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

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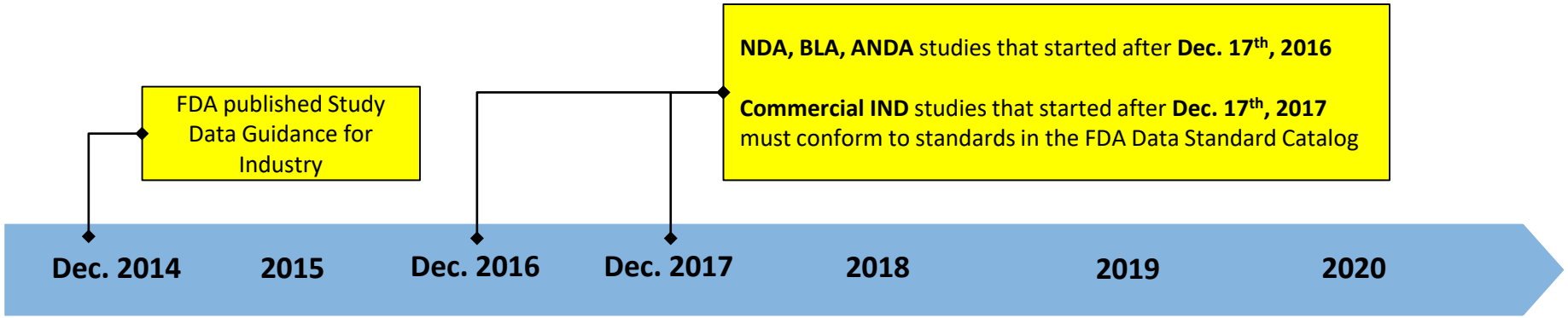
Agenda

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

FDA Guidance and Data Standards Catalog

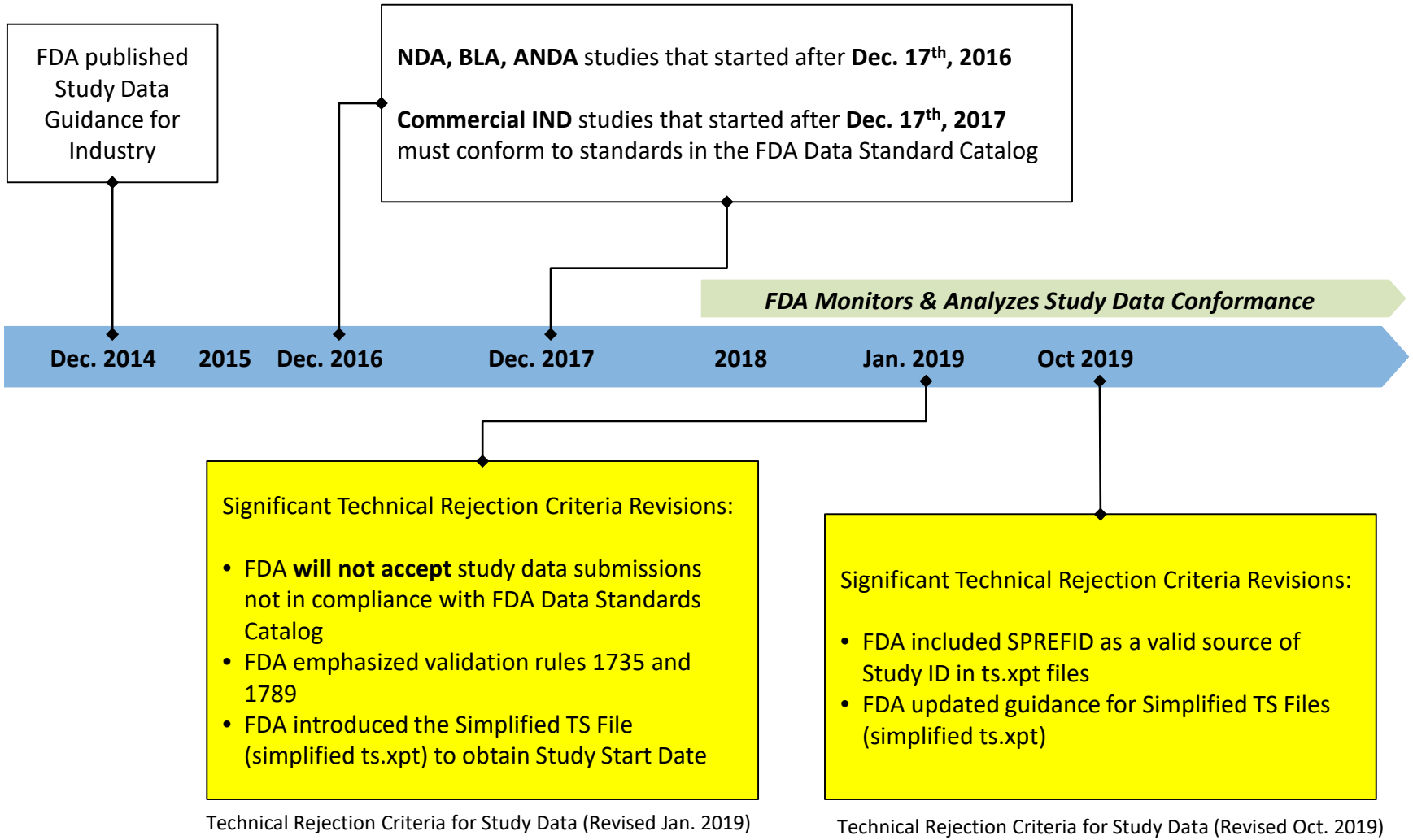
FDA Guidance and Data Standards Catalog

- 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



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

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

References:
FDA Study Data Technical Rejection Criteria (Revised Jan. 2019); FDA Study Data Technical Rejection Criteria (Revised Oct. 2019)

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.

