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.
Heather Crandall
Division of Data Management Services and Solutions,
Office of Business Informatics | CDER | US FDA
FDA Study Data Technical Rejection Update

PharmaSUG 2021
November 12, 2021
Agenda

- Technical Rejection Criteria for Study Data (TRC)
- Tools to Help Industry Pass TRC Validation
- TRC Validation Overview
- Addressing Common TRC Errors:
  - Error 1734
  - Error 1789
  - Error 1735
- Summary
Technical Rejection Criteria for Study Data (TRC)
Technical Rejection Criteria for Study Data – What’s New

- eCTD Validations 1734, 1735, 1736, 1737, and 1789 are now effective (starting Sept. 15th, 2021)

- If a submission contains study information and fails eCTD validations listed in the Technical Rejection Criteria for Study Data, CDER and CBER will reject the submission

- Sponsors will receive a rejection notice if a submission fails eCTD validations

Validation Rule 1734 in the Specifications for eCTD Validation Criteria:

<table>
<thead>
<tr>
<th>Number</th>
<th>1734</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>General</td>
</tr>
<tr>
<td>Description:</td>
<td>A dataset named ts.xpt with information on study start date must be present for each study in Module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4, and in Module 5, sections 5.3.1.1, 5.3.1.2, 5.3.1.3, 5.3.1.5, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2</td>
</tr>
<tr>
<td>Severity Description:</td>
<td>High</td>
</tr>
<tr>
<td>US DTD Version</td>
<td>2.01 and 3.3</td>
</tr>
<tr>
<td>Effective Date</td>
<td>9/15/2021</td>
</tr>
<tr>
<td>Problem:</td>
<td>You have not submitted a dataset named ts.xpt with information on study start date for each study in Module 4, section 4.2, or in Module 5, section 5.3</td>
</tr>
<tr>
<td>Corrective Action:</td>
<td>Resubmit, including a dataset named ts.xpt with information on study start date for each study in Module 4, section 4.2, and in Module 5, section 5.3</td>
</tr>
<tr>
<td>Guidance Source:</td>
<td>Providing Regulatory Submissions in Electronic Format – Standardized Study Data; Study Data Technical Conformance Guide</td>
</tr>
</tbody>
</table>
eCTD Rejection Notice

- Sponsors receive a rejection notice from FDA when an eCTD validation error is identified.
- Rejection notices specify each error and provide: Error Code; Error Reason; STF Study ID; eCTD Section (if applicable).
Overview of Technical Rejection Criteria

eCTD validation rule 1789 has different expectations than 1734, 1735, and 1736.

<table>
<thead>
<tr>
<th>Error</th>
<th>Description (Reference to FDA Study Data Technical Rejection Criteria March 2021 version)</th>
<th>Severity Level</th>
<th>Effective Date</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>
<td>High</td>
<td>Sept. 15, 2021</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
# Overview of Technical Rejection Criteria

The TRC are eCTD validation criteria to determine compliance with requirements for submitting standardized study data in required sections in Modules 4 and 5, including:

- 4.2.3.1, 4.2.3.2, 4.2.3.4
- 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

<table>
<thead>
<tr>
<th>Error</th>
<th>Description (Reference to FDA Study Data Technical Rejection Criteria <a href="#">March 2021 version</a>)</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></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></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 | Sept. 15, 2021 |
TRC Rejections (September 15th – October 31st, 2021)

- 1734 is the most common rejection reason, especially for Commercial IND submissions
- 1789 is the second largest rejection reason and is particularly high for Commercial IND submissions

Note: Rejection metrics generated by CDER between September 15th and October 31st, 2021
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/)
Addressing Common TRC Errors

Error 1734
Causes of 1734 Errors

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

CDER Submissions: September 15th – October 31st 2021

- 740 Submissions with Study Data
- 434 Submissions with Study Data in TRC Applicable Sections
- 60 Submissions with Error 1734

14% of submissions with study data in TRC applicable sections

59% of Study Errors: Missing TS File

31% No Study Start Date
9% Invalid Study Start Date
1% Missing ts.xpt
1% Study ID Mistmatch

**136 Studies in 60 Submissions with Error 1734 (September 15th – October 31st, 2021)

* 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

**
Verifying Rule 1734 Using Self-Check Worksheet

✓ Trial Summary Dataset (ts.xpt) is present

**Section 3 helps check if non-clinical studies without .xpt datasets require a TS file:**

<table>
<thead>
<tr>
<th>3f. Are XPT Datasets (other than the ts.xpt File) Included?*</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes ☒ No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3g. If the Study is Nonclinical (m4), are any Study Files Tagged as &quot;pre-clinical-study-report,&quot; &quot;legacy-clinical-study-report,&quot; or &quot;study-report-body&quot;?*</th>
</tr>
</thead>
<tbody>
<tr>
<td>☒ Yes □ No</td>
</tr>
</tbody>
</table>

**Section 4 helps check if a Full or Simplified TS file is required:**

**Section 4: TS File Information**

4a. If the Study is for a Commercial IND Application, Is the Study Start Date:

<table>
<thead>
<tr>
<th>Prior to or on 17-Dec-2017</th>
<th>After 17-Dec-2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>☒</td>
</tr>
</tbody>
</table>

4b. If the Study Is for an NDA, BLA, or ANDA Application, Is the Study Start Date:

<table>
<thead>
<tr>
<th>Prior to or on 17-Dec-2016</th>
<th>After 17-Dec-2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

4e. If TS File is Required, What Type of TS File is Required?

<table>
<thead>
<tr>
<th>Full TS</th>
<th>Simplified TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>☒</td>
</tr>
</tbody>
</table>

Refer to guidelines in chart above. See the Study Data Technical Conformance Guide for more information on submitting a Simplified TS for nonclinical data.

