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GRx+Biosims™

Generic + Biosimilar Medicines Conference

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

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Agenda

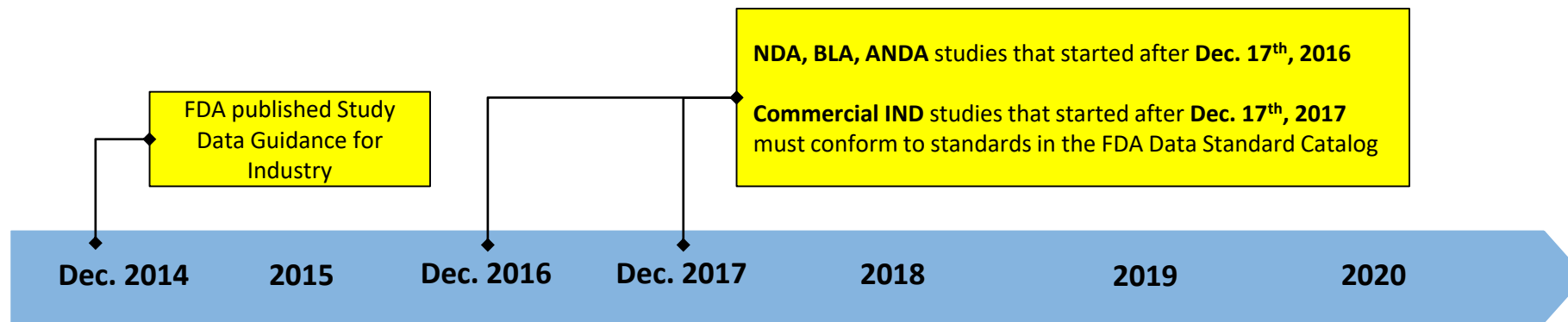
- FDA Guidance and Data Standards Catalog
- Revised Technical Rejection Criteria for Study Data
- Study Data Technical Rejection Criteria Conformance Trend
- Technical Rejection Criteria Validation Process
- Typical Error Examples and Demo of the Self-Check Worksheet
- Implementation Timeline



FDA Guidance and Data Standards Catalog

FDA Guidance and Data Standards Catalog

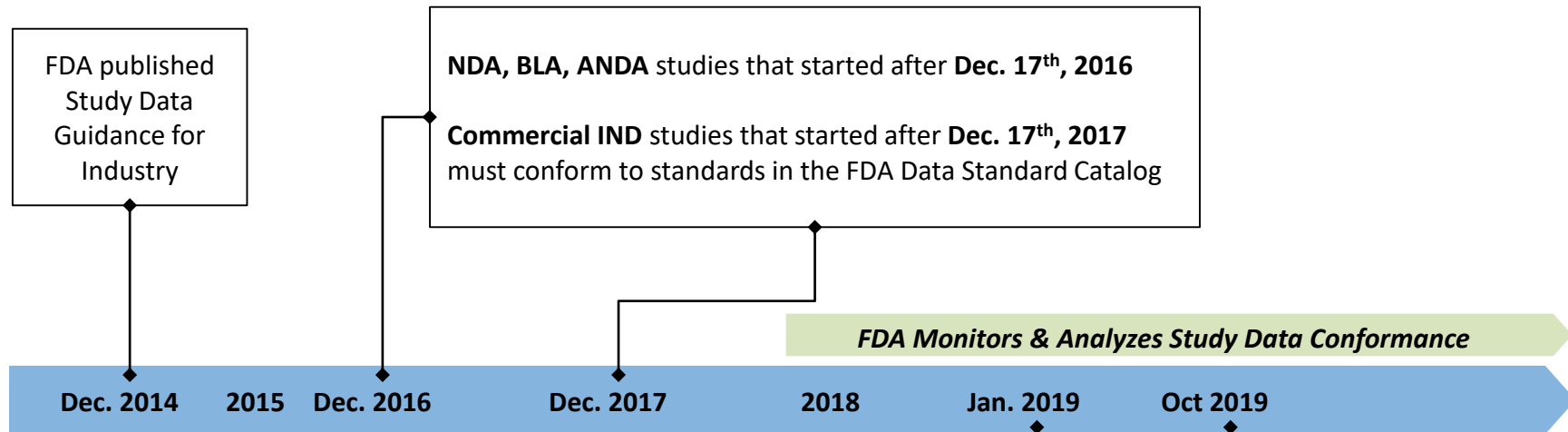
- ❖ Per FD&C Act Section 745A(a), drug application sponsors must use the standards defined in the FDA Data Standards Catalog starting 24 months after final guidance for a specific submission type.
- ❖ FDA issued “Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry” in December 2014.
- ❖ 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

Technical Rejection Criteria for Study Data (Revised Jan. 2019)

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)

Technical Rejection Criteria for Study Data (Revised Oct. 2019)

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

| Refuse to file → Will not accept | |
|---|--|
| <p>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</p> | <p>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</p> |

| Revised TRC rules and elevated 1735 and 1789 to high severity errors | | |
|--|---|----------|
| Error | Description | Severity |
| 1734 | Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections* | High |
| 1735 | Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections* | High |
| 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 |

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:

| STUDYID | TSPARMCD | TSVAL | TSVALNF |
|-----------------|----------|-------|--------------------|
| study ID in STF | SSTDTC | | Use the value 'NA' |

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 and STF need to contain matching study ID values.

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.

Study Data Technical Rejection Criteria (SDTRC) Revisions (Oct. 2019)

Example in Revised TRC -SPREFID for Study ID matching

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).

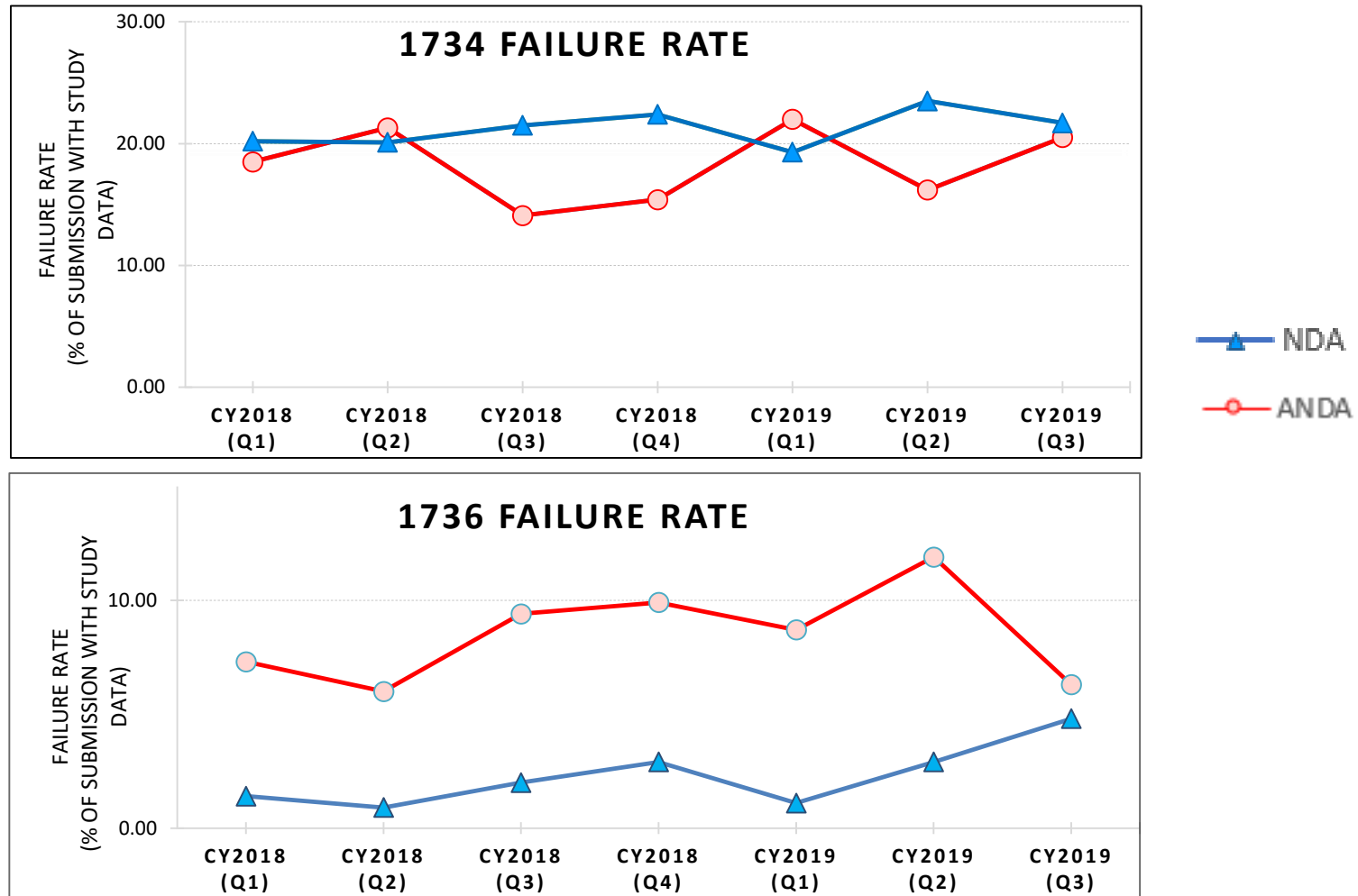
- ❖ Additional parameter in the ts.xpt for matching study id with STF study id to pass validation 1734
 - The SPREFID parameter allows for an alternate way for Sponsors provide a matching study id
 - Multiple SPREFID values are allowed in the ts.xpt