References:
FDA Study Data Technical Rejection Criteria (Revised Jan. 2019); FDA Study Data Technical Rejection Criteria (Revised Oct. 2019)

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

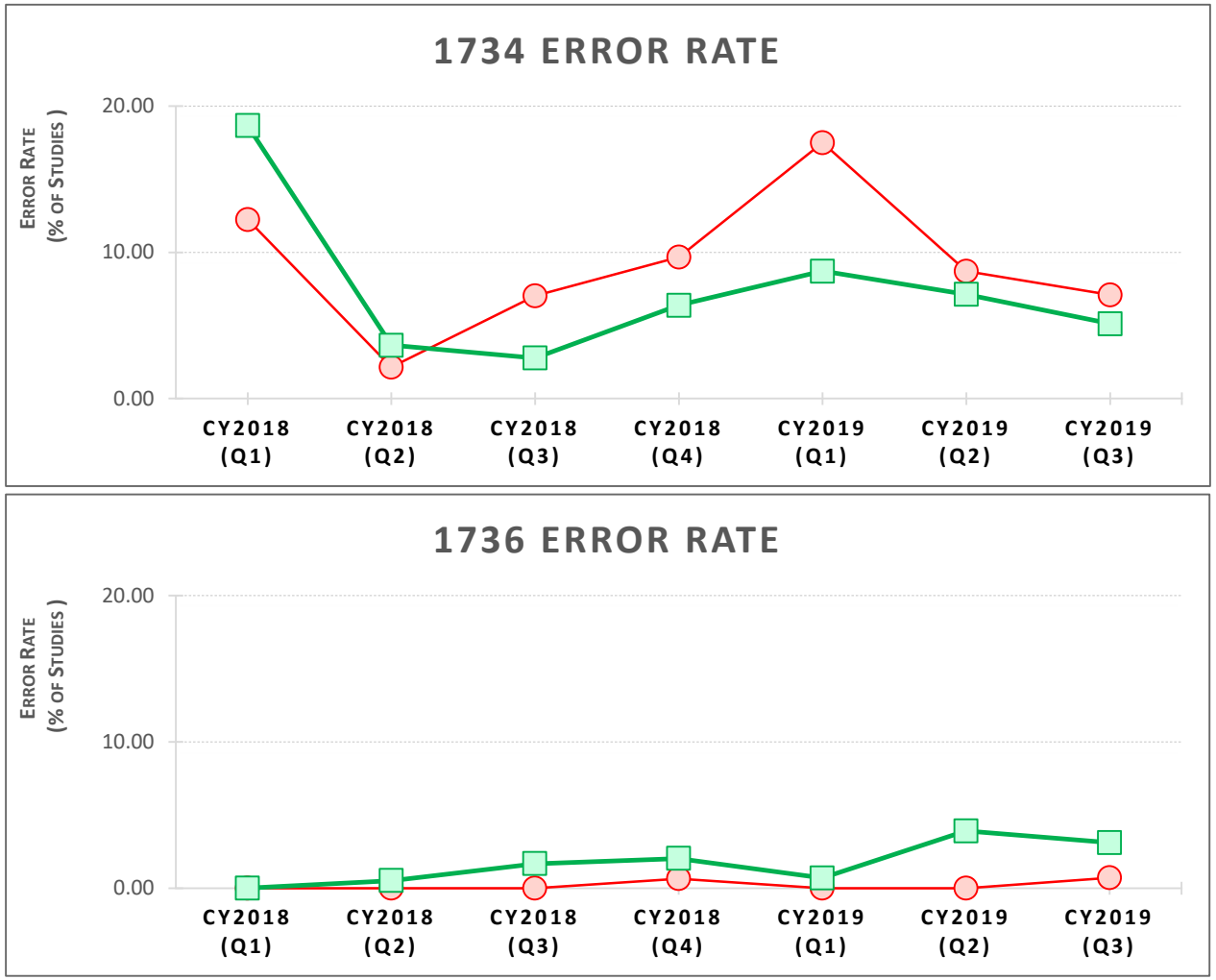
Example in Revised TRC -SPREFID for Study ID matching
A study in standardized format is submitted to FDA and the study files are referenced in a STF, a ts.xpt dataset is included in the study. The SPREFID in the ts.xpt dataset matches the study ID (study-id) in the STF. The Study Start Date in the ts.xpt 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 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



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)

	NDA		Comm-IND	
	CY 2018	CY2019 (Q1-Q3)	CY 2018	CY2019 (Q1-Q3)
	m4	m4	m4	m4
Total Number of Submissions with Study Data	78	56	291	478
Total Number of Studies in the TRC Applicable Sections	403	313	883	1269
Total Number Studies with Critical Errors	39	46	105	215
Error 1734	33	32	65	84
Error 1735	6	13	36	119
Error 1736	1	1	11	36
Error Rate (% among failed studies with Study Data in TRC Applicable Sections)	**10%**	**15%**	**12%**	**17%**

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)

	NDA m4	Comm-IND M4	Total
Total Number of non-clinical studies in TRC Applicable sections	313	1269	**1582**
TS File do not Exist	18	47	**65**
TS File Exist	295	1222	**1517**
• STF Study ID matches with TS STUDYID	215	843	**1058**
• STF Study ID does not matches with TS STUDYID	80	379	**459**
• TS File contains SPREFID	78	320	**398**
• TS file SPREFID Match	39	242	**281**
• TS file SPREFID does not Match	39	78	**117**
Pass Rate without SPREFID	**68.69%**	**66.43%**	**66.87%**
Pass Rate with SPREFID	**81.15%**	**85.50%**	**84.63%**

Notes

1. Analysis includes NDA and Commercial IND non-clinical studies received by CDER between 1/1/2019 to 9/30/2019 (1582 studies)

