FDA View: Technical Rejection Criteria for Study Data

Heather Crandall
Office of Business Informatics
Center for Drug Evaluation and Research

June 27, 2019
FDA Disclaimer

The views and opinions presented here represent those of the speakers and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration
Agenda

- TRC Revisions
- CDER Conformance Analysis Trend
- CBER Conformance Analysis Trend
- Typical Error Examples
- Implementation Timeline
- Summary
Revised Technical Rejection Criteria
**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**

Technical Rejection Criteria for Study Data (Revised 05/01/2018)

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.

Technical Rejection Criteria for Study Data (Revised 01/22/2019)

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.

References:
FDA Study Data Technical Rejection Criteria (Revised May 2018)
FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

<table>
<thead>
<tr>
<th>Error</th>
<th>Description - Technical Rejection Criteria for Study Data (Revised 05/01/2018)</th>
<th>Severity Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1734</td>
<td>Trial Summary (TS) dataset must be present for each study in eCTD section 4.2 and 5.3</td>
<td>High</td>
</tr>
<tr>
<td>1736</td>
<td>Demographic dataset (DM) and the define.xml must be submitted in Module 4 for nonclinical data; DM dataset, the subject-level analysis dataset (ADSL) and define.xml must be submitted in Module 5 for clinical data</td>
<td>High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Error</th>
<th>Description - Technical Rejection Criteria for Study Data (Revised 01/22/2019)</th>
<th>Severity Level</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           |

* Refer to the latest Technical Rejection Criteria for Study Data  
** From Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specification, Section J: Datasets must only be provided in modules 3, 4, or 5 and not in modules 1 or 2
Study Data Technical Rejection Criteria Conformance Trend
Study Data Conformance Trend Analysis

Study Data was assessed for:
- NDA, BLA, and ANDA Submissions received from 12/18/2016 to 3/31/2019
- Commercial IND Submissions received from 12/18/2017 to 3/31/2019
- No duplicates

Conformance was checked against the two high-level validation rules as described in the Technical Rejection Criteria for Study Data:
- 1734: TS Dataset and Correct Study Start Date must be present
- 1736: DM Dataset, ADSL Dataset and define.xml must be present
Overall Conformance Trend for Validation Errors 1734 & 1736 for CDER

- Submissions with study data shows overall decreases in Validation Error 1734 and 1736 in all application types
- NDAs and INDs are showing the greatest improvements in conformance

Notes:
1) CY2017 analysis average excludes any submissions received in 2018 & 2019 and was conducted according to TRC (Revised May 2018)
2) CY2018 & CY2019 (Q1) analysis are conducted according to the TRC (Revised Jan. 2019)
ANDA, NDA, BLA, and Commercial IND Submissions were assessed for conformance to high-level error, 1789, as defined in the Technical Rejection Criteria for Study Data (Revised Jan. 2019)

<table>
<thead>
<tr>
<th></th>
<th>NDA</th>
<th>ANDA</th>
<th>BLA</th>
<th>Comm. IND</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>CY2018</td>
<td>41,077</td>
<td>11,011</td>
<td>62,695</td>
<td>14,776</td>
<td>11,042</td>
</tr>
<tr>
<td>Error 1789</td>
<td>43</td>
<td>11</td>
<td>225</td>
<td>53</td>
<td>1</td>
</tr>
<tr>
<td>Failure Rate (%)</td>
<td>0.10%</td>
<td>0.10%</td>
<td>0.36%</td>
<td>0.36%</td>
<td>&lt;0.01%</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, BLA, ANDA and Commercial IND submissions received by CDER between 1/1/2018 to 3/31/2019
4) Analysis is conducted according to the revised TRC

**Reference:** FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)
CDER Conformance Analysis: Validation Errors 1734, 1735 & 1736

- ANDA, NDA, BLA, and Commercial IND Submissions were assessed for conformance to three high-level error, 1734, 1735, & 1736, as defined in the Technical Rejection Criteria for Study Data (Revised Jan. 2019)

- Failure Rate for all applications increased 2.3% (average) between 2018 and 2019

