Study Data Technical Rejection Criteria

SEND F2F Spring 2021 Public Meeting

April 27, 2022
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

- Technical Rejection Criteria for Study Data (TRC)
- TRC Conformance Statistics and Trends
- Addressing the Most Common TRC Error
- Importance of Standardized Study Data
Technical Rejection Criteria for Study Data (TRC)
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](#)

www.fda.gov
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)
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.
# eCTD Validation Updates

- **Study Data Validation Effective Date updated:**
  
  9/15/2021 (CBER module 4 sections, 03/16/2023)

<table>
<thead>
<tr>
<th>Error</th>
<th>Description</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>
</tr>
<tr>
<td>1735</td>
<td>Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*</td>
</tr>
</tbody>
</table>
| 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.

<table>
<thead>
<tr>
<th>Error</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1789</td>
<td>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</td>
</tr>
</tbody>
</table>

- 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
TRC Conformance Statistics and Trends
Rejected Submissions: September 15, 2021 – March 15, 2022

- 1734 is the most common error and rejection reason for a missing ts.xpt

- Commercial IND submissions have highest number of errors and rejections overall

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.
228 IND & NDA non-clinical studies failed Rule 1734
71.5% (163 of 228) failed due to a missing ts.xpt
64.0% (146 of 228) were Repeat Dose Toxicology studies

Submitting a simplified ts.xpt for many of these non-clinical studies will greatly reduce the 1734 error rate
SEND datasets require a full ts.xpt

<table>
<thead>
<tr>
<th>Toxicology Sections</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat dose toxicology (m4.2.3.2)</td>
<td>146</td>
</tr>
<tr>
<td>Single dose toxicology (m4.2.3.1)</td>
<td>61</td>
</tr>
<tr>
<td>Carcinogenicity (m4.2.3.4)</td>
<td>21</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>228</strong></td>
</tr>
</tbody>
</table>

228 Non-clinical Studies with Error 1734:

- **Missing TS File**: 71.5%
- **Study ID Mismatch**: 15.8%
- **SSD Incorrectly Formatted**: 12.3%
- **No SSD**: 0.4%

Timeframe: September 15, 2021 – March 15, 2022
### Addressing 1734 Errors: Missing TS File

CDER and CBER expectations for standardized data:

<table>
<thead>
<tr>
<th>Application Type</th>
<th>Data Type</th>
<th>Modules &amp; Sub-Modules</th>
<th>Expectation by CDER</th>
<th>Expectation by CBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA, BLA, ANDA</td>
<td>Non-Clinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td><strong>Study Start Date: On or prior to 2016-12-17</strong>&lt;br&gt;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)</td>
<td><strong>Study Start Date: On or prior to 2023-03-15</strong>&lt;br&gt;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)</td>
</tr>
<tr>
<td>NDA, BLA, ANDA</td>
<td>Clinical</td>
<td>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</td>
<td><strong>Study Start Date: On or prior to 2016-12-17</strong>&lt;br&gt;Rejection criteria will be applied; submit a simplified TS if the study contains an xpt dataset (other than the ts.xpt)</td>
<td><strong>Study Start Date: On or prior to 2023-03-15</strong>&lt;br&gt;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)</td>
</tr>
<tr>
<td>Comm. INDs</td>
<td>Non-Clinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td><strong>Study Start Date: On or prior to 2017-12-17</strong>&lt;br&gt;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)</td>
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<td>Comm. INDs</td>
<td>Clinical</td>
<td>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</td>
<td><strong>Study Start Date: On or prior to 2017-12-17</strong>&lt;br&gt;Rejection criteria will not be applied</td>
<td><strong>Study Start Date: On or prior to 2023-03-15</strong>&lt;br&gt;Rejection criteria will be applied; submit a full TS</td>
</tr>
<tr>
<td>NDA, BLA, ANDA</td>
<td>Non-Clinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td><strong>Study Start Date: After 2016-12-17</strong>&lt;br&gt;Rejection criteria will be applied; submit a full TS</td>
<td><strong>Study Start Date: After 2023-03-15</strong>&lt;br&gt;Rejection criteria will be applied; submit a full TS with standardized data</td>
</tr>
<tr>
<td>NDA, BLA, ANDA</td>
<td>Clinical</td>
<td>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</td>
<td><strong>Study Start Date: After 2016-12-17</strong>&lt;br&gt;Rejection criteria will be applied; submit a full TS</td>
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<td><strong>Study Start Date: After 2023-03-15</strong>&lt;br&gt;Rejection criteria will not be applied</td>
</tr>
</tbody>
</table>
Addressing 1734 Errors: No Study Start Date

Causes of 1734 Missing Study Start Date:

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

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

- No SSD
  - 12.3%
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:**

- **Organized by Study Title and ID**
- **File Tags indicate file types**
- **Unorganized and not connected to a study**
Why is 1734 important?

**Missing ts.xpt:**
- Can’t determine the study start date, if TRC applies and whether standardized datasets are required
- 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:

<table>
<thead>
<tr>
<th>Count of Files by File Type and Submission Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis datasets                          42</td>
</tr>
<tr>
<td>ANotesated CRF                             1</td>
</tr>
<tr>
<td>Case report forms                          1</td>
</tr>
<tr>
<td>Data tabulation                            4</td>
</tr>
<tr>
<td>Protocol or amendment                     11</td>
</tr>
<tr>
<td>Study reports and...                      17</td>
</tr>
<tr>
<td>Synopsis                                    1</td>
</tr>
</tbody>
</table>

ADaM Datasets Grouped

SDTM Datasets Grouped

eCTD Viewer:

[Images and data from eCTD Viewer showing file groups and counts]
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](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

- **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](https://www.fda.gov/regulatory-information/search-fda-guidance-documents)
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: esubprep@fda.hhs.gov
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