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)

| | NDA | | ANDA | | All | |
|---|--------|----------------|--------|----------------|---------|----------------|
| | CY2018 | CY2019 (Q1-Q3) | CY2018 | CY2019 (Q1-Q3) | CY2018 | CY2019 (Q1-Q3) |
| Total Number of Submissions | 41,077 | 34,166 | 62,695 | 45,683 | 103,722 | 79,849 |
| Error 1789 | 43 | 30 | 225 | 145 | 268 | 175 |
| Failure Rate (% among total number of submissions) | 0.10% | 0.09% | 0.36% | 0.32% | 0.25% | 0.22% |

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

| | NDA | | ANDA | | All | |
|---|--------|----------------|--------|----------------|--------|----------------|
| | CY2018 | CY2019 (Q1-Q3) | CY2018 | CY2019 (Q1-Q3) | CY2018 | CY2019 (Q1-Q3) |
| Total Number of Submissions with Study Data | 877 | 704 | 1,078 | 631 | 1,955 | 1,335 |
| Total Number of Submissions with Study Data in TRC Applicable Sections | | 533 | | 582 | | 1,115 |
| Total Number Submissions with Critical Errors | 215 | 194 | 689 | 428 | 904 | 622 |
| Error 1734 | 185 | 150 | 186 | 125 | 371 | 275 |
| Error 1735 | 34 | 43 | 497 | 307 | 531 | 350 |
| Error 1736 | 16 | 20 | 88 | 56 | 104 | 76 |
| Failure Rate (% among submissions with Study Data) | 24.50% | 27.56% | 63.90% | 67.83% | 46.24% | 46.59% |
| Failure Rate (% among submissions with Study Data in TRC Applicable Sections) | | 36.4% | | 73.54% | | 55.78% |

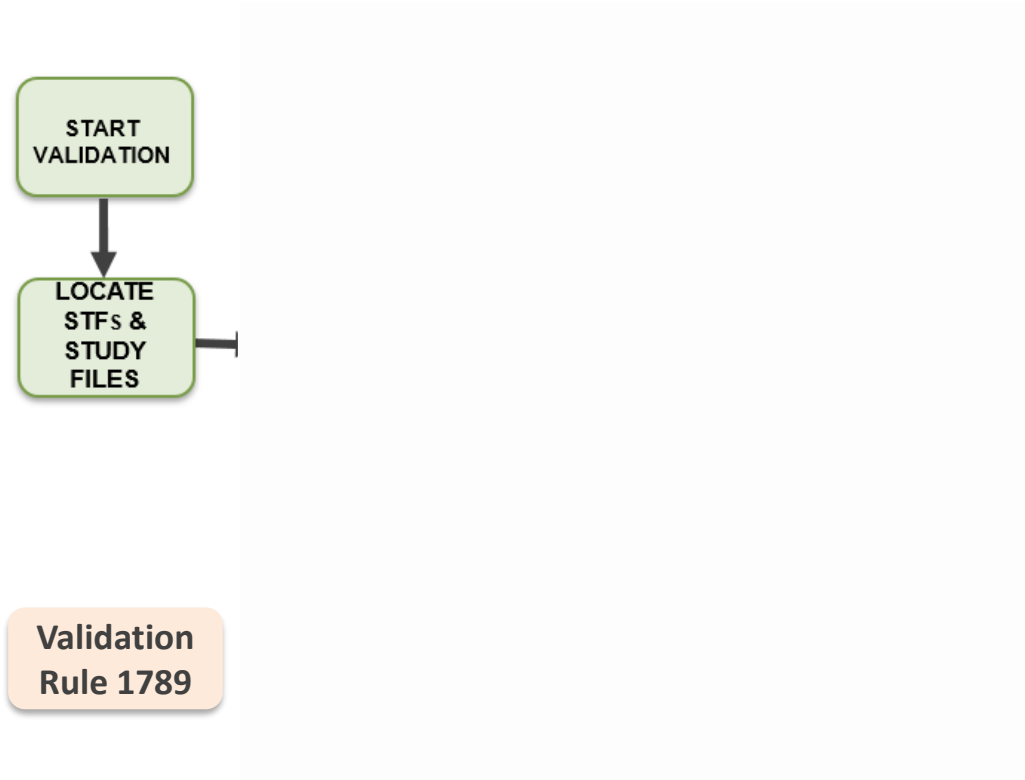
Notes:

- 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)

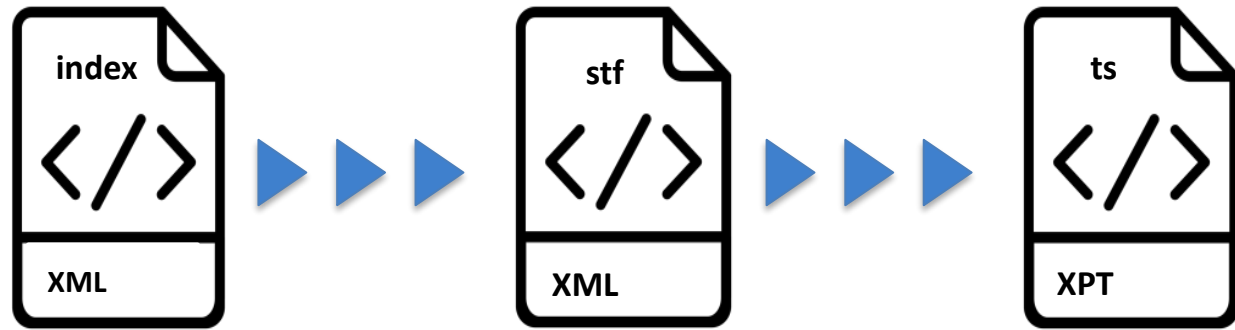


Technical Rejection Criteria Validation Process

SDTRC High Level Validation Process (Revised Oct. 2019)



eCTD Backbone Files

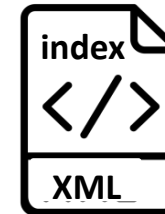


- Leaf ID
- File Path
- File Name

- 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 checksum-type="MD5"
  xlink:type="simple"
  checksum="98723f7594b5500a861509547c384e46" operation="new"
  xlink:href="m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-repcontr/study-s107/ts.xpt"
  application-version="PDF 1.4"
  ID="a103">
  <title>S107 ts.xpt</title>
</leaf>
<leaf checksum-type="MD5"
  xlink:type="simple"
  checksum="25d3b246313a9dbf688a48da2295260e" operation="new"
  xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-repcontr/study-s107/stf-s107.xml"
  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>

```

ID="a103">

INDEX LEAF ID

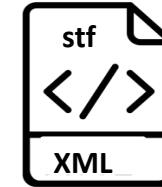
FILE PATH FROM INDEX

FILE NAME FROM INDEX

eCTD Backbone File (stf.xml)

❖ From Index.xml

- Leaf ID
- File Path
- File Name



