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Study Data Technical Rejection Criteria, Validation, and Self-Check Worksheet

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Agenda

- FDA Guidance and Data Standards Catalog
- Revised Technical Rejection Criteria for Study Data
- Study Data Technical Rejection Criteria Conformance Trend
- Technical Rejection Criteria Validation Process
- Typical Error Examples and Demo of the Self-Check Worksheet
- Implementation Timeline
FDA Guidance and Data Standards Catalog

- Per FD&C Act Section 745A(a), drug application sponsors must use the standards defined in the FDA Data Standards Catalog starting 24 months after final guidance for a specific submission type.
- 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 published Study Data Guidance for Industry

NDA, BLA, ANDA studies that started after Dec. 17th, 2016

Commercial IND studies that started after Dec. 17th, 2017 must conform to standards in the FDA Data Standard Catalog
Study Data Technical Rejection Criteria (SDTRC) Revisions

Significant Technical Rejection Criteria Revisions:
- FDA will not accept study data submissions not in compliance with FDA Data Standards Catalog
- FDA emphasized validation rules 1735 and 1789
- FDA introduced the Simplified TS File (simplified ts.xpt) to obtain Study Start Date


Significant Technical Rejection Criteria Revisions:
- FDA included SPREFID as a valid source of Study ID in ts.xpt files
- FDA updated guidance for Simplified TS Files (simplified ts.xpt)

Refuse to file → Will not accept

The FDA may refuse to file (RTF) for NDAs and BLAs, or refuse to receive (RTR) for ANDAs, an electronic submission that does not have study data in conformance to the required standards specified in the FDA Data Standards Catalog.

FDA will not accept an electronic submission that does not have study data in compliance with the required standards specified in the FDA Data Standards Catalog.

Revised TRC rules and elevated 1735 and 1789 to high severity errors

<table>
<thead>
<tr>
<th>Error</th>
<th>Description</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1734</td>
<td>Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections*</td>
<td>High</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>
<td>High</td>
</tr>
<tr>
<td>1736</td>
<td>For SEND data, a DM dataset and define.xml must be submitted in required sections* For SDTM data, a DM dataset and define.xml must be submitted in required sections* For ADaM data, an ADSL dataset and define.xml must be submitted in required sections*</td>
<td>High</td>
</tr>
<tr>
<td>1789**</td>
<td>Study files must be referenced in a Study Tagging File (STF)</td>
<td>High</td>
</tr>
</tbody>
</table>
Included SPREFID for Study ID matching

If a file is referenced within a study section in Module 4 or 5, a STF and ts.xpt must be present to identify the study ID and SSD to which the file belongs. The ts.xpt needs to contain either a study ID (STUDYID) or Sponsor Reference ID (SPREFID) value that matches with the STF study ID.
A study in standardized format is submitted to FDA and the study files are referenced in a STF, a ts.xpt dataset is included in the study. The SPREFID in the ts.xpt dataset matches the study ID (study-id) in the STF. The Study Start Date in the ts.xpt is in SDTM or SEND format and the study begins after December 17, 2016, for NDAs, BLAs, and ANDAs (or December 17, 2017, for Commercial INDs).

- Additional parameter in the ts.xpt for matching study id with STF study id to pass validation 1734
  - The SPREFID parameter allows for an alternate way for Sponsors provide a matching study id
  - Multiple SPREFID values are allowed in the ts.xpt
Study Data Technical Rejection Criteria Conformance Trend
1734 and 1736 Failure Rate Comparison- ANDA’s and NDA’s

- Submissions with study data do not show significant improvements in Validation Errors 1734 and 1736

Note - CY2019 (Q1,Q2 & Q3) analysis conducted according to the TRC (Revised Jan. 2019)
CDER Conformance: Validation Error 1789

- ANDA’s and NDA’s were assessed for conformance to high-level error, 1789, as defined in the SDTRC (Revised Jan. 2019)

<table>
<thead>
<tr>
<th></th>
<th>NDA</th>
<th>ANDA</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CY2018</td>
<td>CY2019 (Q1-Q3)</td>
<td>CY2018</td>
</tr>
<tr>
<td>Total Number of Submissions</td>
<td>41,077</td>
<td>34,166</td>
<td>62,695</td>
</tr>
<tr>
<td>Error 1789</td>
<td>43</td>
<td>30</td>
<td>225</td>
</tr>
<tr>
<td>Failure Rate (% among total number of submissions)</td>
<td>0.10%</td>
<td>0.09%</td>
<td>0.36%</td>
</tr>
</tbody>
</table>