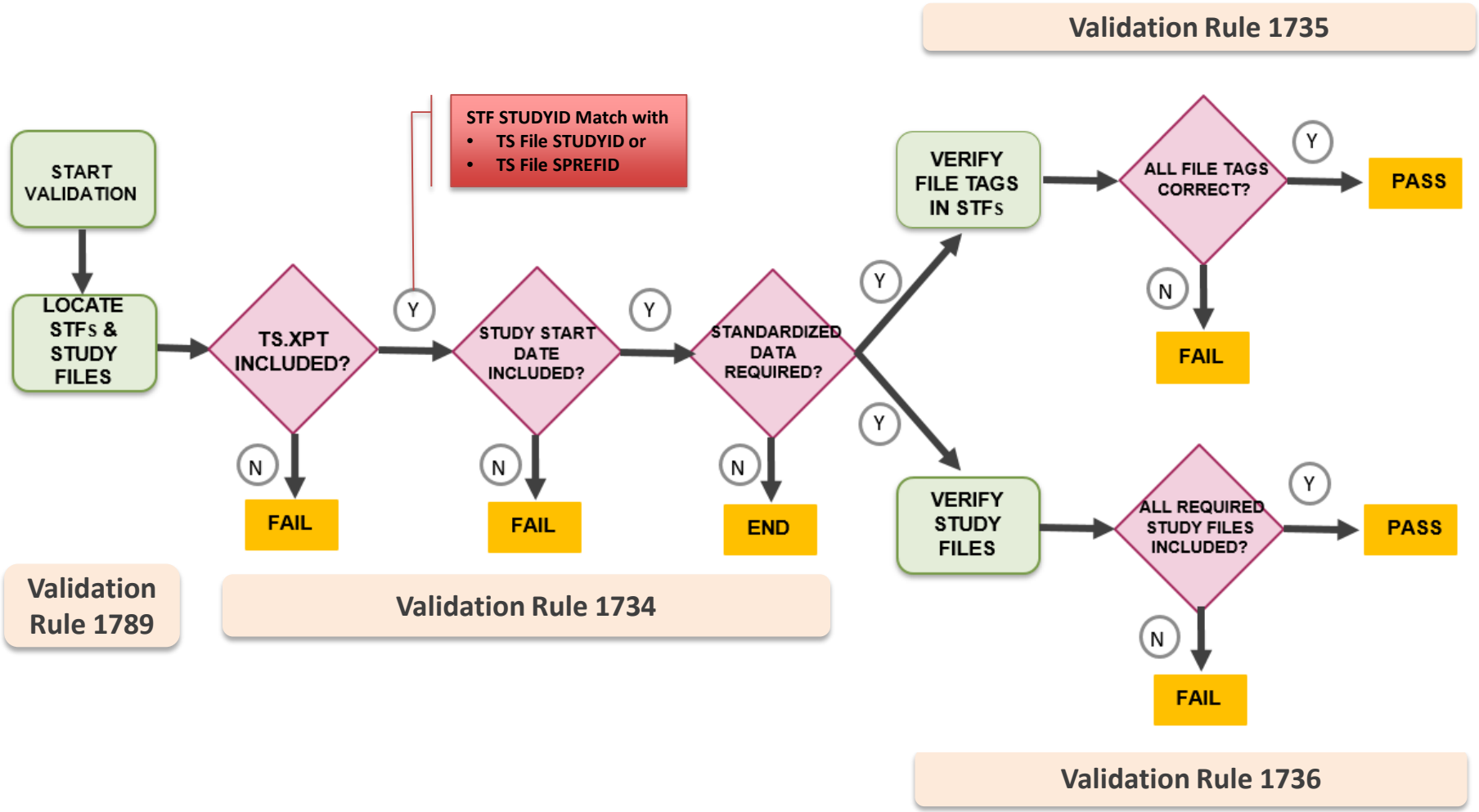
CDER Conformance: SPREFID Analysis (CY2019 Q1-Q3) Summary

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

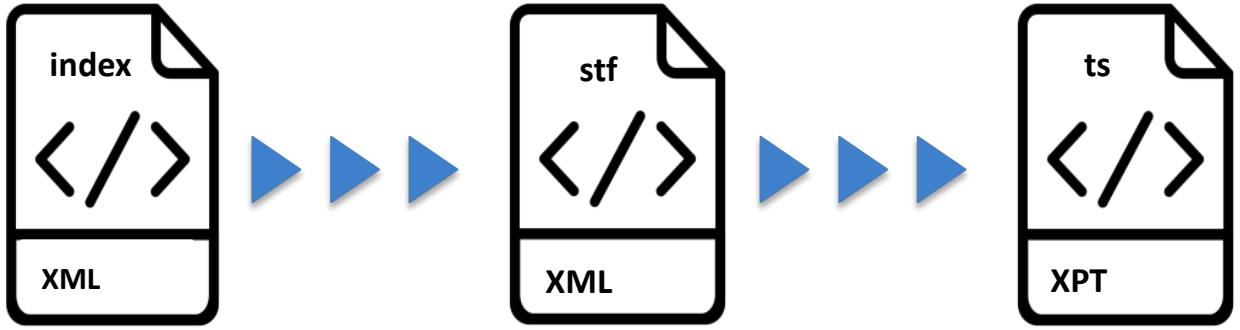
- 66.9% Studies where Study ID in the ts.xpt file **Match** with STF study-id
- 29% Studies where Study ID in the ts.xpt file **Do Not Match** with STF study-id
  - 25.2% Studies already contain SPREFID in the ts.xpt file
  - 17.8% Studies where SPREFID in the ts.xpt file **Match** STF STUDYID
  - 7.4% 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)



eCTD Backbone Files

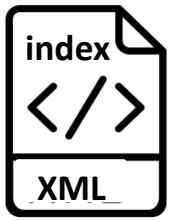


- Leaf ID
- File Path
- File Name

- Leaf ID
- STF Study ID
- File-Tag

- TS STUDYID
  or SPREFID
- Study Start Date

eCTD Backbone Files (index.xml)

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 application-version="PDF 1.4"
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 </leaf>
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 </leaf>
</m4-2-3-1-single-dose-toxicity>
```

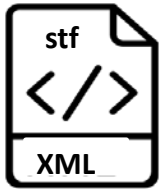
INDEX LEAF ID

FILE PATH FROM INDEX

FILE NAME FROM INDEX

eCTD Backbone File (stf.xml)

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

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<?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 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#a101"/>
 <file-tag name="data-tabulation-dataset-send" info-type="ich"/>
 </doc-content>
 </study-document>
</ectd:study>
```

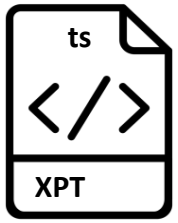
STF STUDY ID

Index.xml LEAF ID

FILE TAG ASSOCIATED TO STUDY DOCUMENT

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	S108
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

