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Technical Rejection Criteria for Study Data and Self-Check Worksheet

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Center for Drug Evaluation and Research
Agenda

- Revised Technical Rejection Criteria for Study Data
- Technical Rejection Criteria Validation Process
- Implementation Timeline
- Demo of the Self-Check Worksheet
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

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

FDA Monitors & Analyzes Study Data Conformance


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)

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     |
Nonclinical study that are required to qualify for TRC including any study in module 4 ECTD modules 4.2.3.1, 4.2.3.2, or 4.2.3.4 that includes one of the following three file tags:

- ‘pre-clinical-study-report’
- ‘legacy-clinical-study-report’
- ‘study-report-body’

The qualifying non-clinical study must be submitted according to SEND specification.

Certain Non-Clinical studies are exempted for TRC (See Study Data Technical Conformance Guide Section 8.2.2 for details): https://www.fda.gov/media/131872/download

- Non-Clinical Studies does not require SEND Data
- Non-Clinical Study Initiation Dates not relevant

A simplified ts.xpt must submitted for exempted Non-Clinical Studies as below:

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>TSPARMCD</th>
<th>TSVAL</th>
<th>TSVALNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>study ID in STF</td>
<td>STSSTDTC</td>
<td>Use the value ‘NA’</td>
<td></td>
</tr>
</tbody>
</table>
Included Additional Reference for Study ID Match (Oct. 2019)

- Feedback from industry pointed scenarios where ts.xpt study-id may not be able to matched (Ex. when a study is bought by another company and the study id is already established)
- Proposed solution with feedback was inclusion of Sponsor Reference ID (SPREFID) parameter to match the STF study-id
- After analysis, SPREFID parameter matching with STF study-id added to October 2019 SDTRC revision

### Included SPREFID for Study ID matching

<table>
<thead>
<tr>
<th></th>
<th>TRC January 2019</th>
<th>TRC October 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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 and STF need to contain matching study ID values.</td>
<td>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.</td>
</tr>
</tbody>
</table>
SDTRC High Level Validation Process (Revised Oct. 2019)

Validation Rule 1734

START VALIDATION

LOCATE STFs & STUDY FILES

Validation Rule 1789

TS.XPT INCLUDED?

N

FAIL

Y

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

Validation Rule 1736

STUDY START DATE INCLUDED?

N

FAIL

Y

STANDARDIZED DATA REQUIRED?

N

END

Y

VERIFY STUDY FILES

Validation Rule 1735

VERIFY FILE TAGS IN STFs

Y

PASS

N

FAIL

ALL FILE TAGS CORRECT?

Y

PASS

N

FAIL

ALL REQUIRED STUDY FILES INCLUDED?
FDA published Revised Study Data Technical Rejection Criteria (Revised Jan. 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

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

www.fda.gov
FDA is developing tools and resources to help sponsors meet study data standard requirements and provide more transparency on the validation process.

**Online Resources**

- 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

**Gateway**

- 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.
Common TRC Errors Based on CY2019 conformance analysis

**1734** - Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections

- Missing ts.xpt when the CDER or CBER when expect to find one
  - Simplified ts.xpt
  - Full ts.xpt

- Non-matching study-id or SPREFID

- Missing or incorrectly formatted study start date

**1735 & 1736** – For SEND, SDTM, & ADaM datasets a define.xml and dm.xpt and/or adsl.xpt must present and file-tagged correctly

- Missing and/or improperly tagged
  - Define.xml
  - dm.xpt
  - adsl.xpt

Self-Check Worksheet: https://www.fda.gov/media/123098/download
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