```

<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="../../../../util/style/ich-stf-stylesheet.xsl"?>
<!DOCTYPE ectd:study SYSTEM "../../../../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="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-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>
  
```

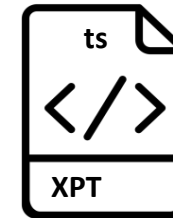
STF STUDY ID (points to <study-id>S107</study-id>)

Index.xml LEAF ID (points to ../../../../index.xml#a103)

FILE TAG ASSOCIATED TO STUDY DOCUMENT (points to <file-tag name="data-tabulation-dataset-sdtm" info-type="ich"/>)

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



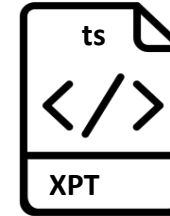
| | STUDYID | DOMAIN | TSSEQ | TSGRPID | TSPARMCD | TSPARM | TSVAL |
|----|---------|--------|-------|---------|----------|------------------------------|------------|
| 27 | pqr-456 | TS | 1 | | SPLRNAM | Test Subject Supplier | Strain X |
| 28 | pqr-456 | TS | 1 | | SPREFID | Sponsor's Study Reference ID | S107 |
| 29 | pqr-456 | TS | 1 | | SRANDOM | Study Is Randomized | FDA |
| 36 | pqr-456 | TS | 1 | | STSTDTC | Study Start Date | 2019-01-01 |
| 37 | pqr-456 | TS | 1 | 1 | TFCNTRY | Test Facility Country | USA |

Diagram annotations:

- Red box around 'pqr-456' in row 37, with an arrow pointing to a box labeled 'TS Study ID'.
- Red box around '2019-01-01' in row 36, with an arrow pointing to a box labeled 'Study Start Date'.
- Red box around 'S107' in row 28, with an arrow pointing to a box labeled 'SPREFID'.

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



Library Properties ts.xpt

Freeze Hide Show... Format Filter... Font... Find

Table View

| | STUDYID | TSPARMCD | TSVAL | TSVALNF |
|-----|---------|----------|------------|---------|
| ▶ 1 | S107 | SSTDTC | 2019-01-01 | |

TS Study ID

Study Start Date



Typical Error Examples and Demo of the Self-Check Worksheet

Tools for Industry

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



Online Resources



Gateway

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 with feedback, highlighting the errors found during the processing of the sample submission

Sponsor submits an application with study data

How Many People are aware of Study Data Self-Check Worksheet?



How Many People use Study Data Self-Check Worksheet?

Self-Check Worksheet

| Section | Contents |
|---------|--|
| 1 | Application & Submission Information <ul style="list-style-type: none"> Provides high level information about the application and submission |
| 2 | Study Information <ul style="list-style-type: none"> Provides more detailed information about the specific study |
| 3 | STF File Information (1789 Validation Error) <ul style="list-style-type: none"> Provide information about STF file |

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
SELF-CHECK WORKSHEET FOR STUDY DATA PREPARATION

Note: This self-check Worksheet is not required for submissions of study data and is designed to help prepare newly submitted study data to FDA, i.e. studies for which no files have been previously submitted.

***Required Field**

Section 1: Application & Submission Information

1a. FDA Center*
 CDER CBER NDA BLA ANDA Commercial IND

1b. Application Type*
 NDA BLA ANDA Commercial IND

1c. Application Number*

1d. eCTD Sequence Number

1e. eCTD Submission Type

1f. eCTD Submission Sub Type

Note: Repeat Sections 2 through 5 for each study included in the submission.

Section 2: Study Information

2a. Study ID*

(Study ID is the unique identifier across application documents. Therefore, the study ID must be consistent across all the files being submitted for the same study, i.e. STF File, ts.xml, dm.xml, etc.)

2b. Is This the First Time Study Data is Being Submitted for This Study as Part of This Application?
 Yes No

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

2c. Title of the Study

2d. Study Section - eCTD Heading (Example: m4-2-1-1)*

2e. Module*
 Nonclinical (m4) Clinical (m5)

2f. Study Dataset Type(s)*
 Tabulation Analysis Other

Section 3: Study Information

3a. Are Files Included in a Study Section? (Not Applicable to Sections 4.3, 5.2, 5.3.6, and 5.4)*
 Yes No

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.

3b. Is STF File Included?*

3c. Does STF File Reference all Associated Study Files?*

[Referenced Validation Error Number 1789](#)

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

3d. Study ID in STF File*

3e. Does the Study ID in the STF File Match Field 2a?
 Yes No

If you answered "No" in Field 3e, ensure the study ID is consistent across all the files being submitted for the same study.

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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>

Self-Check Worksheet (1734 Validation Error)

| Section | Contents |
|---------|--|
| 4 | TS File Information (1734 Validation Error) <ul style="list-style-type: none"> Provide information about ts.xpt file with study start date |

Section 4: TS File Information

4a. What Type of TS File is Required? (Refer to guidelines in chart below.)

Full TS
 Simplified TS
 Not Required

| Study Start Date | Application Type | Data Type | Study Section | Required TS File Type (by Center) CDER | Required TS File Type (by Center) CBER |
|--------------------------|-------------------|-------------|---|--|--|
| Prior to or on 17-Dec-16 | NDA, BLA, or ANDA | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | Simplified TS | Not Required |
| Prior to or on 17-Dec-16 | NDA, BLA, or ANDA | Clinical | 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 | Simplified TS | Simplified TS |
| Prior to or on 17-Dec-17 | Commercial IND | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | Simplified TS | Not Required |
| Prior to or on 17-Dec-17 | Commercial IND | Clinical | 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 | Not Required | Not Required |
| After 17-Dec-16 | NDA, BLA, or ANDA | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | Full TS | Not Required |