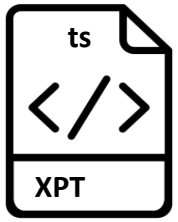
TS Study ID

Study Start Date

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	S108	STSTDTC	2010-07-14	

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

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

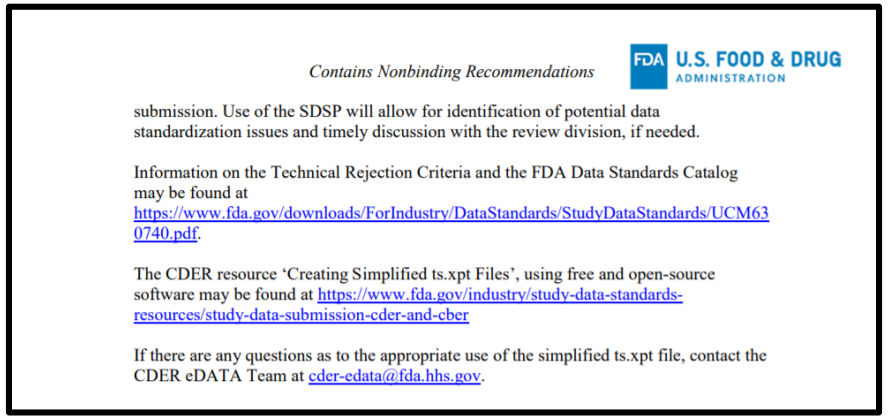
Gateway

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*

Study Data TCG (Oct 2019) references the Guide



Contains Nonbinding Recommendations

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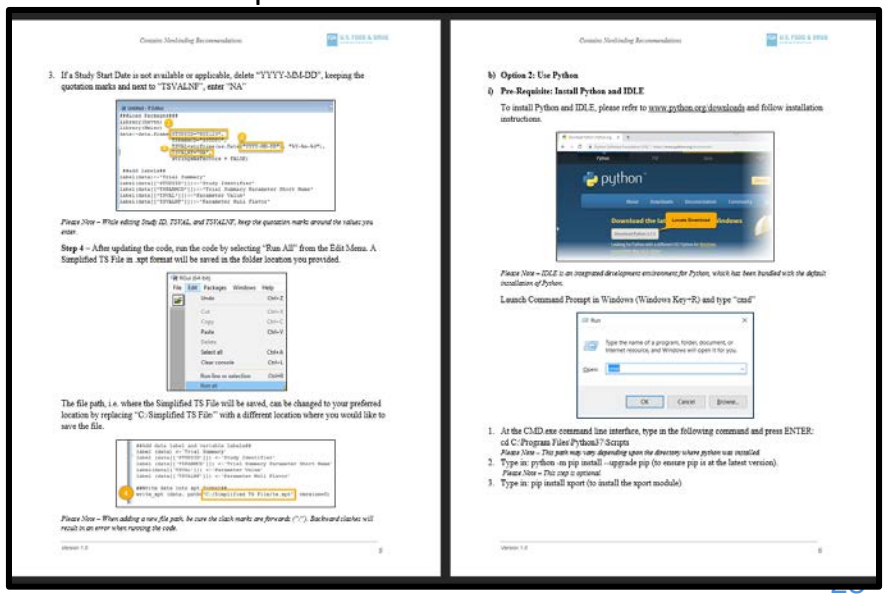
submission. Use of the SDSP will allow for identification of potential data standardization issues and timely discussion with the review division, if needed.

Information on the Technical Rejection Criteria and the FDA Data Standards Catalog may be found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630740.pdf.

The CDER resource 'Creating Simplified ts.xpt Files', using free and open-source software may be found at https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

If there are any questions as to the appropriate use of the simplified ts.xpt file, contact the CDER eDATA Team at cder-edata@fda.hhs.gov.

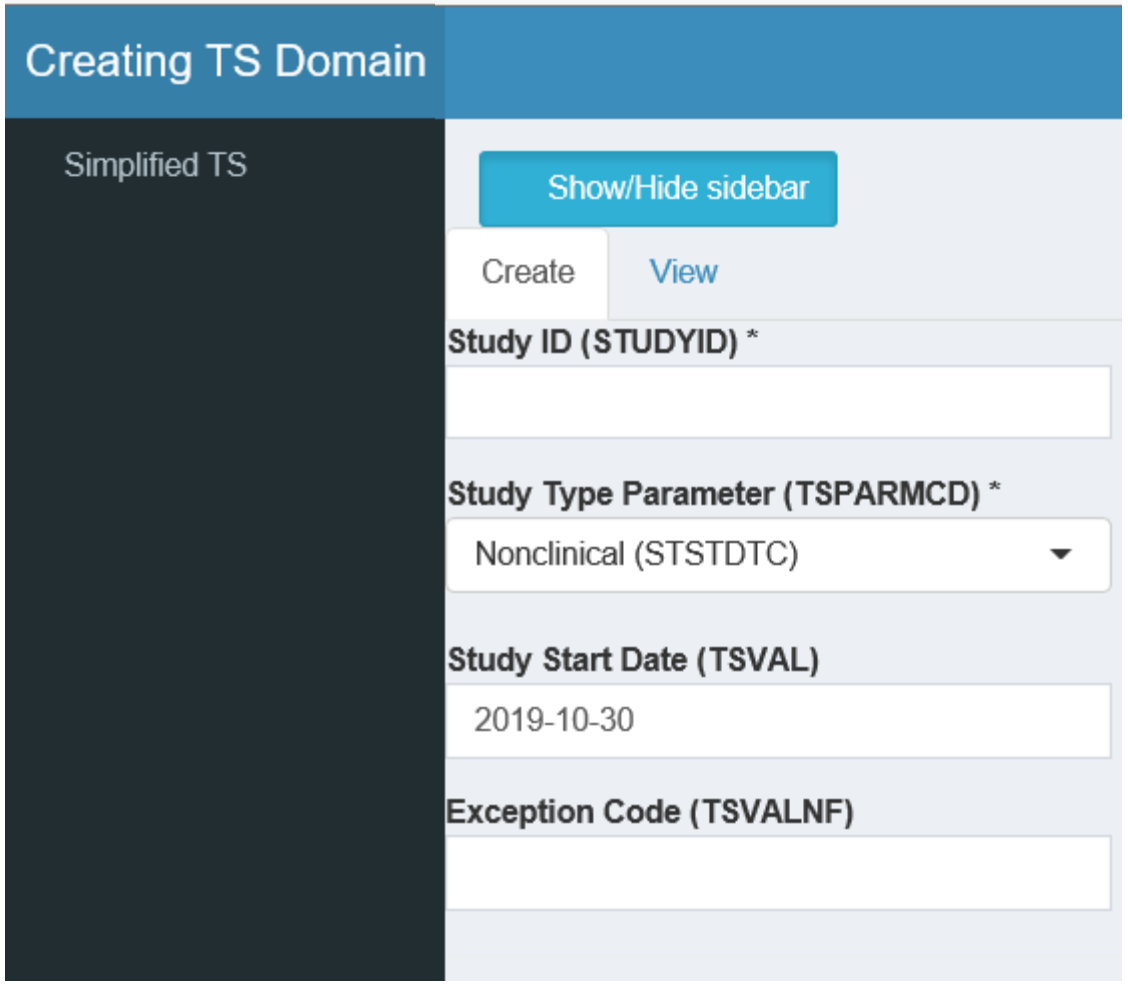
Simplified TS File Creation Guide



PhUSE Utility to Generate Simplified TS Files

- **Purpose** –PhUSE has developed a free web utility to generate a simplified TS
- This utility provides is 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/