<table>
<thead>
<tr>
<th>NDA</th>
<th>ANDA</th>
<th>BLA</th>
<th>Comm. IND</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>CY2018</td>
<td>CY2019 (Q1)</td>
<td>CY2018</td>
<td>CY2019 (Q1)</td>
<td>CY2018</td>
</tr>
<tr>
<td>Total Number of Submissions with Study Data</td>
<td>877</td>
<td>270</td>
<td>1078</td>
<td>243</td>
</tr>
<tr>
<td>Total Number of Submissions with Study Data in TRC Applicable Sections</td>
<td>204</td>
<td>226</td>
<td>57</td>
<td>172</td>
</tr>
<tr>
<td>Total Number Submissions with Critical Errors</td>
<td>215</td>
<td>71</td>
<td>689</td>
<td>181</td>
</tr>
<tr>
<td>Error 1734</td>
<td>185</td>
<td>52</td>
<td>186</td>
<td>53</td>
</tr>
<tr>
<td>Error 1735</td>
<td>34</td>
<td>23</td>
<td>497</td>
<td>130</td>
</tr>
<tr>
<td>Error 1736</td>
<td>16</td>
<td>3</td>
<td>88</td>
<td>21</td>
</tr>
<tr>
<td>Failure Rate (% among submissions with Study Data)</td>
<td>24.50%</td>
<td>26.30%</td>
<td>63.90%</td>
<td>73.70%</td>
</tr>
<tr>
<td>Failure Rate (% among submissions with Study Data in TRC Applicable Sections)</td>
<td>34.80%</td>
<td>80.10%</td>
<td>26.30%</td>
<td>24.40%</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, BLA, ANDA and Commercial IND submissions received by CDER between 1/1/2018 to 3/31/2019
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
CBER Conformance Analysis including Validation Rules for 1734, 1735, 1736 and 1789
CBER Conformance Analysis: Validation Errors 1734, 1735, 1736 & 1789

CBER BLA Submissions were assessed for conformance to four high-level errors, 1734, 1735, 1736 and 1789 as defined in the Technical Rejection Criteria for Study Data (Revised Jan. 2019)

<table>
<thead>
<tr>
<th>BLA</th>
<th>CY2018</th>
<th>CY2019 (Q1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of studies with Study Data</td>
<td>6062</td>
<td>1644</td>
</tr>
<tr>
<td>Error 1789</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Failure Rate (% among studies with Study Data)</td>
<td>0.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Total Number of Submissions with Study Data in TRC Applicable Sections</td>
<td>49</td>
<td>12</td>
</tr>
<tr>
<td>Total Number of studies with Critical Errors</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Error 1734</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Error 1735</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Error 1736</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Failure Rate (% among studies with Study Data)</td>
<td>30.6%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Failure Rate (% among submissions with Study Data in TRC Applicable Sections)</td>
<td>50.0%</td>
<td>50.0%</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 BLA submissions received by CBER between 1/1/2018 to 3/31/2019
3) Analysis is conducted according to the revised TRC
4) Submission with multiple studies can report both Errors 1734, 1735 and 1736
5) Validation of errors 1735 and 1736 are not performed if a study has Error 1734

Top Error Examples
eCTD Backbone Files

- Leaf ID
- File Path
- File Name

- Leaf ID
- STF Study ID
- File-Tag

- TS Study ID
- Study Start Date
INDEX LEAF ID
<leaf checksum-type="MD5"
xlink:type="simple"
    checksum="98723f7594b5500a861509547c384e46" operation="new"
ID="a103">
    <title>S107 ts.xpt</title>
</leaf>

FILE PATH FROM INDEX
<leaf checksum-type="MD5"
xlink:type="simple"
    checksum="25d3b246313a9dbf688a48da2295260e" operation="new"
ID="a104">
    <title>Study Tagging File for S107</title>
</leaf>

FILE NAME FROM INDEX
</m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
From Index.xml
- Leaf ID
- File Path
- File Name

```xml
<study-identifier>
  <title>Wonderdrug Study S107</title>
  <study-id>S107</study-id>
  <category name="type-of-control" info-type="ich">no-treatment</category>
</study-identifier>
<study-document>
  <doc-content xlink:href="../index.xml#a103">
    <file-tag name="data-tabulation-dataset-sdtm" info-type="ich"/>
  </doc-content>
</study-document>
</ectd:study>
```
eCTD Backbone Files (ts.xpt)

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

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

---

![Diagram showing TS Study ID and Study Start Date]
A dataset named ts.xpt with information on Study Start Date (SSD) 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, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2.