* Fields 4f-4k are applicable if a Full TS File is submitted, Fields 4l-4p are applicable if a simplified TS file is submitted.

Note: TS files must be named ts.xpt and cannot be customized or changed (other standardized datasets, such as dm.xpt and adsl.xpt, must also be named correctly)
**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.

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

**Option 2**
Use a 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>

When SEND datasets are required, submit a Full TS.

---

*4e. If TS File is Required, What Type of TS File is Required?*

- [x] Full TS
- [ ] Simplified TS

Refer to guidelines in chart above. See the Study Data Technical Conformance Guide for more information on submitting a Simplified TS for nonclinical data.

*Field 4I-4k are applicable if a Full TS File is submitted, Fields 4I-4p are applicable if a simplified TS file is submitted.*
Addressing Common TRC Errors

Error 1789
Validation Rule 1789

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).

✓ All study files are included in a Study Tagging File (STF)

1789 errors are the second largest source of TRC failures

Submission Types for 1789 Errors*

- 65% Commercial IND
- ANDA
- BLA
- NDA
- IND

*26 1789 failures out of 100 total rejections September 15 – October 31, 2021
Verifying Error 1789 Using Self-Check Worksheet

Section 3 helps check if all study files in applicable eCTD sections are referenced in a Study Tagging File:

<table>
<thead>
<tr>
<th>Section 3: STF File Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a. Are Files Included in a Study Section? <em>(Not Applicable to Sections 4.3, 5.2, 5.3.6, and 5.4)</em></td>
</tr>
<tr>
<td>☑ Yes ☐ No</td>
</tr>
<tr>
<td>If you answered “No” in Field 3a, and no files are included in a study section, excluding sections 4.3, 5.2, 5.3.6, and 5.4, then Validation Rules 1734, 1735, 1736, and 1789 do not apply. Do not proceed.</td>
</tr>
<tr>
<td>3b. Is STF File Included?*</td>
</tr>
<tr>
<td>☑ Yes ☐ No</td>
</tr>
<tr>
<td>3c. Does STF File Reference all Associated Study Files?*</td>
</tr>
<tr>
<td>☑ Yes ☐ No</td>
</tr>
</tbody>
</table>

If you answered “No” in Fields 3b or 3c, Validation Rule 1789 FAILS. Do not proceed.

<table>
<thead>
<tr>
<th>3d. Study ID (study-id) in STF File*</th>
</tr>
</thead>
<tbody>
<tr>
<td>xyz-123</td>
</tr>
<tr>
<td>If you answered “No” in Field 3d, ensure the study ID is consistent across all the files being submitted for the same study.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3e. Does the Study ID in the STF File Match Field 2a?</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑ Yes ☐ No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3f. Are XPT Datasets (other than the ts.xpt File) Included?*</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑ Yes ☐ No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3g. If the Study is Nonclinical (m4), are any Study Files Tagged as “pre-clinical-study-report,” “legacy-clinical-study-report,” or “study-report-body”?*</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑ Yes ☐ No</td>
</tr>
</tbody>
</table>

Referenced Validation Error Number 1789
Addressing 1789 Errors

When placing files in applicable sections within Modules 4 and 5, they should also be referenced within an STF for the study to which they belong.

Applicable eCTD Section*

Example Index.xml:

Example STF:

The file, bw.xpt, is included in the Index.xml but not referenced in the STF for the study.

Correction: Add missing file reference to the STF file for the study

*STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports.
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*

- Standardized dataset domains (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

- Define.xml files are tagged as:
  - “data-tabulation-data-definition” for SDTM & SEND
  - “analysis-data-definition” for ADaM

**Submission Types for 1735 Errors**

**11 1735 failures out of 100 total rejections September 15 – October 31st, 2021**

*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
Section 5 helps check—when standardized data is required—if standardized datasets are tagged correctly in the STF and if required datasets are included:

### Clinical (m5)

Tabulation (SDTM datasets)

<table>
<thead>
<tr>
<th>5f. Is DM File Included?*</th>
<th>5g. Is Define File Included?*</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes □ No</td>
<td>□ Yes □ No</td>
</tr>
</tbody>
</table>

If you answered "No" in Fields 5f or 5g, Validation Rule 1736 FAILS. Proceed to Fields 5h and 5i for Validation Rule 1735.

### Analysis (ADaM datasets)

<table>
<thead>
<tr>
<th>5j. Is ADSL File Included?**</th>
<th>5k. Is Define File Included?*</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes □ No</td>
<td>□ Yes □ No</td>
</tr>
</tbody>
</table>

If you answered "No" in Fields 5j or 5k, Validation Rule 1735 FAILS. Proceed to Fields 5l and 5m for Validation Rule 1735.

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**Note:** Fields marked with an asterisk (*) or double asterisk (**) require specific validation rules.
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

1735 Error Reasons*

- 67% Invalid File Tag for Define.xml
- Invalid file tag for dm.xpt or adsl.xpt
- Standardized dataset domains (e.g. dm.xpt)

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

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

*15 studies with Error 1735 between September 15 – October 31, 2021
References

❖ Study Data Standards Resources

• Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [June 2021]
• Study Data Technical Conformance Guide [Oct 2021]
• FDA Data Standards Catalog [Sept 2021]
• 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 For Study Data [Aug 2021]
• 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

CDER eData Mailbox: cder-edata@fda.hhs.gov
CBER eData Mailbox: cber-edata@fda.hhs.gov
References

❖ eCTD Standards Resources

- Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications Guidance for Industry [Feb 2020]
- eCTD Submission Standards [Oct 2021]

❖ 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

CDER eSub Mailbox: esub@fda.hhs.gov
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