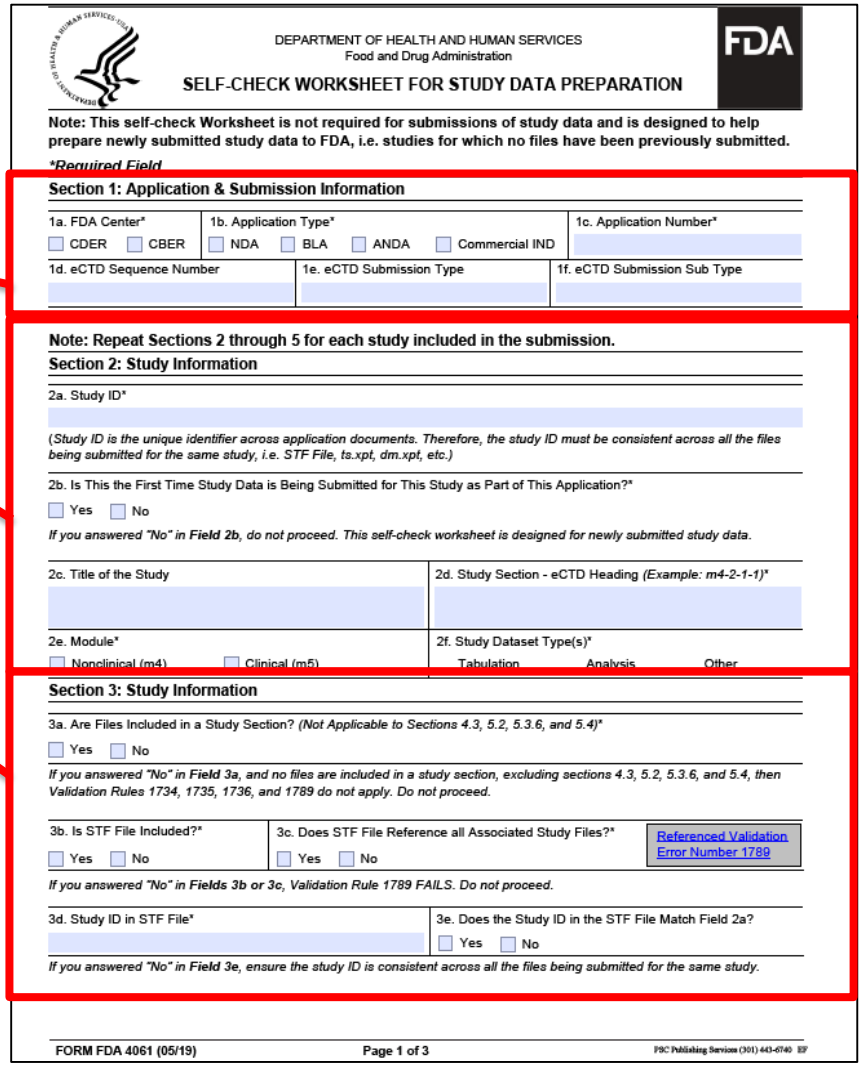


How Many People are aware of Study Data Self-Check Worksheet?

How Many People use Study Data Self-Check Worksheet?

Self-Check Worksheet

Section	Contents
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



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 | 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.xpt, dm.xpt, 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?* ☐ Yes ☐ No | 3c. Does STF File Reference all Associated Study Files?* ☐ Yes ☐ No | 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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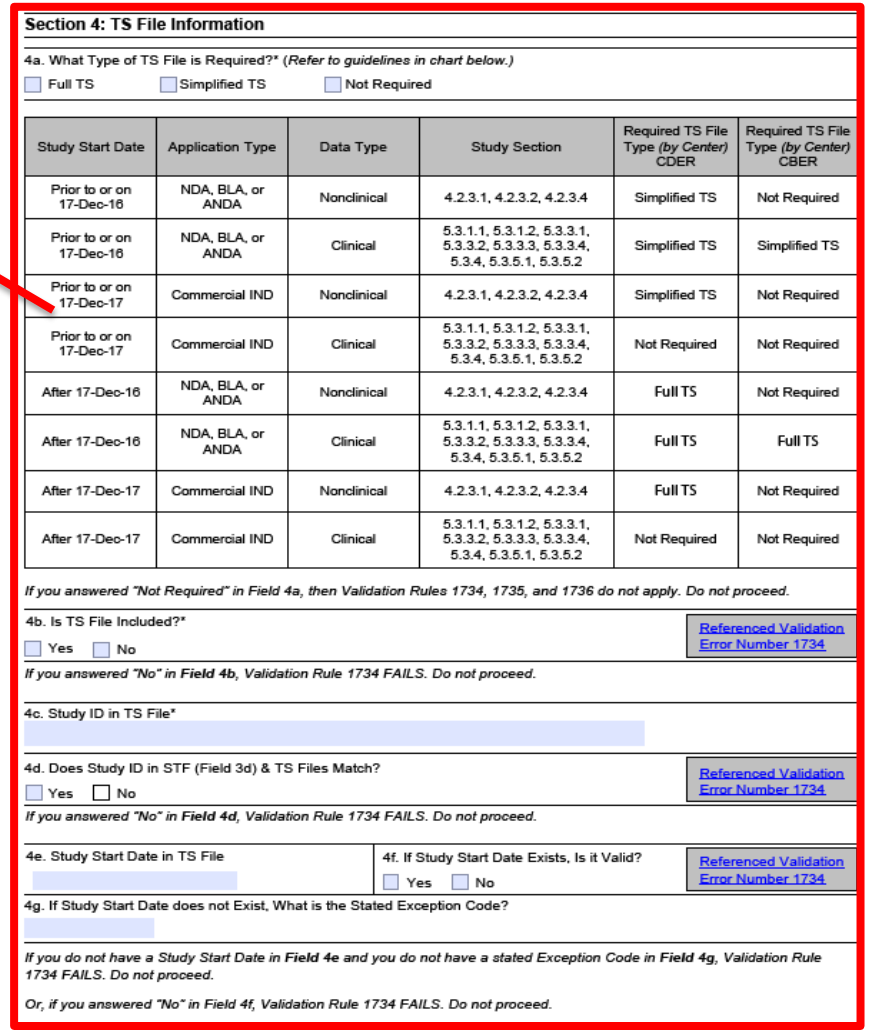
Reference:
"Technical Rejection Criteria Self-Check Worksheet"
https://www.fda.gov/media/123098/download
"Technical Rejection Criteria Self-Check Worksheet Instructions" https://www.fda.gov/media/123099/download