| After 17-Dec-16 | NDA, BLA, or ANDA | Clinical | 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 | Full TS | Full TS |
| After 17-Dec-17 | Commercial IND | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | Full TS | Not Required |
| After 17-Dec-17 | Commercial IND | Clinical | 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 | Not Required | Not Required |

If you answered "Not Required" in Field 4a, then Validation Rules 1734, 1735, and 1736 do not apply. Do not proceed.

4b. Is TS File Included? [Referenced Validation Error Number 1734](#)

Yes No

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

4c. Study ID in TS File*

4d. Does Study ID in STF (Field 3d) & TS Files Match? [Referenced Validation Error Number 1734](#)

Yes No

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

| | | |
|---|---|---|
| 4e. Study Start Date in TS File <input style="width: 100%;" type="text"/> | 4f. If Study Start Date Exists, Is it Valid? <input type="checkbox"/> Yes <input type="checkbox"/> No | Referenced Validation Error Number 1734 |
|---|---|---|

4g. If Study Start Date does not Exist, What is the Stated Exception Code?

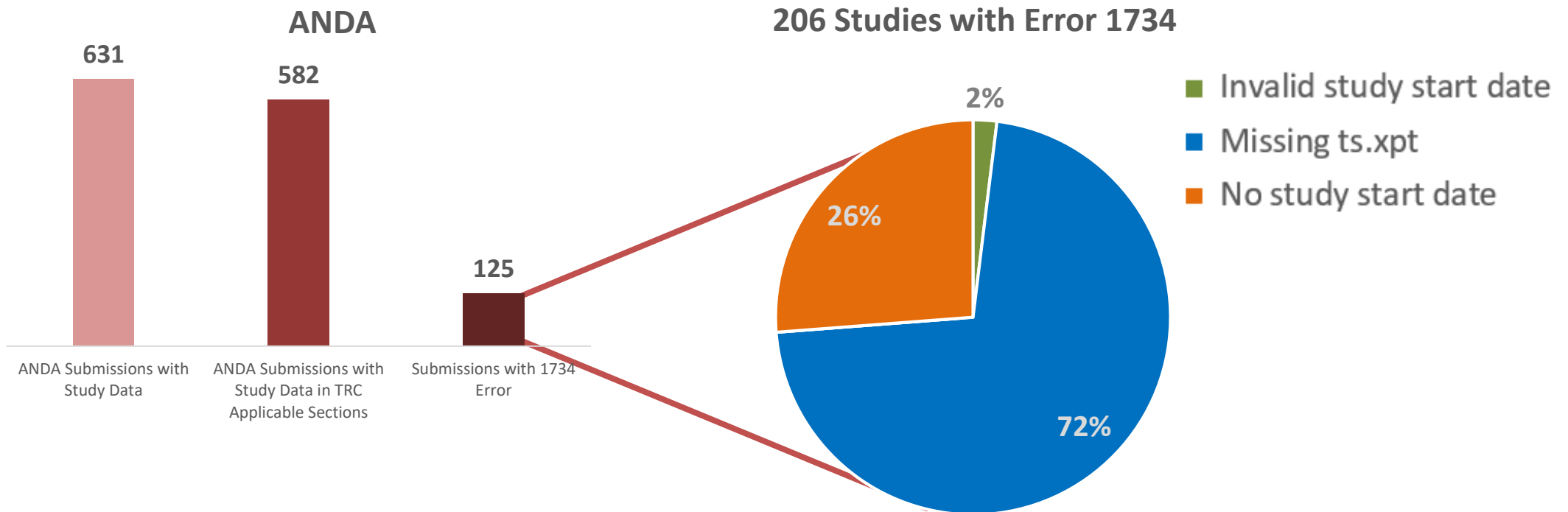
If you do not have a Study Start Date in Field 4e and you do not have a stated Exception Code in Field 4g, Validation Rule 1734 FAILS. Do not proceed.

Or, if you answered "No" in Field 4f, Validation Rule 1734 FAILS. Do not proceed.

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 1734

- ❖ 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



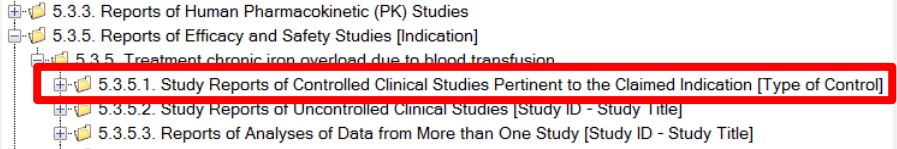
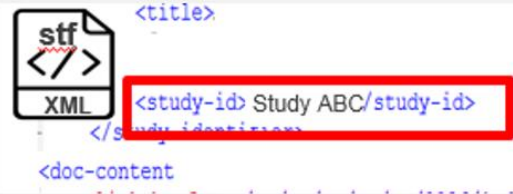
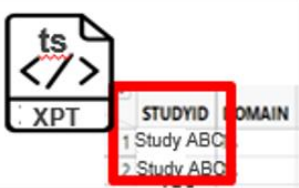

TRC Validation Rule 1734 (Section 4c)

- ❖ 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 | Self-Check Worksheet | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|----------------------|---------------|---|--|--|--------|--------|--------|--------|------------|--------|--------|--------|--------|--------|------------|--------|--|--------|--------|--------|------------|--------|--|-----------|--------|------------|------------|--------|--|---|------------------|------------------|-----------|---------------|--|--|--------------------------|-------------------|-------------|---------------------------|---------------|--------------|--------------------------|-------------------|----------|---|---------------|---------------|--------------------------|----------------|-------------|---------------------------|---------------|--------------|--------------------------|----------------|----------|---|--------------|--------------|-----------------|-------------------|-------------|---------------------------|---------|--------------|-----------------|-------------------|----------|---|---------|---------|-----------------|----------------|-------------|---------------------------|---------|--------------|-----------------|----------------|----------|---|--------------|--------------|
| <p>2. Study Files and/or datasets submitted in m5-3-5-1 (TRC applicable study section) Study Start Date: 2018-01-01 TRC Requirement: <u>Full TS is needed</u></p> <p>5.3.3. Reports of Human Pharmacokinetic (PK) Studies 5.3.5. Reports of Efficacy and Safety Studies [Indication] 5.3.5.1. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication [Type of Control] 5.3.5.2. Study Reports of Uncontrolled Clinical Studies [Study ID - Study Title] 5.3.5.3. Reports of Analyses of Data from More than One Study [Study ID - Study Title]</p> <p>Files Referenced in stf.xml</p> <table border="1"> <tr> <td>acrf.pdf</td> <td>ds.xpt</td> <td>mh.xpt</td> <td>suppda.xpt</td> <td>suppmh.xpt</td> <td>tv.xpt</td> </tr> <tr> <td>ae.xpt</td> <td>dv.xpt</td> <td>pe.xpt</td> <td>suppdm.xpt</td> <td>sv.xpt</td> <td>vs.xpt</td> </tr> <tr> <td>cm.xpt</td> <td>eg.xpt</td> <td>sc.xpt</td> <td>suppds.xpt</td> <td>ta.xpt</td> <td></td> </tr> <tr> <td>co.xpt</td> <td>ex.xpt</td> <td>se.xpt</td> <td>suppeg.xpt</td> <td>te.xpt</td> <td></td> </tr> <tr> <td>csdrq.pdf</td> <td>ie.xpt</td> <td>suppae.xpt</td> <td>suppex.xpt</td> <td>ti.xpt</td> <td></td> </tr> </table> <p style="text-align: center;">ts.xpt does not exist</p> <p style="text-align: center;"> Fail Rule 1734</p> | acrf.pdf | ds.xpt | mh.xpt | suppda.xpt | suppmh.xpt | tv.xpt | ae.xpt | dv.xpt | pe.xpt | suppdm.xpt | sv.xpt | vs.xpt | cm.xpt | eg.xpt | sc.xpt | suppds.xpt | ta.xpt | | co.xpt | ex.xpt | se.xpt | suppeg.xpt | te.xpt | | csdrq.pdf | ie.xpt | suppae.xpt | suppex.xpt | ti.xpt | | <p>3b. Is STF File Included?*</p> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Referenced Validation Error Number 1789 <p>3c. Does STF File Reference all Associated Study Files?*</p> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <p><i>If you answered "No" in Fields 3b or 3c, Validation Rule 1789 FAILS. Do not proceed.</i></p> <p>3d. Study ID in STF File*</p> <input type="text" value="ABC 123"/> 3e. Does the Study ID in the STF File Match Field 2a? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <p><i>If you answered "No" in Field 3e, ensure the study ID is consistent across all the files being submitted for the same study.</i></p> <p>Section 4: TS File Information</p> <p>4a. What Type of TS File is Required? (Refer to guidelines in chart below.)