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

Heather Crandall
Operations Research Analyst, DDMSS, OBI, OSP, CDER, FDA
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
Revised Technical Rejection Criteria for Study Data
Study Data Technical Rejection Criteria (SDTRC) Revisions

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 Monitors & Analyzes Study Data Conformance


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)

# Study Data Technical Rejection Criteria (SDTRC) Revisions (Jan. 2019)

## 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>
</tbody>
</table>
| 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* | High     |
| 1789** | Study files must be referenced in a Study Tagging File (STF)                | High     |

**References:**
# Study Data Technical Rejection Criteria (SDTRC) Revisions (Oct. 2019)

## Introduced the Simplified TS File (simplified ts.xpt) and TSVALNF

For a study without a valid SSD:

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>TSPARMCD</th>
<th>TSVAL</th>
<th>TSVALID</th>
</tr>
</thead>
<tbody>
<tr>
<td>study ID in STF</td>
<td>SSTDTC</td>
<td>Use the value ‘NA’</td>
<td></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.

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.

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**References:**

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
1734 and 1736 Error Rate Comparison - Commercial IND’s and NDA’s in Module 4

- IND Submissions with study data shows improvement in the 1734 Validation Error Rate but have a slight increase in Error Rate for Validation Errors 1736

Note - CY2019 (Q1,Q2 & Q3) analysis conducted according to the TRC (Revised Jan. 2019)

Notes:
1) Analysis is conducted according to the revised TRC (Revised Jan. 2019)
CDER Conformance: Study Level Validation Errors 1734, 1735 & 1736

Commercial IND’s and NDA’s were assessed for conformance to three high-level error, 1734, 1735, & 1736, as defined in the SDTRC (Revised Jan. 2019)

<table>
<thead>
<tr>
<th></th>
<th>NDA</th>
<th>Comm-IND</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CY 2018</td>
<td>CY2019 (Q1-Q3)</td>
</tr>
<tr>
<td>Total Number of Submissions with Study Data</td>
<td>78</td>
<td>56</td>
</tr>
<tr>
<td>Total Number of Studies in the TRC Applicable Sections</td>
<td>403</td>
<td>313</td>
</tr>
<tr>
<td>Total Number Studies with Critical Errors</td>
<td>39</td>
<td>46</td>
</tr>
<tr>
<td>Error 1734</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Error 1735</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Error 1736</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Error Rate (% among failed studies with Study Data in TRC Applicable Sections)</td>
<td>10%</td>
<td>15%</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 Commercial IND 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)
CDER Conformance: SPREFID Analysis (CY2019 Q1-Q3)

- With SPREFID as a possible match to the STF study-id, the pass rate increases by 17.76% (Revised Oct. 2019)

<table>
<thead>
<tr>
<th>Total Number of non-clinical studies in TRC Applicable sections</th>
<th>NDA m4</th>
<th>Comm-IND M4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS File do not Exist</td>
<td>18</td>
<td>47</td>
<td>65</td>
</tr>
<tr>
<td>TS File Exist</td>
<td>295</td>
<td>1222</td>
<td>1517</td>
</tr>
<tr>
<td>• STF Study ID matches with TS STUDYID</td>
<td>215</td>
<td>843</td>
<td>1058</td>
</tr>
<tr>
<td>• STF Study ID does not matches with TS STUDYID</td>
<td>80</td>
<td>379</td>
<td>459</td>
</tr>
<tr>
<td>• TS File contains SPREFID</td>
<td>78</td>
<td>320</td>
<td>398</td>
</tr>
<tr>
<td>• TS file SPREFID Match</td>
<td>39</td>
<td>242</td>
<td>281</td>
</tr>
<tr>
<td>• TS file SPREFID does not Match</td>
<td>39</td>
<td>78</td>
<td>117</td>
</tr>
<tr>
<td>Pass Rate without SPREFID</td>
<td>68.69%</td>
<td>66.43%</td>
<td>66.87%</td>
</tr>
<tr>
<td>Pass Rate with SPREFID</td>
<td>81.15%</td>
<td>85.50%</td>
<td>84.63%</td>
</tr>
</tbody>
</table>

Notes
1. Analysis includes NDA and Commercial IND non-clinical studies received by CDER between 1/1/2019 to 9/30/2019 (1582 studies)
CDER Conformance: SPREFID Analysis (CY2019 Q1-Q3) Summary

- Total number of non-clinical studies evaluated for NDA and Commercial IND = 1582 studies