Self-Check Worksheet (1734 Validation Error)

Section	Contents
4	**TS File Information** (1734 Validation Error) • 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?* ☐ Yes ☐ No — Referenced Validation Error Number 1734

*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? ☐ Yes ☐ No — Referenced Validation Error Number 1734

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

4e. Study Start Date in TS File

4f. If Study Start Date Exists, Is it Valid? ☐ Yes ☐ 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

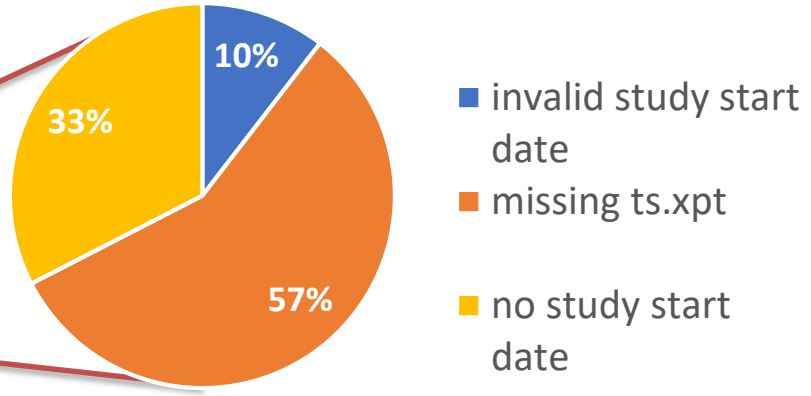
CY2019 (Q1-Q3) CDER Error Reasons for IND Non-Clinical studies- Validation Rule 1734

- A dataset named ts.xpt with information on Study Start Date (SSD) must be present for each study
- **Common error reason for Commercial INDs:**
  - A missing ts.xpt file
  - A missing study start date in the ts.xpt

IND m4 Non-Clinical

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

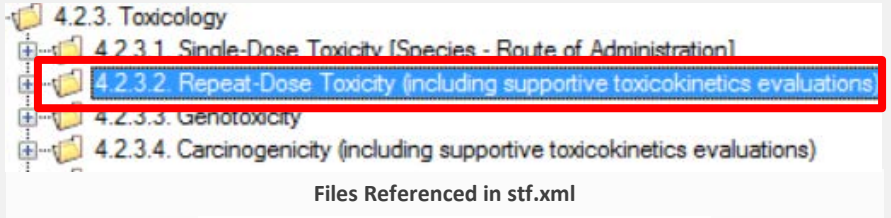


TRC Validation Rule 1734 (Section 4a-4b)

- 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



Files Referenced in stf.xml

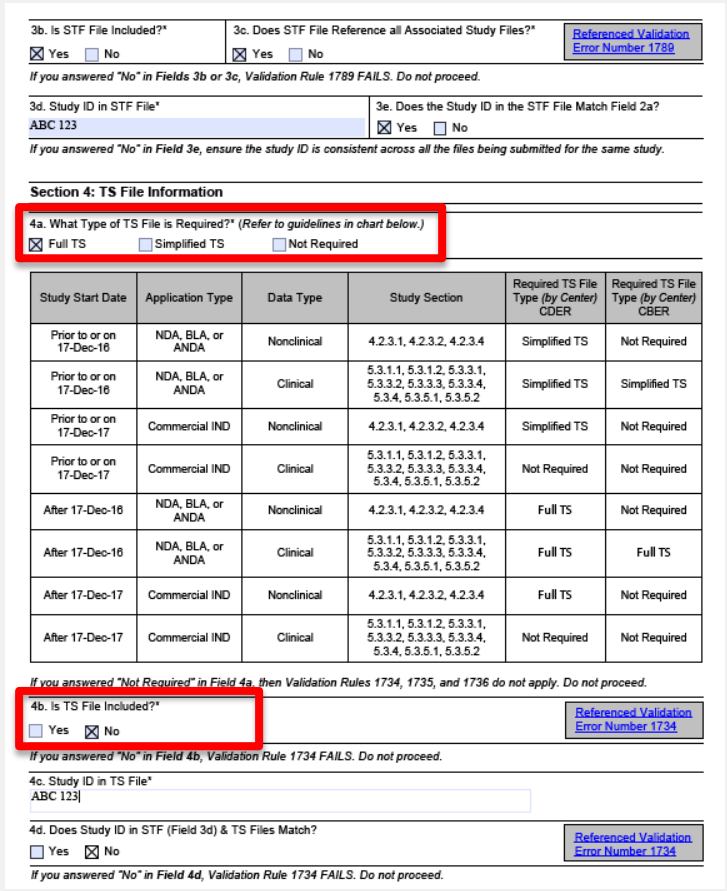
nsdrg.pdf	define.xml
cl.xpt	co.xpt
eg.xpt	ex.xpt
mi.xpt	om.xpt
relrec.xpt	sc.xpt
suppmi.xpt	ta.xpt
vs.xpt	define2-0-0.xsl

ts.xpt does not exist

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

Fail Rule 1734

Self-Check Worksheet



3b. Is STF File Included?* ☒ Yes ☐ No
3c. Does STF File Reference all Associated Study Files?* ☒ Yes ☐ No — 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* ABC 123
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.