</p> <input checked="" type="checkbox"/> Full TS <input type="checkbox"/> Simplified TS <input type="checkbox"/> Not Required <table border="1"> <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) CDER</th> <th>Required TS File Type (by Center) CBER</th> </tr> </thead> <tbody> <tr> <td>Prior to or on 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 or on 17-Dec-16</td> <td>NDA, BLA, or ANDA</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>Simplified TS</td> <td>Simplified TS</td> </tr> <tr> <td>Prior to or on 17-Dec-17</td> <td>Commercial IND</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 or on 17-Dec-17</td> <td>Commercial IND</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>Not Required</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>Full TS</td> <td>Not Required</td> </tr> <tr> <td>After 17-Dec-16</td> <td>NDA, BLA, or ANDA</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>Full TS</td> <td>Full TS</td> </tr> <tr> <td>After 17-Dec-17</td> <td>Commercial IND</td> <td>Nonclinical</td> <td>4.2.3.1, 4.2.3.2, 4.2.3.4</td> <td>Full TS</td> <td>Not Required</td> </tr> <tr> <td>After 17-Dec-17</td> <td>Commercial IND</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>Not Required</td> <td>Not Required</td> </tr> </tbody> </table> <p><i>If you answered "Not Required" in Field 4a, then Validation Rules 1734, 1735, and 1736 do not apply. Do not proceed.</i></p> <p>4b. Is TS File Included?*</p> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Referenced Validation Error Number 1734 <p><i>If you answered "No" in Field 4b, Validation Rule 1734 FAILS. Do not proceed.</i></p> <p>4c. Study ID in TS File*</p> <input type="text" value="ABC 123"/> <p>4d. Does Study ID in STF (Field 3d) & TS Files Match?</p> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Referenced Validation Error Number 1734 <p><i>If you answered "No" in Field 4d, Validation Rule 1734 FAILS. Do not proceed.</i></p> | Study Start Date | Application Type | Data Type | Study Section | Required TS File Type (by Center) CDER | Required TS File Type (by Center) CBER | Prior to or on 17-Dec-16 | NDA, BLA, or ANDA | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | Simplified TS | Not Required | Prior to or on 17-Dec-16 | NDA, BLA, or ANDA | Clinical | 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 | Simplified TS | Simplified TS | Prior to or on 17-Dec-17 | Commercial IND | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | Simplified TS | Not Required | Prior to or on 17-Dec-17 | Commercial IND | Clinical | 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 | Not Required | Not Required | After 17-Dec-16 | NDA, BLA, or ANDA | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | Full TS | Not Required | After 17-Dec-16 | NDA, BLA, or ANDA | Clinical | 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 | Full TS | Full TS | After 17-Dec-17 | Commercial IND | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | Full TS | Not Required | After 17-Dec-17 | Commercial IND | Clinical | 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 | Not Required | Not Required |
| acrf.pdf | ds.xpt | mh.xpt | suppda.xpt | suppmh.xpt | tv.xpt | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ae.xpt | dv.xpt | pe.xpt | suppdm.xpt | sv.xpt | vs.xpt | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| cm.xpt | eg.xpt | sc.xpt | suppds.xpt | ta.xpt | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| co.xpt | ex.xpt | se.xpt | suppeg.xpt | te.xpt | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| csdrq.pdf | ie.xpt | suppae.xpt | suppex.xpt | ti.xpt | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Study Start Date | Application Type | Data Type | Study Section | Required TS File Type (by Center) CDER | Required TS File Type (by Center) CBER | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prior to or on 17-Dec-16 | NDA, BLA, or ANDA | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | Simplified TS | Not Required | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prior to or on 17-Dec-16 | NDA, BLA, or ANDA | Clinical | 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 | Simplified TS | Simplified TS | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prior to or on 17-Dec-17 | Commercial IND | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | Simplified TS | Not Required | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prior to or on 17-Dec-17 | Commercial IND | Clinical | 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 | Not Required | Not Required | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| After 17-Dec-16 | NDA, BLA, or ANDA | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | Full TS | Not Required | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| After 17-Dec-16 | NDA, BLA, or ANDA | Clinical | 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 | Full TS | Full TS | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| After 17-Dec-17 | Commercial IND | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | Full TS | Not Required | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| After 17-Dec-17 | Commercial IND | Clinical | 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 | Not Required | Not Required | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

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 | Self-Check Worksheet |
|--|---|
| <p>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</p>  <p>[Study IDs Match Requirement]</p>   <p> Pass Rule 1734</p> | <p>Section 4: TS File Information</p> <p>4a. What Type of TS File is Required? (Refer to guidelines in chart below.) <input type="checkbox"/> Full TS <input type="checkbox"/> Sim</p> <p>3d. Study ID in STF File* <input type="text" value="Study ABC"/> Referenced Validation Error Number 1734</p> <p>4b. Is TS File Included?*</p> <input type="checkbox"/> Yes <input type="checkbox"/> No <i>If you answered "No" in Field 4b, Validation Rule 1734 FAILS. Do not proceed.</i> <p>4c. Study ID in TS File* <input type="text" value="Study ABC"/></p> <p>4d. Does Study ID in STF (Field 3d) & TS Files Match? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Referenced Validation Error Number 1734</p> <p><i>If you answered "No" in Field 4d, Validation Rule 1734 FAILS. Do not proceed.</i></p> <p>4e. Study Start Date in TS File <input type="text" value=""/> <input type="checkbox"/> Yes <input type="checkbox"/> No Referenced Validation Error Number 1734</p> <p>4f. If Study Start Date Exists, Is it Valid? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>4g. If Study Start Date does not Exist, What is the Stated Exception Code? <input type="text" value=""/></p> |