- 66.9% Studies where Study ID in the ts.xpt file **Match** with STF study-id
- 29% Studies where Study ID in the ts.xpt file **Do Not Match** with STF study-id
  - 25.2% Studies already contain SPREFID in the ts.xpt file
  - 17.8% Studies where SPREFID in the ts.xpt file **Match** STF STUDYID
  - 7.4% Studies where SPREFID in the ts.xpt file **Do Not** match STF STUDYID
Technical Rejection Criteria Validation Process
SDTRC High Level Validation Process (Revised Oct. 2019)

Validation Rule 1734

START VALIDATION

LOCATE STFs & STUDY FILES

TS.XPT INCLUDED?

Y

FAIL

N

STF STUDYID Match with
• TS File STUDYID or
• TS File SPREFID

Y

STANDARDIZED DATA REQUIRED?

Y

END

N

N

N

N

N

N

STF STUDYID Match with
• TS File STUDYID or
• TS File SPREFID

Y

VERIFY FILE TAGS IN STFs

Y

PASS

N

FAIL

N

FAIL

N

CHECK EFFECTIVE DATE

Y

Y

N

ALL REQUIRED STUDY FILES INCLUDED?

Y

PASS

N

FAIL

N

CHECK EFFECTIVE DATE
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)

```
<leaf checksum-type="MD5"
xlink:type="simple"
checksum="421e55366d62fad0e9510f6aed005272" operation="new"
application-version="PDF 1.4"
ID="a101">
  <title>S108 ts.xpt</title>
</leaf>
<leaf checksum-type="MD5"
xlink:type="simple"
checksum="25d3b246313a9dbf688a48da2295260e" operation="new"
version="stf version 2.2"
ID="a104">
  <title>Study Tagging File for S108</title>
</leaf>
```

INDEX LEAF ID: m4-2-3-1-single-dose-toxicity
FILE NAME FROM INDEX: S108 ts.xpt

INDEX LEAF ID: m4-2-3-1-single-dose-toxicity
FILE NAME FROM INDEX: Study Tagging File for S108
eCTD Backbone File (stf.xml)

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

```xml
<?xml version="1.0" encoding="UTF-8"?>
  <study-identifier>
    <title>Wonderdrug Study S108</title>
    <study-id>S108</study-id>
    <category name="type-of-control" info-type="ich">no-treatment</category>
  </study-identifier>
  <study-document>
    <doc-content xlink:href="../.../index.xml#s101">
      <file-tag name="data-tabulation-dataset-send" info-type="ich"/>
    </doc-content>
  </study-document>
</ectd:study>
```
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

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>DOMAIN</th>
<th>TSSEQ</th>
<th>TSGRPID</th>
<th>TSPARMCD</th>
<th>TSPARM</th>
<th>TSVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>pqr-456</td>
<td>TS</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>Strain X</td>
</tr>
<tr>
<td>pqr-456</td>
<td>TS</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>FDA</td>
</tr>
<tr>
<td>pqr-456</td>
<td>TS</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>Random</td>
</tr>
<tr>
<td>pqr-456</td>
<td>TS</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2019-01-01</td>
</tr>
<tr>
<td>pqr-456</td>
<td>TS</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>Ora</td>
</tr>
<tr>
<td>pqr-456</td>
<td>TS</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>USA</td>
</tr>
</tbody>
</table>
**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

---

**TS Study ID**

**Study Start Date**
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 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.

Sponsor submits an application with study data.
FDA Tool - Simplified TS File Creation Guide

**Purpose** – The *Simplified ts.xpt Creation Guide* is a resource that FDA is providing industry to help create a simplified TS file using free and open-source software

- R
- Python

This Guide provides step by step instructions to install the necessary software to create and view the simplified ts.xpt file

Users can simply copy paste the code from the guide to generate the simplified ts.xpt

This guide is intended for users with non programming background to create the simplified ts.xpt with ease

This link to this Guide will be available on the FDA’s Web Page - *Study Data for Submission to CDER and CBER*
PhUSE Utility to Generate Simplified TS Files

- **Purpose** – PhUSE has developed a free web utility to generate a simplified TS

  - This utility provides an simple user interface to generate and view the simplified ts.xpt file

  - Users can download the ts.xpt file after filling the necessary information on the web page like – Study ID, TSPARMCD, TSVAL and TSVALNF