Notes:
1) One drug application could contain multiple submissions throughout its review life-cycle, such as original, supplements, and amendments
2) Each submission may contain more than one study
3) Analysis includes NDA and ANDA submissions received by CDER between 1/1/2018 to 9/30/2019
4) Analysis is conducted according to the revised TRC (Revised Jan. 2019)
CDER Conformance: Validation Errors 1734, 1735 & 1736

- ANDA and NDA were assessed for conformance to three high-level error, 1734, 1735, & 1736, as defined in the SDTRC (Revised Jan. 2019)
- Failure Rate for ANDA application increased between 2018 and 2019 and remains significantly higher than NDA applications

### Table: NDA ANDA All

<table>
<thead>
<tr>
<th></th>
<th>CY2018</th>
<th>CY2019 (Q1-Q3)</th>
<th>CY2018 (Q1-Q3)</th>
<th>CY2018</th>
<th>CY2019 (Q1-Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Submissions with Study Data</td>
<td>877</td>
<td>704</td>
<td>1,078</td>
<td>631</td>
<td>1,955</td>
</tr>
<tr>
<td>Total Number of Submissions with Study Data in TRC Applicable Sections</td>
<td>533</td>
<td>582</td>
<td>1,115</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Number Submissions with Critical Errors</td>
<td>215</td>
<td>194</td>
<td>689</td>
<td>428</td>
<td>904</td>
</tr>
<tr>
<td>Error 1734</td>
<td>185</td>
<td>150</td>
<td>186</td>
<td>125</td>
<td>371</td>
</tr>
<tr>
<td>Error 1735</td>
<td>34</td>
<td>43</td>
<td>497</td>
<td>307</td>
<td>531</td>
</tr>
<tr>
<td>Error 1736</td>
<td>16</td>
<td>20</td>
<td>88</td>
<td>56</td>
<td>104</td>
</tr>
<tr>
<td>Failure Rate (% among submissions with Study Data)</td>
<td>24.50%</td>
<td>27.56%</td>
<td>63.90%</td>
<td>67.83%</td>
<td>46.24%</td>
</tr>
<tr>
<td>Failure Rate (% among submissions with Study Data in TRC Applicable Sections)</td>
<td>36.4%</td>
<td>73.54%</td>
<td>55.78%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
1) One drug application could contain multiple submissions throughout its review life-cycle, such as original, supplements, and amendments
2) Analysis includes NDA and ANDA submissions received by CDER between 1/1/2018 to 9/30/2019
3) Submission with multiple studies can report both Errors 1734, 1735 and 1736
4) Validation of errors 1735 and 1736 are not performed if a study has Error 1734
5) Analysis is conducted according to the revised TRC (Revised Jan. 2019)
Technical Rejection Criteria Validation Process
eCTD Backbone Files

- Leaf ID
- File Path
- File Name

- Leaf ID
- STF Study ID
- File-Tag

- TS STUDYID or SPREFID
- Study Start Date
eCTD Backbone Files (index.xml)

```
<m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
  <leaf checkum-type="MD5"
    xlink:type="simple"
    checksum="98723f7594b5500a861509547c384e46" operation="new"
    application-version="PDF 1.4"
    ID="a103">
    <title>S107 ts.xpt</title>
  </leaf>
  <leaf checkum-type="MD5"
    xlink:type="simple"
    checksum="25d3b24631a9dbf688a48da2295260e" operation="new"
    version="stf version 2.2"
    ID="a104">
    <title>Study Tagging File for S107</title>
  </leaf>
</m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
```
eCTD Backbone File (stf.xml)

- From Index.xml
  - Leaf ID
  - File Path
  - File Name

```xml
<?xml version="1.0" encoding="UTF-8"?>
<ectd:study SYSTEM "http://www.ich.org/ectd" xml:lang="en" dtd-version="2.2"
xmlns:xlink="http://www.w3.org/1999/xlink">
  <study-identifier>
    <title>Wonderdrug Study S107</title>
  </study-identifier>
  <study-document>
    <doc-content xlink:href="/.../.../index.xml#e103"/>
    <file-tag name="data-tabulation-dataset-sdtm" info-type="ich"/>
  </study-document>
</ectd:study>
```