TRC Validation Rule 1734 (Section 4c)

- ❖ 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 | Self-Check Worksheet | | | | | | | | |
|---|---|------------|--|--------|------------------|------------|--|---|---|
| <p>2. Study Files and/or datasets submitted in m5-3-5-1 (TRC applicable study section) Study Start Date: 2018-01-01 TRC Requirement: <u>Full TS is needed</u></p> <p>[Study Date Format Requirement]</p> <ul style="list-style-type: none"> • yyyy-mm-dd <table border="1" style="width: 100%; text-align: center;"> <thead> <tr> <th colspan="3">TS.XPT</th> </tr> </thead> <tbody> <tr> <td style="width: 30%;">SSTDTC</td> <td style="width: 30%; border: 2px solid red;">Study Start Date</td> <td style="width: 40%; border: 2px solid red;">2018-01-01</td> </tr> </tbody> </table> <div style="text-align: center; margin-top: 20px;"> Pass Rule 1734 </div> | TS.XPT | | | SSTDTC | Study Start Date | 2018-01-01 | <div style="border: 1px solid black; padding: 5px;"> <p>Section 4: TS File Information</p> <hr/> <p>4a. What Type of TS File is Required?* (Refer to guidelines in chart below.)</p> <p> <input checked="" type="checkbox"/> Full TS <input type="checkbox"/> Simplified TS <input type="checkbox"/> Not Required </p> <hr/> <p>4b. Is TS File Included?*</p> <p> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No </p> <p style="font-size: small; color: gray;">If you answered "No" in Field 4b, Validation Rule 1734 FAILS. Do not proceed.</p> <hr/> <p>4c. Study ID in TS File*</p> <p style="background-color: #e6f2ff; padding: 2px;">Study ABC</p> <hr/> <p>4d. Does Study ID in STF (Field 3d) & TS Files Match?</p> <p> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No </p> <p style="font-size: small; color: gray;">If you answered "No" in Field 4d, Validation Rule 1734 FAILS. Do not proceed.</p> <hr/> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 60%; border: 2px solid red; padding: 2px;"> 4e. Study Start Date in TS File <div style="background-color: #e6f2ff; padding: 2px;">2018-01-01</div> </td> <td style="width: 40%; border: 2px solid red; padding: 2px;"> 4f. If Study Start Date Exists, Is it Valid? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No </td> </tr> </table> <p style="font-size: x-small; color: gray;">4g. If Study Start Date does not Exist, what is the Stated Exception Code? <div style="background-color: #e6f2ff; height: 15px; width: 100%;"></div> </p> </div> | 4e. Study Start Date in TS File <div style="background-color: #e6f2ff; padding: 2px;">2018-01-01</div> | 4f. If Study Start Date Exists, Is it Valid? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| TS.XPT | | | | | | | | | |
| SSTDTC | Study Start Date | 2018-01-01 | | | | | | | |
| 4e. Study Start Date in TS File <div style="background-color: #e6f2ff; padding: 2px;">2018-01-01</div> | 4f. If Study Start Date Exists, Is it Valid? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No | | | | | | | | |

Self-Check Worksheet (1735 & 1736 Validation Error)

| Section | Contents |
|---------|--|
| 5 | Standardized Dataset Information (1735 & 1736 Validation Error) <ul style="list-style-type: none"> Provide information about SEND or STDM and/or ADaM dataset and define.xml Provide information about STF File-tags |

Section 5: Standardized Datasets (SEND, SDTM, ADaM)

5a. Are Standardized Datasets Required?
 Yes No

| Study Start Date | Application Type | Standardized Datasets Required? |
|--------------------------|-------------------|---------------------------------|
| Prior to or on 17-Dec-16 | NDA, BLA, or ANDA | Not Required |
| After 17-Dec-16 | NDA, BLA, or ANDA | Required |
| Prior to or on 17-Dec-17 | Commercial IND | Not Required |
| After 17-Dec-17 | Commercial IND | Required |

If you answered "No" in Field 5a, standardized datasets are not required and Validation Rules 1735 and 1736 do not apply. Do not proceed.

Fields 5b-5e are applicable to nonclinical tabulation datasets (SEND), Fields 5f-5i are applicable to clinical tabulation datasets (SDTM), and Fields 5j-5m are applicable to clinical analysis datasets (ADaM).

Note: For clinical data in Commercial INDs standardized datasets are required if the study start data is after the date stated, however, study data technical rejection criteria will not be applicable until further notice.

Clinical (m5)

Tabulation (SDTM datasets)

5f. Is DM File Included? Yes No

5g. Is Define File Included? Yes No

[Referenced Validation Error Number 1738](#)

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

5h. Are the STF File-Tags for the SDTM Datasets "data-tabulation-dataset-sdtm"?? Yes No

5i. Is the STF File-Tag for the Define File "data-tabulation-data-definition"?? Yes No

[Referenced Validation Error Number 1735](#)

If you answered "No" in Fields 5h or 5i, Validation Rule 1735 FAILS.

Analysis (ADaM datasets)

5j. Is ADSL File Included? Yes No

5k. Is Define File Included? Yes No

[Referenced Validation Error Number 1738](#)

If you answered "No" in Fields 5j or 5k, Validation Rule 1736 FAILS. Proceed to Fields 5l and 5m for Validation Rule 1735.

5l. Are the STF File-Tags for the ADaM Datasets "analysis-dataset-adam"?? Yes No

5m. Is the STF File-tag for the Define File "analysis-data-definition"?? Yes No

[Referenced Validation Error Number 1735](#)

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Fillable Self-Check Worksheet

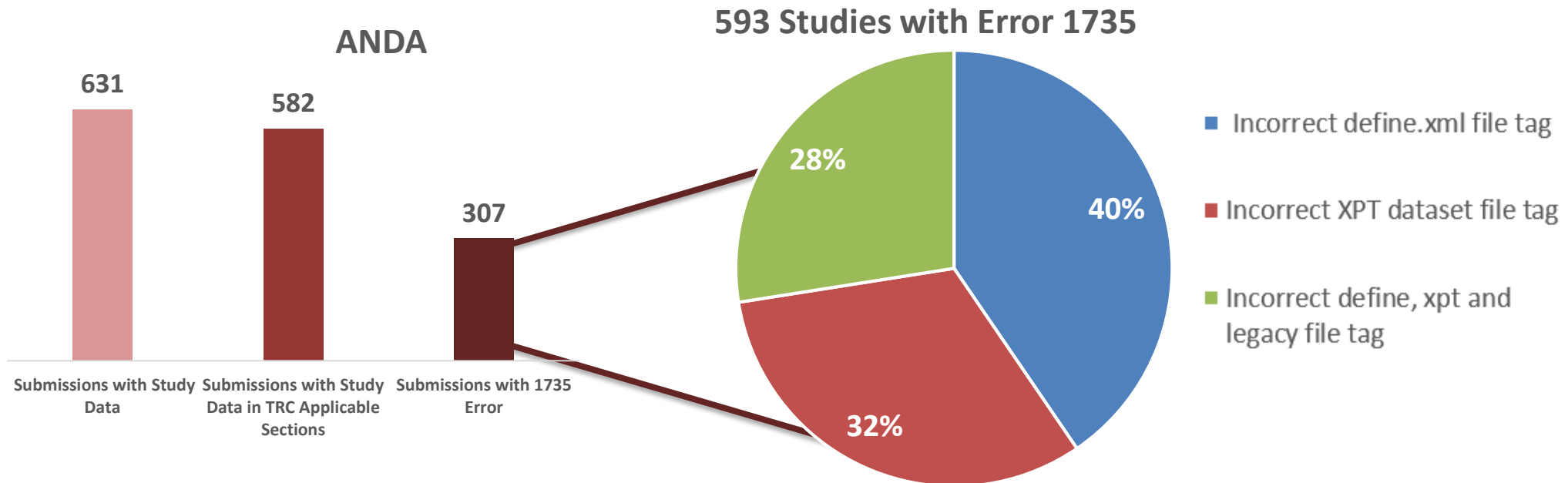
Reference:
 "Technical Rejection Criteria Self-Check Worksheet"
<https://www.fda.gov/media/123098/download>
 "Technical Rejection Criteria Self-Check Worksheet Instructions"
<https://www.fda.gov/media/123099/download>

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

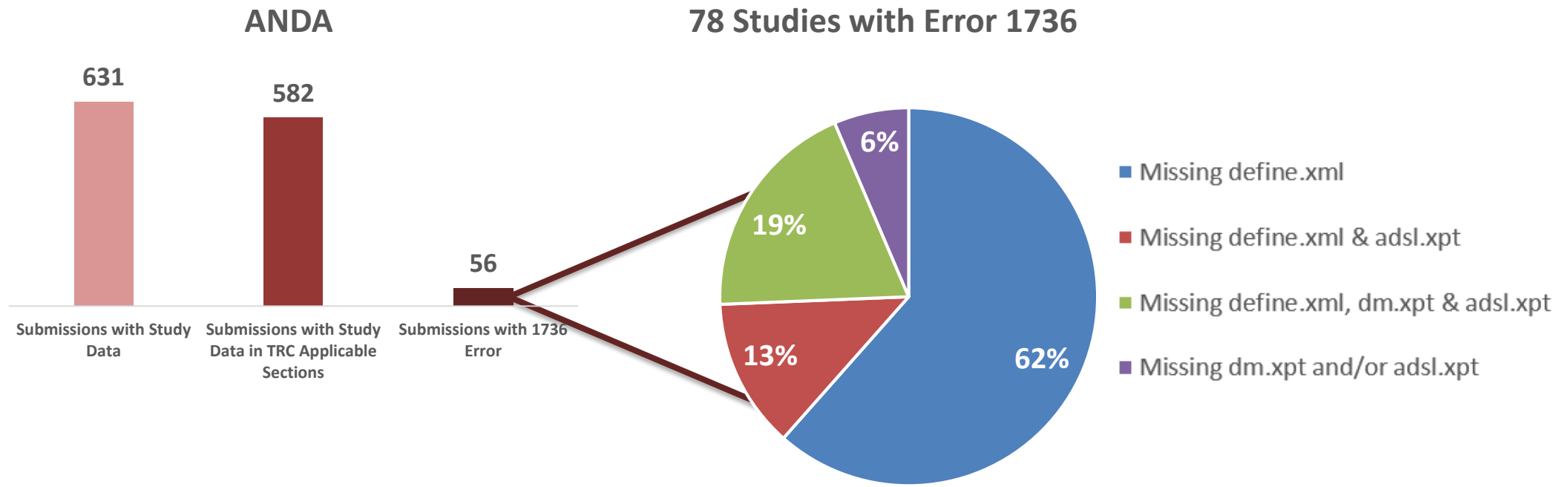
❖ **Common error reason for ANDAs:**

- An incorrect file tag for a define.xml file
- An incorrect file tag for a XPT file



