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.
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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. She also has ten years of experience on clinical trial data analysis and clinical data management within the pharmaceutical industry.
Technical Rejection Criteria for Study Data (TRC) and Beyond

PharmaSUG SDE
October 21, 2022

Presenter: Lina Cong
Co-host: Jiang Xu
Agenda

❖ Technical Rejection Criteria for Study Data (TRC)
❖ Tools to Help Industry Pass TRC Validation
❖ Study Data Validation Overview
❖ Addressing Common TRC Errors:
  ▪ Error 1734
  ▪ Error 1735
  ▪ Error 1736
❖ Summary
❖ Frequently Asked Questions
Technical Rejection Criteria for Study Data (TRC)
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
eCTD Validation Updates

- Study Data Validation Effective Date for CBER Module 4 Sections: 3/16/2023

<table>
<thead>
<tr>
<th>Error</th>
<th>Severity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1734</td>
<td>High</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>High</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  | High     | 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* |

* 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

- Effective date for changes to Rule 1737 and new Rule 1738: 3/16/2023
- Applies to clinical and non-clinical study data submitted to CDER or CBER as part of an NDA, BLA, IND, ANDA, or master file submission

<table>
<thead>
<tr>
<th>Error</th>
<th>Severity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1737</td>
<td>Medium</td>
<td>For each study referenced by an STF file in Module 4 and Module 5, no more than one dataset of the same file name and leaf title should be submitted using the lifecycle operator 'new'*</td>
</tr>
<tr>
<td>1738</td>
<td>Medium</td>
<td>Study ID for STF should match STUDYID listed in the referenced Trial Summary (ts.xpt) file*</td>
</tr>
</tbody>
</table>

* Applies to all sections except 4.3, 5.2, 5.4, & 5.3.6 Postmarketing reports

Please review eCTD Validation Specification all details are not included in this presentation
1734 is the most common error and rejection reason for a missing ts.xpt.

Commercial IND submissions have the highest number of errors and rejections overall.

Notes: Metrics generated from data between September 15, 2021 - September 15, 2022. CDER began rejecting submissions with TRC errors on September 15, 2021.
CDER Rejection Rate Trend

Notes: Metrics generated from data between August 16, 2021 - September 15, 2022
CDER began rejecting submissions with TRC errors on September 15, 2021
The Aug 16 - Sept 15, 2021 time period includes warnings for TRC errors, not rejections
Warnings/Rejections include submissions rejected due to TRC errors 1734, 1735, and 1736
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
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/)

**Additional Information:**

- Step 1: Download the necessary software (R and Python) from the FDA's web page.
- Step 2: Create a new ts.xpt file using the template provided in the guide.
- Step 3: Copy and paste the code samples from the guide into R or Python.
- Step 4: Run the code to generate the ts.xpt file.
- Step 5: Submit the ts.xpt file to the appropriate regulatory agency.

**Important Notes:**

- This guide assumes basic familiarity with R and Python.
- Additional resources and support are available on the FDA's web page.
Study Data Validation Overview
TRC Validation Rule Flow

*Not every submission will proceed beyond 1734 to 1735 and 1736, depending on the Study Start Date (SSD)*
Validation Rule Flow: 1737, 1738, & 1789

Begin Validation

Start

Sponsor submits to FDA

Locate all XPT datasets

Are XPT datasets unique?

No

Medium Error 1737

Yes

Pass 1737

Locate all STF files

Locate all study files

Are all study files referenced in an stf.xml file?

No

Fail 1789

Yes

Pass 1789

Locate Trial Summary dataset (ts.xpt)

Obtain Study ID in STF

Do Study IDs between ts.xpt and stf.xml match?

No

Medium Error 1738

Yes

Pass 1738

Legend
- High validation errors lead to rejection of the submission
- Validation passes
- Medium severity errors do not lead to a rejection
Addressing Common TRC Errors

Error 1734
Validation Rule 1734

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 3/16/2023

1734 Error Reasons**

- 71% Missing TS File
- 18% Study ID Mismatch
- 10% No SSD
- 1% Invalid SSD

**421 studies from September 15, 2021 – September 15, 2022

*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
Addressing 1734 Errors for Missing TS File

Providing a TS File for non-clinical studies which require a Simplified TS will address the biggest root cause of Error 1734.