- **STF STUDY ID**: `S107`
- **Index.xml LEAF ID**: `stf.xml#e103`
- **FILE TAG ASSOCIATED TO STUDY DOCUMENT**: `data-tabulation-dataset-sdtm`
eCTD Backbone Files (Full ts.xpt)

- From Index.xml
  - Leaf ID
  - File Path
  - File Name
- From STF.xml
  - Leaf ID
  - STF Study ID
  - File-Tag
eCTD Backbone Files (Simplified ts.xpt)

- From Index.xml
  - Leaf ID
  - File Path
  - File Name

- From STF.xml
  - Leaf ID
  - STF Study ID
  - File-Tag

![Diagram showing ts.xpt file and the table with columns STUDYID, TSPARMCD, TSVAL, TSVALNF and rows with TS Study ID and Study Start Date.](image-url)
Typical Error Examples and Demo of the Self-Check Worksheet
FDA is developing tools and resources to help sponsors meet study data standard requirements and provide more transparency on the validation process.

**Sponsor reviews Study Data Standard Resources and Tools for Industry:**

- Study Data Technical Rejection Criteria with *eCTD Validation Table and Example Submission Scenarios*

- Simplified TS File Generator Utility (PhUSE)
  - OR
  - Simplified TS File Creation Guide

- Study Data Self-Check Worksheet & Instructions

**Sponsor submits an application with study data**

Sponsor submits a eCTD and/or Standardized Data Sample to the FDA for validation.

After review, FDA will provide feedback, highlighting the errors found during the processing of the sample submission.
How Many People are aware of Study Data Self-Check Worksheet?

How Many People use Study Data Self-Check Worksheet?
Self-Check Worksheet

<table>
<thead>
<tr>
<th>Section</th>
<th>Contents</th>
</tr>
</thead>
</table>
| 1       | Application & Submission Information  
• Provides high level information about the application and submission |
| 2       | Study Information  
• Provides more detailed information about the specific study |
| 3       | STF File Information (1789 Validation Error)  
• Provide information about STF file |

Reference:  
“Technical Rejection Criteria Self-Check Worksheet”  
https://www.fda.gov/media/123098/download  
“Technical Rejection Criteria Self-Check Worksheet Instructions”  
https://www.fda.gov/media/123099/download
Section 4: TS File Information

- Provide information about ts.xpt file with study start date

Reference:

“Technical Rejection Criteria Self-Check Worksheet”
https://www.fda.gov/media/123098/download

“Technical Rejection Criteria Self-Check Worksheet Instructions”
https://www.fda.gov/media/123099/download
A dataset named ts.xpt with information on Study Start Date (SSD) must be present for each study.

Common error reason for ANDAs:
- A missing ts.xpt file
- A missing study start date in the ts.xpt

206 Studies with Error 1734
- 72% Missing ts.xpt
- 26% No study start date
- 2% Invalid study start date
## TRC Validation Rule 1734 (Section 4a-4b)

- Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections
- 72% of studies with 1734 error are because of a missing ts.xpt file

### Example

2. Study Files and/or datasets submitted in **m5-3-5-1** (TRC applicable study section)

<table>
<thead>
<tr>
<th>Study Start Date: 2018-01-01</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRC Requirement: <strong>Full TS is needed</strong></td>
</tr>
</tbody>
</table>

### Self-Check Worksheet

<table>
<thead>
<tr>
<th>ts.xpt File Included?</th>
<th>ts.xpt File Reference in Associated Study Files?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**TRC Validation Rule 1734 (Section 4a-4b)**

- Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections
- 72% of studies with 1734 error are because of a missing ts.xpt file
TRC Validation Rule 1734 (Section 4c)

- Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections
- 72% of studies with 1734 error are because of a missing ts.xpt file

### Example

2. Study Files and/or datasets submitted in **m5-3-5-1** (TRC applicable study section)

**Study Start Date:** 2018-01-01

**TRC Requirement:** Full TS is needed

### Self-Check Worksheet

<table>
<thead>
<tr>
<th>Section 4: TS File Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a. What Type of TS File is Required? (Reflects validation in check box)</td>
</tr>
<tr>
<td>[ ] Full TS</td>
</tr>
<tr>
<td>[ ] Ser.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4b. Is TS File Included?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes</td>
</tr>
<tr>
<td>[x] No</td>
</tr>
</tbody>
</table>

If you answered “No” in Field 4b, Validation Rule 1734 fails. Do not proceed.