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?* ☐ Yes ☒ No — Referenced Validation Error Number 1734
If you answered "No" in Field 4b, Validation Rule 1734 FAILS. Do not proceed.

4c. Study ID in TS File* ABC 123

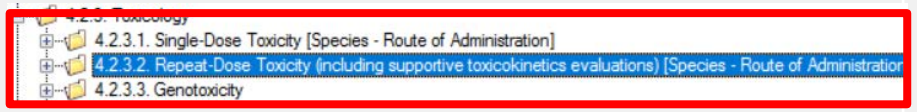
4d. Does Study ID in STF (Field 3d) & TS Files Match? ☐ Yes ☒ No — Referenced Validation Error Number 1734
If you answered "No" in Field 4d, Validation Rule 1734 FAILS. Do not proceed.

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



Files Referenced in stf.xml

ts.xpt does exist (Simplified ts.xpt)

Pass Rule 1734

Self-Check Worksheet

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?*
☒ Yes ☐ No

Referenced Validation Error Number 1734

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

4c. Study ID in TS File*
Study ABC

4d. Does Study ID in STF (Field 3d) & TS Files Match?
☒ Yes ☐ No

Referenced Validation Error Number 1734

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

TRC Validation Rule 1734 (Section 4c)

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

Example	Self-Check Worksheet
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	Section 4: TS File Information 4a. What Type of TS File is Required?* (Refer to guidelines in chart below.) Full TS Sim 4b. Is TS File Included?* Yes No 3d. Study ID in STF File* Study ABC Referenced Validation Error Number 1734 If you answered "No" in Field 4b, Validation Rule 1734 FAILS. Do not proceed. 4c. Study ID in TS File* Study ABC 4d. Does Study ID in STF (Field 3d) & TS Files Match? Yes No Referenced Validation Error Number 1734 If you answered "No" in Field 4d, Validation Rule 1734 FAILS. Do not proceed. 4e. Study Start Date in TS File 4f. If Study Start Date Exists, Is it Valid? Yes No Referenced Validation Error Number 1734 4g. If Study Start Date does not Exist, What is the Stated Exception Code?
4.2.3. Toxicology 4.2.3.1. Single-Dose Toxicity [Species - Route of Administration] 4.2.3.2. Repeat-Dose Toxicity (including supportive toxicokinetics evaluations) [Species - Route of Administration] 4.2.3.3. Genotoxicity	
[Study IDs Match Requirement] stf XML <title> <study-id> Study ABC/study-id> <doc-content> ts XPT STUDYID DOMAIN 1 Study ABC 2 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

Example	Self-Check Worksheet

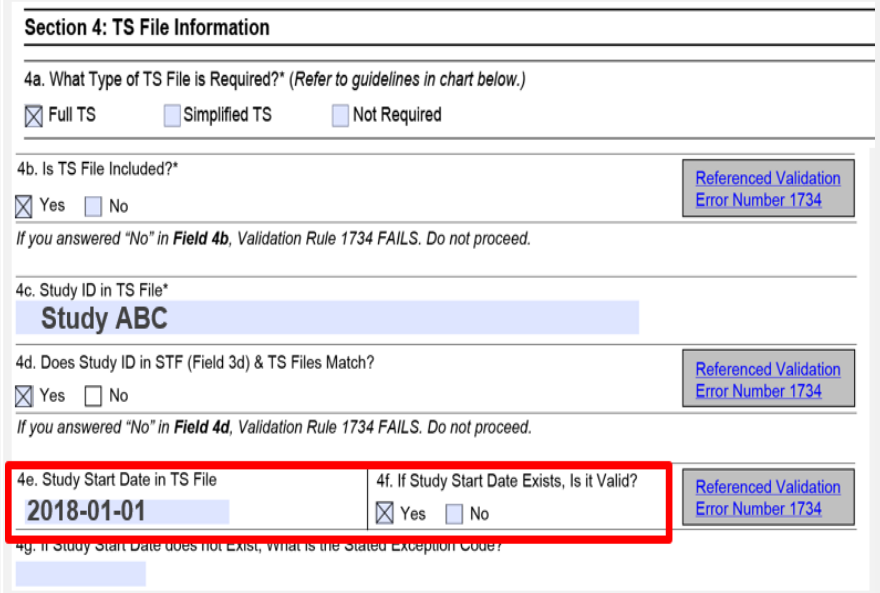
2. Study Files and/or datasets submitted in **m4-2-3-2 (TRC applicable study section)**
Study Start Date: 2018-01-01
TRC Requirement: Full TS is needed