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 5b-5m)

- ❖ 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 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|------------|------------|------------|------------|--------|--------|--------|--------|------------|--------|--------|--------|--------|--------|------------|--------|--|--------|--------|--------|------------|--------|--|-----------|--------|------------|------------|--------|--|--|---------------------------|-------------------------------|---|---|
| <p>Study Files and/or datasets submitted in m5-3-5-1 (clinical) Study Start Date: 2018-01-01 Dataset Type: Tabulation (SDTM)</p> <div style="border: 1px solid #ccc; padding: 5px; margin: 5px 0;"> <p style="text-align: center; margin: 0;">Files Referenced in stf.xml</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td> acrf.pdf</td> <td> ds.xpt</td> <td> mh.xpt</td> <td> suppda.xpt</td> <td> suppmh.xpt</td> <td> tv.xpt</td> </tr> <tr> <td> ae.xpt</td> <td> dv.xpt</td> <td> pe.xpt</td> <td> suppdm.xpt</td> <td> sv.xpt</td> <td> vs.xpt</td> </tr> <tr> <td> cm.xpt</td> <td> eg.xpt</td> <td> sc.xpt</td> <td> suppds.xpt</td> <td> ta.xpt</td> <td></td> </tr> <tr> <td> co.xpt</td> <td> ex.xpt</td> <td> se.xpt</td> <td> suppeg.xpt</td> <td> te.xpt</td> <td></td> </tr> <tr> <td> csdrq.pdf</td> <td> ie.xpt</td> <td> suppae.xpt</td> <td> suppex.xpt</td> <td> ti.xpt</td> <td></td> </tr> </table> </div> <div style="text-align: center; margin-top: 20px;"> <h3 style="color: red; margin: 0;">Fail Rule 1736</h3> </div> | acrf.pdf | ds.xpt | mh.xpt | suppda.xpt | suppmh.xpt | tv.xpt | ae.xpt | dv.xpt | pe.xpt | suppdm.xpt | sv.xpt | vs.xpt | cm.xpt | eg.xpt | sc.xpt | suppds.xpt | ta.xpt | | co.xpt | ex.xpt | se.xpt | suppeg.xpt | te.xpt | | csdrq.pdf | ie.xpt | suppae.xpt | suppex.xpt | ti.xpt | | <div style="border: 1px solid #ccc; padding: 5px; margin-bottom: 10px;"> <p style="margin: 0;">Clinical (m5)</p> <p style="margin: 0;"><i>Tabulation (SDTM datasets)</i></p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-right: 1px solid #ccc;"> 5f. Is DM File Included?*</td> <td style="width: 50%;"> 5g. Is Define File Included?*</td> </tr> <tr> <td style="border-right: 1px solid #ccc;"> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</td> <td> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</td> </tr> </table> <div style="text-align: right; margin-top: 5px;"> Referenced Validation Error Number 1736 </div> <p style="font-size: small; margin-top: 5px;">If you answered "No" in Fields 5f or 5g, Validation Rule 1736 FAILS. Proceed to Fields 5h and 5i for Validation Rule 1735.</p> </div> <p style="color: red; font-weight: bold; margin-top: 20px;">dm.xpt and define.xml are not included</p> <p style="color: red; font-weight: bold; margin-top: 20px;">❖ 62% of studies with 1736 error are because of missing define.xml file</p> | 5f. Is DM File Included?* | 5g. Is Define File Included?* | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| acrf.pdf | ds.xpt | mh.xpt | suppda.xpt | suppmh.xpt | tv.xpt | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| cm.xpt | eg.xpt | sc.xpt | suppds.xpt | ta.xpt | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| 5f. Is DM File Included?* | 5g. Is Define File Included?* | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

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 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---------------------------------|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|------------------|------------------|---------------------------------|--------------------------|-------------------|--------------|-----------------|-------------------|----------|--------------------------|----------------|--------------|-----------------|----------------|----------|
| <p>Study Files and/or datasets submitted in m5-3-5-1 (clinical) Study Start Date: 2018-01-01 Dataset Type: Tabulation (SDTM)</p> <div style="border: 1px solid #ccc; padding: 5px; margin-top: 10px;"> <p style="text-align: center;">Dataset Folder</p> <table border="0"> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table> </div> <div style="text-align: center; margin-top: 20px;"> <h2 style="color: green;">Pass Rule 1736</h2> </div> | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | <div style="border: 1px solid #ccc; padding: 5px;"> <p>Section 5: Standardized Datasets (SEND, SDTM, ADaM)</p> <p>5a. Are Standardized Datasets Required?*</p> <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Study Start Date</th> <th>Application Type</th> <th>Standardized Datasets Required?</th> </tr> </thead> <tbody> <tr> <td>Prior to or on 17-Dec-16</td> <td>NDA, BLA, or ANDA</td> <td>Not Required</td> </tr> <tr> <td>After 17-Dec-16</td> <td>NDA, BLA, or ANDA</td> <td>Required</td> </tr> <tr> <td>Prior to or on 17-Dec-17</td> <td>Commercial IND</td> <td>Not Required</td> </tr> <tr> <td>After 17-Dec-17</td> <td>Commercial IND</td> <td>Required</td> </tr> </tbody> </table> <p>Clinical (m5)</p> <p>Tabulation (SDTM datasets)</p> <div style="border: 2px solid red; padding: 5px; margin-top: 5px;"> <p>5i. Is the DM File included? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>5j. Is the Define File included? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="font-size: small;">If you answered "No" in Fields 5i or 5j, Validation Rule 1736 FAILS. Proceed to Fields 5h and 5l for Validation Rule 1735.</p> </div> <p style="text-align: right; font-size: small;">Referenced Validation Error Number 1736</p> <p>5i. Is the STF File-Tag for the Define File "data-tabulation-data-definition"?</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="text-align: right; font-size: small;">Referenced Validation Error Number 1735</p> <p style="font-size: x-small;">If you answered "No" in Fields 5h or 5i, Validation Rule 1735 FAILS.</p> </div> | Study Start Date | Application Type | Standardized Datasets Required? | Prior to or on 17-Dec-16 | NDA, BLA, or ANDA | Not Required | After 17-Dec-16 | NDA, BLA, or ANDA | Required | Prior to or on 17-Dec-17 | Commercial IND | Not Required | After 17-Dec-17 | Commercial IND | Required |