#### 3d. Study ID in STF File*

<table>
<thead>
<tr>
<th>Study ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study ABC</td>
</tr>
</tbody>
</table>

- [Study IDs Match Requirement]

Pass Rule 1734
### TRC Validation Rule 1734 (Section 4e-4f)

- Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections
- 26% of studies with 1734 error are because of invalid study start date

#### Example

2. Study Files and/or datasets submitted in **m5-3-5-1** (TRC applicable study section)
   - **Study Start Date:** 2018-01-01
   - **TRC Requirement:** Full TS is needed

#### Self-Check Worksheet

<table>
<thead>
<tr>
<th>Section 4: TS File Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a. What Type of TS File is Required? <em>(Refer to guidelines in chart below.)</em></td>
</tr>
<tr>
<td>[ ] Full TS</td>
</tr>
</tbody>
</table>

4b. Is TS File Included?  
[ ] Yes [ ] No

If you answered "No" in Field 4b, Validation Rule 1734 FAILS. Do not proceed.

4c. Study ID in TS File?
   - [ ] Yes
   - [ ] No

If you answered "No" in Field 4d, Validation Rule 1734 FAILS. Do not proceed.

4d. Does Study ID in SFTP (Field 3d) & TS Files Match?  
[ ] Yes [ ] No

4e. Study Start Date in TS File
   - 2018-01-01
   - [ ] Yes [ ] No

4f. If Study Start Date Exists, Is It Valid?
   - [ ] Yes [ ] No

---

**Pass Rule 1734**
Self-Check Worksheet (1735 & 1736 Validation Error)

Section 5: Standardized Dataset Information (1735 & 1736 Validation Error)
- Provide information about SEND or STDM and/or ADaM dataset and define.xml
- Provide information about STF File-tags

Reference:
“Technical Rejection Criteria Self-Check Worksheet”
https://www.fda.gov/media/123098/download
“Technical Rejection Criteria Self-Check Worksheet Instructions”
https://www.fda.gov/media/123099/download
**CY2019 (Q1-Q3) CDER Error Reasons for Validation Rule 1735**

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

- **Common error reason for ANDAs:**
  - An incorrect file tag for a define.xml file
  - An incorrect file tag for a XPT file

![Error Reason Pie Chart]

593 Studies with Error 1735

- **40% Incorrect define.xml file tag**
- **32% Incorrect XPT dataset file tag**
- **28% Incorrect define, xpt and legacy file tag**

<table>
<thead>
<tr>
<th>Submissions</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>with Study Data</td>
<td>631</td>
</tr>
<tr>
<td>with Study Data in TRC Applicable Sections</td>
<td>582</td>
</tr>
<tr>
<td>with 1735 Error</td>
<td>307</td>
</tr>
</tbody>
</table>
CY2019 (Q1-Q3) CDER Error Reasons for Validation Rule 1736

- For SEND data, a DM dataset and define.xml must be submitted
- For SDTM data, a DM dataset and define.xml must be submitted
- For ADaM data, an ADSL dataset and define.xml must be submitted
- **Common error reason for ANDAs:**
  - A missing define.xml files
  - A missing define.xml, dm.xpt, and adsl.xpt files
TRC Validation Rule 1735 and 1736 (Section 5f-5g)

- Rule 1735: Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections
- Rule 1736: For SEND data, a DM dataset and define xml must be submitted in required sections
  - For SDTM data, a DM dataset and define.xml must be submitted in required sections
  - For ADaM data, an ADSL dataset and define.xml must be submitted in required sections

### Example Self-Check Worksheet

**Study Files and/or datasets submitted in m5-3-5-1 (clinical)**

- **Study Start Date:** 2018-01-01
- **Dataset Type:** Tabulation (SDTM)

```
Files Referenced in stf.xml

- acrt.pdf
- ex.xpt
- mxxpt
- supnda.xpt
- suppdm.xpt
- svxpt
- tvxpt
- csmxpt
- egmxpt
- scap.xpt
- suppd.s.xpt
- ta.xpt
- cxpt
- expt
- te.xpt
- suppg.e.xpt
- txpt
- csdro.pdf
- i.e.xpt
- suppaex.xpt
- suppe.xpt
- tixpt
```