- This link to this Guide will be available on the PhUSE Web Page – https://geotiger.shinyapps.io/07_genTS/
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 |

### Section 1: Application & Submission Information

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1a. FDA Center*</td>
<td>1b. Application Type*</td>
</tr>
<tr>
<td>CDHR</td>
<td>CRFD</td>
</tr>
<tr>
<td>NDA</td>
<td>RLA</td>
</tr>
<tr>
<td>ANOIA</td>
<td>Commercial IND</td>
</tr>
</tbody>
</table>

### Section 2: Study Information

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2a. Study ID*</td>
<td></td>
</tr>
<tr>
<td>(Study ID is the unique identifier across application documents. Therefore, the study ID must be consistent across all files being submitted for the same study, i.e., STF File, eCTD, ARP, etc.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2b. Is the First Time Study Data is Being Submitted for This Study as Part of This Application?*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

If you answered "No" in Field 2b, do not proceed. This self-check worksheet is designed for newly submitted study data.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2c. Title of the Study</td>
<td></td>
</tr>
<tr>
<td>2d. Study Section - eCTD Heading (Example: m4D-2-15)*</td>
<td></td>
</tr>
</tbody>
</table>

### Section 3: Study Information

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3a. Are Files Included in a Study Section? (Not Applicable to Sections 4, 5, 6, 7, 8 &amp; 9.4)*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>3b. If you answered &quot;No&quot; in Field 3a, and no files are included in a study section, excluding sections 4, 5, 6, 7, 8, and 9.4, then Validation Rules 1700, 1701, 1702, and 1708 do not apply. Do not proceed.</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

### Reference:

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

“Technical Rejection Criteria Self-Check Worksheet Instructions”  
[https://www.fda.gov/media/123099/download](https://www.fda.gov/media/123099/download)
TS File Information (1734 Validation Error)

- Provide information about ts.xpt file with study start date
A dataset named ts.xpt with information on Study Start Date (SSD) must be present for each study.

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

| Total Number of Submissions with Study Data | 711 |
| Total Number of Studies in the TRC Applicable Sections | 1269 |
| Total Number Studies with Critical Errors | 215 |
| • Error 1734 | 84 |
| Error Rate (% among submissions with Study Data in TRC Applicable Sections) | 17% |

**84 Studies with Error 1734**

- Invalid study start date: 33%
- Missing ts.xpt: 10%
- No study start date: 57%
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.

### Example

2. Study Files and/or datasets submitted in m4-2-3-2 (TRC applicable study section)

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

**TRC Requirement:** Full TS is needed

**ts.xpt does not exist**

- 57% of studies with 1734 error are because of a missing ts.xpt file

**Fail Rule 1734**
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

### Example

2. Study Files and/or datasets submitted in m4-2-3-2
   (TRC applicable study section)

**Study Start Date:** 2017-01-01

**TRC Requirement:** Simplified TS is needed

### Self-Check Worksheet

<table>
<thead>
<tr>
<th>Study Start Date</th>
<th>Application Type</th>
<th>Data Type</th>
<th>Study Section</th>
<th>Required TS File Type (By Center) CDBR</th>
<th>Required TS File Type (TS File) CDBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to an 17-Dec-16</td>
<td>NDA, BLA, or ANDA</td>
<td>Nonclinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td>Simplified TS</td>
<td>Not Required</td>
</tr>
<tr>
<td>Prior to an 17-Dec-17</td>
<td>Commercial IND</td>
<td>Clinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td>Simplified TS</td>
<td>Not Required</td>
</tr>
<tr>
<td>After 17-Dec-16</td>
<td>NDA, BLA, or ANDA</td>
<td>Nonclinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td>FaTS</td>
<td>Not Required</td>
</tr>
<tr>
<td>After 17-Dec-17</td>
<td>Commercial IND</td>
<td>Clinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td>FaTS</td>
<td>Not Required</td>
</tr>
</tbody>
</table>

**Files Referenced in stf.xml**

- ts.xpt
- Data Tabulation Data
- Data Tabulation Dataset Send

- ts.xpt does exist (Simplified ts.xpt)

- **Pass Rule 1734**
TRC Validation Rule 1734 (Section 4c)

- Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections

---

<table>
<thead>
<tr>
<th>Example</th>
<th>Self-Check Worksheet</th>
</tr>
</thead>
</table>
| 2. Study Files and/or datasets submitted in **m4-2-3-2** (TRC applicable study section)  
**Study Start Date:** 2018-01-01  
**TRC Requirement:** Full TS is needed | 
3d. Study ID in STF File*  
**Study ABC** |

