/2023)</td>
</tr>
</tbody>
</table>
| 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, 5.3.1.3, 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

Legend
- Validation errors lead to rejection of the submission
- When no validation errors occur, the submission is not rejected

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www.fda.gov

Start
Sponsor submits to FDA

Begin Validation

Identify Study Files

Are there study files submitted in applicable sections?†

Y

N

End Validation

Validate TS.XPT

Is a TS File Present?‡

Y

N

Pass 1734

Fail 1734

Is Study ID or SPREFID Valid?∂

Y

N

Is Study Start Date (SSD) Valid?тех

Y

N

Does TSVALNF = NA or is SSD before the cut-off date?

Y

N

Validate File Tags

Are Files Tagged Correctly?

Y

Pass 1735

N

Fail 1735

Validate Key Study Files P

Are Key Files Present?

Y

Pass 1736

N

Fail 1736

† 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
тех Valid Study Start Date in ISO 8601 format (i.e. YYYY-MM-DD)
P Key Files are dm.xpt or adsl.xpt and corresponding define.xml
CDER & CBER SEND REQUIREMENTS & TRC
The following nonclinical study types are required to have SEND datasets as defined by study initiation date:

<table>
<thead>
<tr>
<th>Study Types Modeled in SEND</th>
<th>NDAs/BLAs</th>
<th>Commercial INDs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single Dose Toxicity, Repeat Dose Toxicity, and Carcinogenicity Studies</strong></td>
<td>December 17, 2016</td>
<td>December 17, 2017</td>
</tr>
<tr>
<td></td>
<td>(SENDIG v3.0)</td>
<td>(SENDIG v3.0)</td>
</tr>
<tr>
<td></td>
<td>March 15, 2019</td>
<td>March 15, 2020</td>
</tr>
<tr>
<td></td>
<td>(SENDIG v3.1)</td>
<td>(SENDIG v3.1)</td>
</tr>
<tr>
<td><strong>Cardiovascular and Respiratory Safety Pharmacology Studies</strong></td>
<td>March 15, 2019</td>
<td>March 15, 2020</td>
</tr>
<tr>
<td></td>
<td>(SENDIG v3.1)</td>
<td>(SENDIG v3.1)</td>
</tr>
<tr>
<td><strong>Animal Rule (Natural History and Efficacy Studies)</strong></td>
<td>March 15, 2022</td>
<td>March 15, 2023</td>
</tr>
<tr>
<td></td>
<td>(SENDIG AR v1.0)</td>
<td>(SENDIG AR v1.0)</td>
</tr>
</tbody>
</table>
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).

For nonclinical studies, the current Technical Rejection Criteria (TRC) will only apply to eCTD Modules 4.2.3.1 (single-dose toxicity), 4.2.3.2 (repeat-dose toxicity), and 4.2.3.4 (carcinogenicity).
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

**Automated Process**

1. **Nonclinical Study Report**
   - Send (Full ts.xpt) - SEND Requirement based on Study Type (supported SENDIG) and Study Initiation Date (see FDA Data Standards Catalog)
   - 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)

2. **Neither SEND (TS) nor simplified ts.xpt = TRC Rejection**
TRC REJECTIONS & TOP ERROR REASONS
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
MONTHLY TRC WARNING & REJECTION TREND (CDER)

Average Warning Rate: 47.4%

Average Rejection Rate: 17.1%

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.
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

11%

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

Causes of 1734 Missing Study Start Date:
- Missing Value for SSD
- Missing Parameter Code
- Incorrect Parameter Code

No ts.xpt with value for SSD found (and no null flavor value)

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:

![Diagram showing eCTD Viewer with ADaM and 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