**Common error reason across all application types:**
- a missing ts.xpt file (66% of studies with error 1734)
- a missing study start date in the ts.xpt (25% of studies with error 1734)
### Top Error for Rule 1734: Missing ts.xpt

A missing ts.xpt file (66% of studies with error 1734)

<table>
<thead>
<tr>
<th>Study Start Date</th>
<th>Application Type</th>
<th>Data Type</th>
<th>Study Sections</th>
<th>Expectation by Center</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior to or on 17-Dec-2017</strong></td>
<td>Commercial INDs</td>
<td>Nonclinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td>Rejection criteria will be applied; submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)</td>
</tr>
<tr>
<td></td>
<td></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>Rejection criteria will not be applied</td>
</tr>
<tr>
<td><strong>After 17-Dec-2017</strong></td>
<td>Commercial INDs</td>
<td>Nonclinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td>Rejection criteria will be applied; submit a full TS</td>
</tr>
<tr>
<td></td>
<td></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>Rejection criteria will not be applied</td>
</tr>
<tr>
<td><strong>Prior to or on 17-Dec-2016</strong></td>
<td>NDA, BLA, ANDA</td>
<td>Nonclinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td>Rejection criteria will be applied; submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)</td>
</tr>
<tr>
<td></td>
<td></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>Rejection criteria will be applied; submit a full TS</td>
</tr>
<tr>
<td><strong>After 17-Dec-2016</strong></td>
<td>NDA, BLA, ANDA</td>
<td>Nonclinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td>Rejection criteria will be applied; submit a full TS</td>
</tr>
<tr>
<td></td>
<td></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>Rejection criteria will be applied; submit a full TS</td>
</tr>
</tbody>
</table>
Top Error for Rule 1734: Incorrect Study Start Date Format in ts.xpt

- A missing study start date (TSVAL) in the ts.xpt (25% of studies with error 1734)

<table>
<thead>
<tr>
<th>Correct Study Start Date Format</th>
<th>yyyy-mm-dd</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Incorrect Study Start Date Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>yyyy-mm</td>
</tr>
<tr>
<td>SAS Date Format</td>
</tr>
<tr>
<td>mm/dd/yyyy</td>
</tr>
<tr>
<td>dd-mmm-yy</td>
</tr>
<tr>
<td>yyyy</td>
</tr>
<tr>
<td>mm/dd/yy</td>
</tr>
</tbody>
</table>

This Photo by Unknown Author is licensed under CC BY-NC-ND
The correct STF file tags must be used for all standardized datasets and corresponding define.xml files 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, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2.

Common error reason for ANDAs:
– an incorrect file tag for a define.xml file (42% of ANDA studies with error 1735)

Common error reason for NDAs:
– a dataset tagged as legacy when standardized datasets are required (80% of NDA studies with error 1735)
The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files 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, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2

STUDY TAGGING FILE: “stf-s107.xml”

You have submitted XPT files or define.xml files without correct file tag.

Valid file tags for XPT files are:
data-tabulation-dataset-sdtm
data-tabulation-dataset-send
analysis-dataset-adam

Valid file tags for corresponding define.xml files are:
data-tabulation-data-definition
analysis-data-definition

define.xml is tagged as “data-tabulation-dataset-sdtm”. It should be “data-tabulation-data-definition”
For SEND data, a DM dataset and define.xml must be submitted in module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4

For SDTM data, a DM dataset and define.xml must be submitted 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

For ADaM data, an ADSL dataset and define.xml must be submitted in 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

Common reason across all application types:
- a missing define.xml file (39% of studies)
- a missing define.xml, dm.xpt, and adsl.xpt files (31% of studies)

Common error reason for NDAs:
- missing define.xml and adsl.xpt files
Published Technical Rejection Criteria for Study Data & 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
Implementation Timeline
Study Data Technical Rejection Criteria are REQUIRED but NOT IMPLEMENTED

FDA issued “Providing Regulatory Submissions in Electronic Format – Standardized Study Data: Guidance for Industry”

- Per FD&C Act Section 745A(a), sponsors must conform to standards in the FDA Data Standard Catalog
- 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

Study Data Technical Rejection Criteria are Implemented*

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

Based on the revised TRC, about 40% all submissions were received with non-critical errors for 1734, 1735, and 1736.

FDA requires the submission of standardized Study Data as defined in the FDA Data Standard Catalog.

FDA has not rejected any submission that contains errors as reflected in this analysis.

FDA plans to use technical rejection criteria to identify applications that are not fulfilling this requirement.

TIP

To avoid validation errors, it is important for sponsors and applicants to understand the requirements specified in guidance and recommendations for submitting study data in the Study Data Technical Conformance Guide.
For questions about submitting study data please contact:
– CDER – edata@fda.hhs.gov
– CBER – cber.cdisc@fda.hhs.gov

For questions about eCTD, including stf.xml and file-tags, please contact:
– CDER - esub@fda.hhs.gov
– CBER – esubprep@fda.hhs.gov
References

- “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
The author would like to thank In Young Choi, Lina Cong, Jiang Xu, Jonathan Resnick, Ethan Chen, Virginia Hussong, Ron Fitzmartin, 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.
Thank You

Heather Crandall
Office of Business Informatics
Center for Drug Evaluation and Research

Join the conversation #DIA2019