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| Study Start Date | Application Type | Standardized Datasets Required? | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prior to or on 17-Dec-16 | NDA, BLA, or ANDA | Not Required | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| After 17-Dec-16 | NDA, BLA, or ANDA | Required | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prior to or on 17-Dec-17 | Commercial IND | Not Required | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| After 17-Dec-17 | Commercial IND | Required | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | ❖ 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 |
|--|---|
| <p>Study Files and/or datasets submitted in m5-3-5-1 (clinical) Study Start Date: 2018-01-01 Dataset Type: Tabulation (SDTM)</p> <div style="border: 1px solid #ccc; padding: 5px; margin-bottom: 10px;"> <p style="text-align: center; margin: 0;">Files Referenced in stf.xml</p> <div style="display: flex; justify-content: space-between; font-size: 0.8em;"> <div style="width: 30%;"> <p>acrf.pdf</p> <p>co.xpt</p> <p>define.xml</p> </div> <div style="width: 30%;"> <p>ae.xpt</p> <p>cstrg.pdf</p> <p>define2-0-0.xsl</p> </div> <div style="width: 30%;"> <p>cm.xpt</p> <p>define.pdf</p> <p>dm.xpt</p> </div> </div> </div> <div style="border: 1px solid #ccc; padding: 5px;"> <p style="text-align: center; margin: 0;">stf.xml</p> <pre style="font-family: monospace; font-size: 0.8em; margin: 0;"> <doc-content xlink:href=".../0001/index.xml#0003"><file-tag name= "data-tabulation-dataset-sdtm" info-type="us" /> <doc-content xlink:href=".../0001/index.xml#0004"><file-tag name= "data-tabulation-data-definition" info-type="us" /></doc-content> </pre> </div> <div style="text-align: center; margin-top: 20px;"> <h2 style="color: green; margin: 0;">Pass Rule 1735</h2> </div> | <div style="border: 2px solid red; padding: 10px; margin-bottom: 20px;"> <p>5h. Are the STF File-Tags for the SDTM Datasets "data-tabulation-dataset-sdtm"?</p> <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <hr/> <p>5i. Is the STF File-Tag for the Define File "data-tabulation-data-definition"?</p> <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="font-size: 0.8em; color: blue;">If you answered "No" in Fields 5h or 5i, Validation Rule 1735 FAILS.</p> </div> <div style="border: 1px solid #ccc; padding: 5px; text-align: center; margin-bottom: 20px;"> <p style="font-size: 0.8em; color: blue;">Referenced Validation Error Number 1735</p> </div> <div style="text-align: center; color: green; font-weight: bold; font-size: 1.2em; margin-bottom: 20px;"> <p>define.xml is tagged as "data-tabulation-data-definition"</p> </div> <div style="color: red; font-weight: bold; font-size: 1.2em;"> <p>❖ 40% of studies with 1735 error are because of improper file tag of define.xml file in the stf.xml</p> </div> |

Published SDTRC and Self-Check Worksheet

Study Data for Submission to CDER and CBER

Sign up for email updates.

Data standards enable FDA to modernize and streamline the review process. They also enable more consistent use of analysis tools to better view drug data and highlight areas of concern.

Study data standards describe a standard way to exchange clinical and nonclinical research data between computer systems. These standards provide a consistent general framework for organizing study data, including templates for datasets, standard names for variables, and standard ways of doing calculations with common variables.

FDA is instituting new requirements for data standards that will apply to most study data submitted to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

Beginning after the dates specified below, FDA may refuse to file for New Drug Applications (NDAs) and Biologics License Applications (BLAs) or refuse to receive for Abbreviated NDAs (ANDAs) any electronic submission whose study data do not conform to the required standards specified in the FDA Data Standards Catalog. See the [Technical Rejection Criteria for Study Data \(PDF\)](#) for more information. FDA conducted an analysis of study data conformance on submissions received during a specified time period and developed a presentation on the overall conformance results. [Study Data Conformance \(PDF\)](#) To assist sponsors when submitting study data, FDA has created the [Technical Rejection Criteria Self-Check Worksheet \(PDF\)](#) and [Worksheet Instructions \(PDF\)](#).

Stay Connected

If you have study data questions for CDER, please contact the CDER eDATA Team at cdere-data@fda.hhs.gov.

For electronic submissions, contact the CDER Electronic Submission (ESUB) Support Team at esub@fda.hhs.gov.

If you have study data questions for CBER, please contact [CDER eDATA](mailto:cdere-data@fda.hhs.gov).

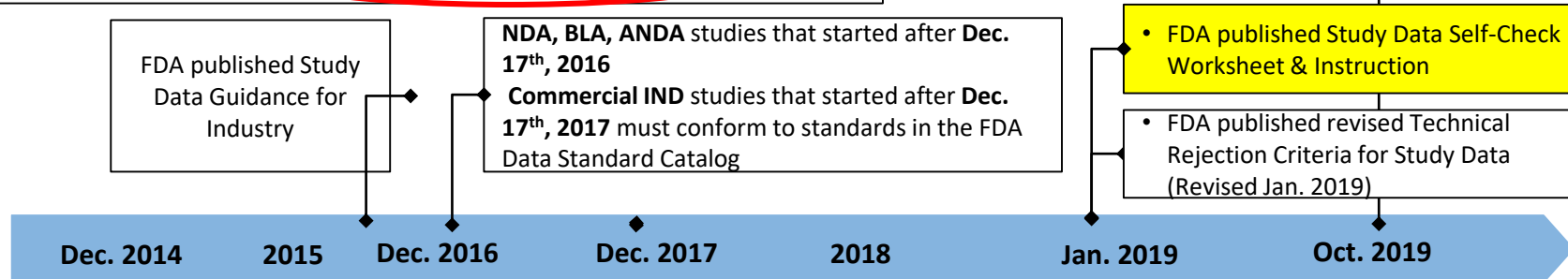
For electronic submissions, contact CBER ESUB at esubprep@fda.hhs.gov.

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

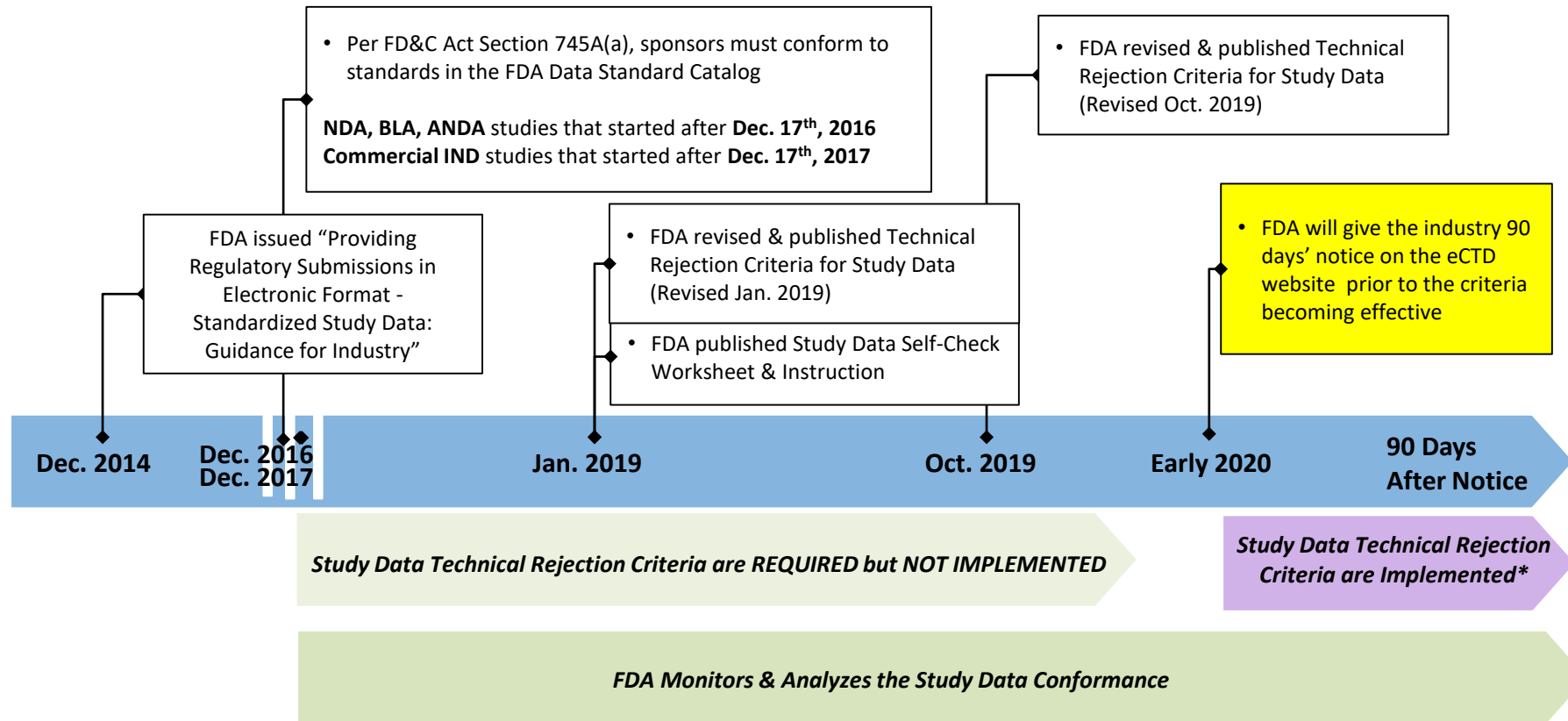




Implementation Timeline

Implementation Timeline

- ❖ FDA published Revised Study Data Technical Rejection Criteria (Revised Oct. 2019) and Study Data Self-Check Worksheet to assist sponsors with the TRC 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” <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>
- ❖ “Providing Regulatory Submissions In Electronic Format - Submissions Under Section 745a(a) Of The FD&C Act: Guidance For Industry” <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384686.pdf>
- ❖ “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” <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630733.pdf>
- ❖ 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/

Acknowledgements

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*Thank
You*