**Fail Rule 1736**

- dm.xpt and define.xml are not included
- 62% of studies with 1736 error are because of missing define.xml file
TRC Validation Rule 1735 and 1736 (Section 5f-5g)

- Rule 1735: Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections
- Rule 1736: For SEND data, a DM dataset and define.xml must be submitted in required sections
  - For SDTM data, a DM dataset and define.xml must be submitted in required sections
  - For ADaM data, an ADSL dataset and define.xml must be submitted in required sections

**Example Self-Check Worksheet**

Study Files and/or datasets submitted in **m5-3-5-1 (clinical)**

**Study Start Date:** 2018-01-01

**Dataset Type:** Tabulation (SDTM)

![Example of dataset files]

Pass Rule 1736

- **62%** of studies with 1736 error are because of missing define.xml file
**TRC Validation Rule 1735 and 1736 (Section 5h-5i)**

- Rule 1735: Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections
- Rule 1736: For SEND data, a DM dataset and define.xml must be submitted in required sections
  - For SDTM data, a DM dataset and define.xml must be submitted in required sections
  - For ADaM data, an ADSL dataset and define.xml must be submitted in required sections

---

**Example Self-Check Worksheet**

**Study Files and/or datasets submitted in m5-3-5-1 (clinical)**

**Study Start Date:** 2018-01-01

**Dataset Type:** Tabulation (SDTM)

---

**Files Referenced in stf.xml**

- define.xml
- dm.xpt

---

**Pass Rule 1735**

**define.xml is tagged as “data-tabulation-data-definition”**

- 40% of studies with 1735 error are because of improper file tag of define.xml file in the stf.xml
Published SDTRC and Self-Check Worksheet

“Technical Rejection Criteria for Study Data”
https://www.fda.gov/media/100743/download

“Technical Rejection Criteria Self-Check Worksheet”
https://www.fda.gov/media/123098/download

“Technical Rejection Criteria Self-Check Worksheet Instructions”
https://www.fda.gov/media/123099/download

FDA published Study Data Guidance for Industry

NDA, BLA, ANDA studies that started after Dec. 17th, 2016
Commercial IND studies that started after Dec. 17th, 2017 must conform to standards in the FDA Data Standard Catalog


• FDA revised & published Technical Rejection Criteria for Study Data (Revised Oct. 2019)

• FDA published Study Data Self-Check Worksheet & Instruction

• FDA published revised Technical Rejection Criteria for Study Data (Revised Jan. 2019)
FDA published Revised Study Data Technical Rejection Criteria (Revised Oct. 2019) and Study Data Self-Check Worksheet to assist sponsors with the TRC Conformance

- Per FD&C Act Section 745A(a), sponsors must conform to standards in the FDA Data Standard Catalog
- NDA, BLA, ANDA studies that started after Dec. 17th, 2016
- Commercial IND studies that started after Dec. 17th, 2017

- FDA issued “Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry”
- FDA published Study Data Self-Check Worksheet & Instruction
- FDA will give the industry 90 days’ notice on the eCTD website prior to the criteria becoming effective

**Implementation Timeline**

- Study Data Technical Rejection Criteria are REQUIRED but NOT IMPLEMENTED
- FDA Monitors & Analyzes the Study Data Conformance

* Note: When a submission is technically-rejected, the submission sequence is not transferred into the FDA electronic document rooms
Questions

❖ For questions about submitting study data please contact: edata@fda.hhs.gov

❖ For questions about eCTD, including stf.xml and file-tags, please contact: esub@fda.hhs.gov
Reference

- “Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry”

- “Providing Regulatory Submissions In Electronic Format - Submissions Under Section 745a(a) Of The FD&C Act: Guidance For Industry”

- “Technical Rejection Criteria For Study Data”
  https://www.fda.gov/media/100743/download

- “Study Data Technical Conformance Guide”
  https://www.fda.gov/media/88173/download

- “FDA Data Standards Catalog”
  https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

- “Technical Denunciation Criteria Self-Check Worksheet”
  https://www.fda.gov/media/123098/download

- “Technical Rejection Criteria Self-Check Worksheet Instructions”

- For FDA instruction of Study Data submission, see the FDA “Study Data for Submission to CDER and CBER”
  https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

- For the full list of Study Data standards, see the FDA “Study Data Standards Resources”
  http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards

- PhUSE utility for Simplified TS File Creation
  https://geotiger.shinyapps.io/07_genTS/
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