Over 70% of Missing TS File Errors are for non-clinical studies with study reports and no .xpt datasets*

<table>
<thead>
<tr>
<th></th>
<th>M4</th>
<th>M5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies with only study reports</td>
<td>73%</td>
<td>N/A</td>
</tr>
<tr>
<td>Studies with only study data</td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>Studies with study data and reports**</td>
<td>17%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Option 1
Use the Simplified ts.xpt Creation Guide to generate a simplified ts.xpt in R or Python:

Option 2
Use publicly available tool developed by PHUSE to generate simplified ts.xpt files:

Example of a Simplified TS file for a non-clinical study:

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>TSPARMCD</th>
<th>TSVAL</th>
<th>TSVALNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S107</td>
<td>STSTDTC</td>
<td>2014-10-26</td>
</tr>
</tbody>
</table>

*Out of 230 studies profiled between September 15, 2021 – September 15, 2022
Addressing Common TRC Errors

Error 1735
Validation Rule 1735

The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*

- Valid file tags for XPT files (e.g., adsl.xpt, dm.xpt) are tagged as:
  - “data-tabulation-dataset-sdtm” for SDTM
  - “analysis-dataset-adam” for ADaM
  - “data-tabulation-dataset-send” for SEND

- Valid file tags for corresponding define.xml files:
  - “data-tabulation-data-definition” for SDTM & SEND
  - “analysis-data-definition” for ADaM

IND submissions have the highest number of 1735 errors**

*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

**115 studies from September 15, 2021 – September 15, 2022
Addressing the Most Common 1735 Error

❖ The most common cause of 1735 errors is incorrectly tagged define.xml files
❖ When preparing STF files, ensure files are tagged properly

Example Study Tagging File (STF) for SDTM:

Sponsors commonly apply the same file tags as datasets or other files for all files submitted, including define.xml files

1735 Error Reasons*

- 37% Invalid File Tag for define.xml
- 63% Invalid File Tag for dm.xpt or adsl.xpt

File tag for define.xml needs to be corrected to: “data-tabulation-data-definition”

*115 studies from September 15, 2021 – September 15, 2022
Addressing Common TRC Errors

Error 1736
Validation Rule 1736

DM datasets and define.xml files are submitted with SDTM and SEND (tabulations) data and an ADSL dataset and define.xml file are submitted with ADaM (analysis) data.

✓ For SEND, a DM dataset and define.xml must be submitted in module 4*

✓ For SDTM data, a DM dataset and define.xml must be submitted in module 5*

✓ For ADaM data, an ADSL dataset and define.xml must be submitted in module 5*

IND submissions have the highest number of 1736 errors**

*Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4, 4.2.3.5
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

**85 studies from September 15, 2021 – September 15, 2022
Addressing the Most Common 1736 Error

The most common cause of 1736 errors is missing define.xml and/or dm.xpt files for non-clinical studies requiring SEND standardized datasets.

<table>
<thead>
<tr>
<th></th>
<th>SEND</th>
<th>SDTM/ADaM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing Datasets</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Missing Define</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Both</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>49 (58%)</td>
<td>36 (42%)</td>
</tr>
</tbody>
</table>

*85 studies from September 15, 2021 – September 15, 2022
Summary
## Summary: Addressing Top 3 Causes of TRC Errors

<table>
<thead>
<tr>
<th>Impact</th>
<th>Rule Summary</th>
<th>1734</th>
<th>1735</th>
<th>1736</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impact</strong></td>
<td></td>
<td>All 1734 71% of Rejections</td>
<td>Comm. IND 52% of Rejections</td>
<td>17% of Rejections</td>
</tr>
<tr>
<td><strong>Rule Summary</strong></td>
<td></td>
<td>A dataset named ts.xpt with information on study start date must be present for each study in required sections</td>
<td>The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files</td>
<td>Checks that DM datasets and define.xml files are submitted with SDTM and SEND (tabulations) data and an ADSL dataset and define.xml file are submitted with ADaM (analysis) data</td>
</tr>
<tr>
<td><strong>1. Check if your study has an error</strong></td>
<td></td>
<td>Self-Check Worksheet Sections 3 &amp; 4</td>
<td>Self-Check Worksheet Section 5</td>
<td>Self-Check Worksheet Section 5</td>
</tr>
<tr>
<td><strong>2. Correct the errors</strong></td>
<td></td>
<td>If a Simplified TS file is required, utilize the Simplified ts.xpt Creation Guide or online PHUSE Utility</td>
<td>Ensure the correct STF file-tags for standardized datasets and define.xml files are used</td>
<td>Ensure that DM, ADSL datasets, and define.xml files are submitted with corresponding data</td>
</tr>
</tbody>
</table>

**Notes:** Metrics generated from data between September 15, 2021 - September 15, 2022. CDER began rejecting submissions with TRC errors on September 15, 2021.
Frequently Asked Questions
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 set 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 [June 2021]
  • FDA Data Standards Catalog [August 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
  • Link: [https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber](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](https://www.fda.gov/regulatory-information/search-fda-guidance-documents)