**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

<table>
<thead>
<tr>
<th>Example</th>
<th>Self-Check Worksheet</th>
</tr>
</thead>
</table>
| 2. Study Files and/or datasets submitted in m4-2-3-2 (TRC applicable study section) Study Start Date: 2018-01-01 TRC Requirement: Full TS is needed | ![Example Self-Check Worksheet](image)

[Study Date Format Requirement] • yyyy-mm-dd

Pass Rule 1734

- 10% of studies with 1734 error are because of invalid study start date
## 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 IND Non-Clinical studies- Validation Rule 1735

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

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

### Total Number of Submissions with Study Data
711

### Total Number of Studies in the TRC Applicable Sections
1269

### Total Number Studies with Critical Errors
215

- Error 17345: 119

### Error Rate (% among submissions with Study Data in TRC Applicable Sections)
17%

## IND m4 Non-Clinical 119 Studies with Error 1735

- define: 67%
- xpt: 14%
- define, xpt & legacy: 10%
- xpt & legacy: 9%
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 Commercial INDs:**
- A missing define.xml files
- A missing define.xml, dm.xpt files

**IND m4 Non-Clinical**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Submissions with Study Data</td>
<td>711</td>
</tr>
<tr>
<td>Total Number of Studies in the TRC Applicable Sections</td>
<td>1269</td>
</tr>
<tr>
<td>Total Number Studies with Critical Errors</td>
<td>215</td>
</tr>
<tr>
<td>- Error 1736</td>
<td>36</td>
</tr>
<tr>
<td>Error Rate (% among submissions with Study Data in TRC Applicable Sections)</td>
<td>17%</td>
</tr>
</tbody>
</table>

**36 Studies with Error 1736**

- Missing define.xml: 80%
- Missing define.xml and dm.xpt: 17%
- Missing dm.xpt: 3%
TRC Validation Rule 1735 and 1736 (Section 5b-5c)

- 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

<table>
<thead>
<tr>
<th>Study Files and/or datasets submitted in <strong>m4-2-3-2</strong> (non-clinical)</th>
<th>Self-Check Worksheet</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Start Date:</strong> 2018-01-01</td>
<td></td>
</tr>
<tr>
<td><strong>Dataset Type:</strong> Tabulation (SEND)</td>
<td></td>
</tr>
</tbody>
</table>

Files Referenced in stf.xml

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<tr>
<th>b1.xpt</th>
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<th>b5.xpt</th>
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</thead>
<tbody>
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<td>g6.xpt</td>
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<tr>
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<tr>
<td>z1.xpt</td>
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<td>z5.xpt</td>
<td>z6.xpt</td>
</tr>
</tbody>
</table>

dm.xpt and define.xml are not included

- 80% of studies with 1736 error are because of missing define.xml file
TRC Validation Rule 1735 and 1736 (Section 5b-5c)

- Rule 1735: Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections
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<table>
<thead>
<tr>
<th>Example</th>
<th>Self-Check Worksheet</th>
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</thead>
<tbody>
<tr>
<td>Study Files and/or datasets submitted in m4-2-3-2 (non-clinical)</td>
<td></td>
</tr>
<tr>
<td>Study Start Date: 2018-01-01</td>
<td></td>
</tr>
<tr>
<td>Dataset Type: Tabulation (SEND)</td>
<td></td>
</tr>
<tr>
<td>Dataset Folder</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Folder contents" /></td>
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</tr>
<tr>
<td>Pass Rule 1736</td>
<td></td>
</tr>
</tbody>
</table>

- 80% 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
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Example Self-Check Worksheet

Study Files and/or datasets submitted in **m4-2-3-2 (non-clinical)**

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

Files Referenced in stf.xml

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

67% 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 published Study Data Self-Check Worksheet & Instruction
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

- **Oct. 2019**: FDA published Study Data Self-Check Worksheet & Instruction
- **Early 2020**: FDA will give the industry 90 days notice on the eCTD website prior to the criteria becoming effective

- **90 Days After Notice**: 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/
The author would like to thank Nitin Guptan, Ryan Olivett, Lina Cong, Jiang Xu, Jonathan Resnick, Ethan Chen, Jeffry Florian, Lisa Lin, Gang Wang, and other FDA staff for their time and effort in helping collect and analyze data and information as presented in this presentation.