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

TS.XPT

SSTDTC	Study Start Date	2018-01-01

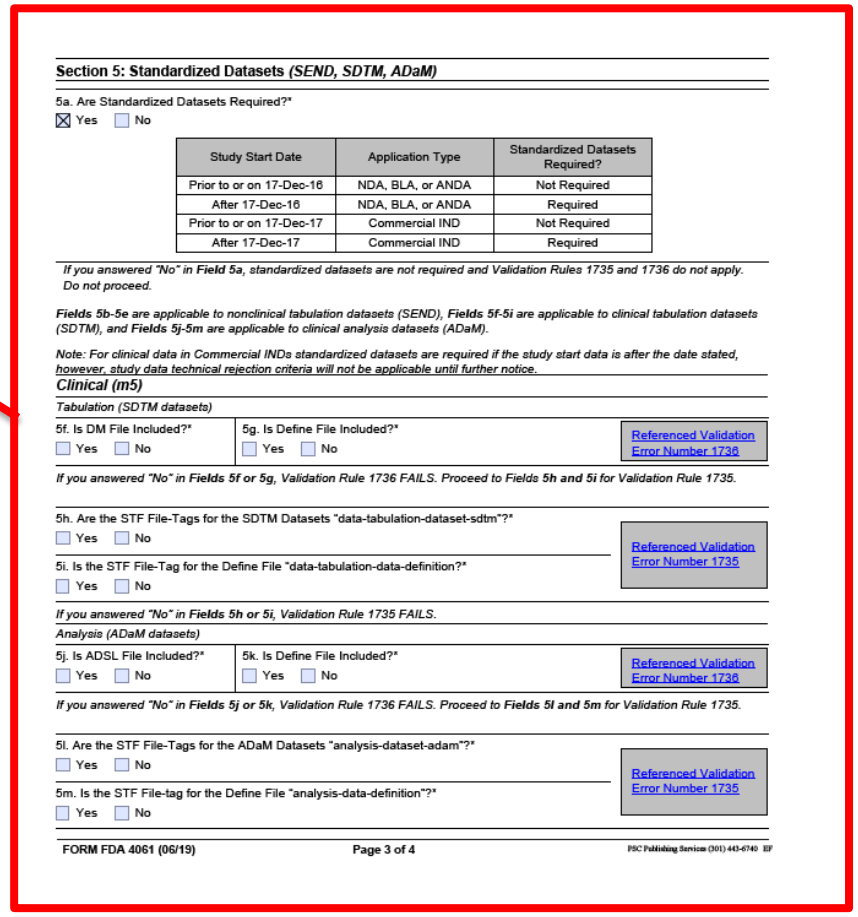
Pass Rule 1734



❖ **10%** of studies with 1734 error are because of invalid study start date

Self-Check Worksheet (1735 & 1736 Validation Error)

Section	Contents
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



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 1736

*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 1736

*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

FORM FDA 4061 (06/19) Page 3 of 4

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 IND Non-Clinical studies- Validation Rule 1735

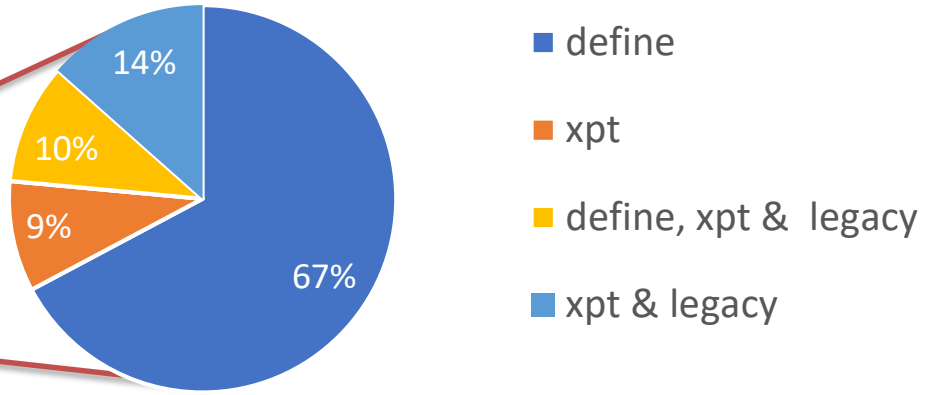
- The correct STF file tags must be used for all standardized datasets and corresponding define.xml files

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

IND m4 Non-Clinical

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%**

119 Studies with Error 1735

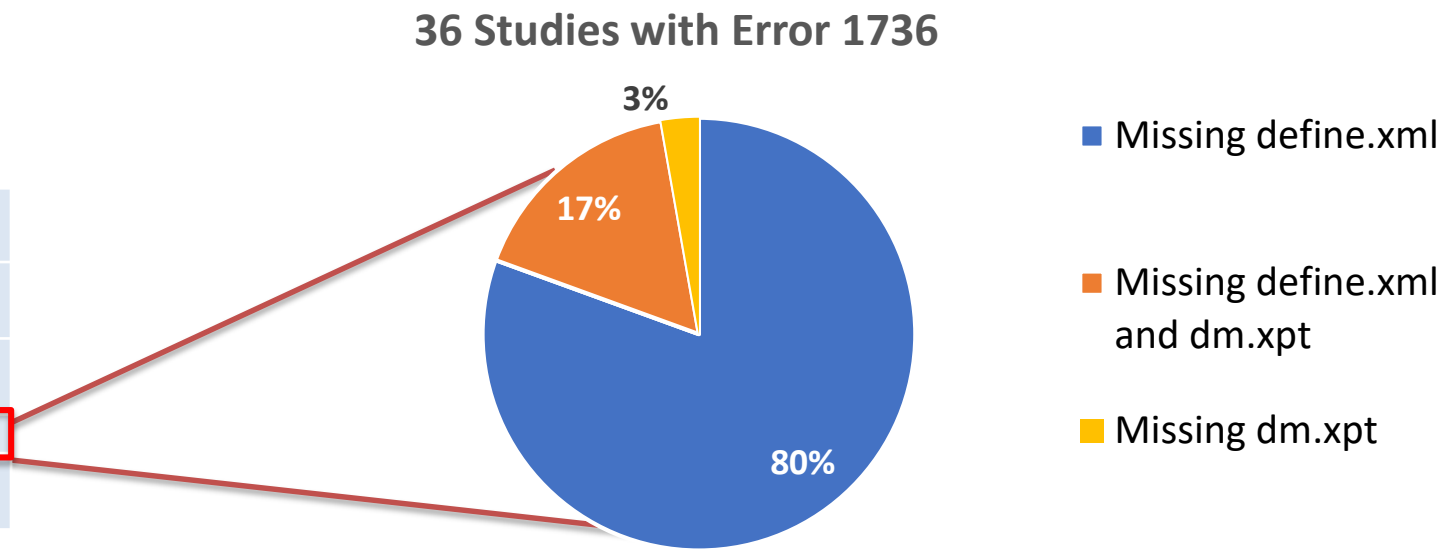


CY2019 (Q1-Q3) CDER Error Reasons for IND Non-Clinical studies- Validation Rule 1736

- 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 Commercial INDs:**
  - A missing define.xml files
  - A missing define.xml, dm.xpt files

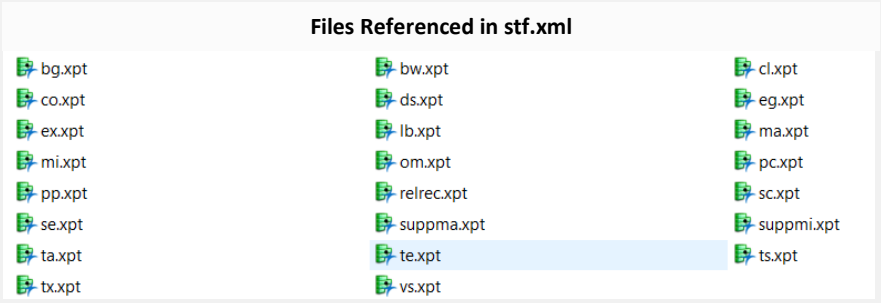
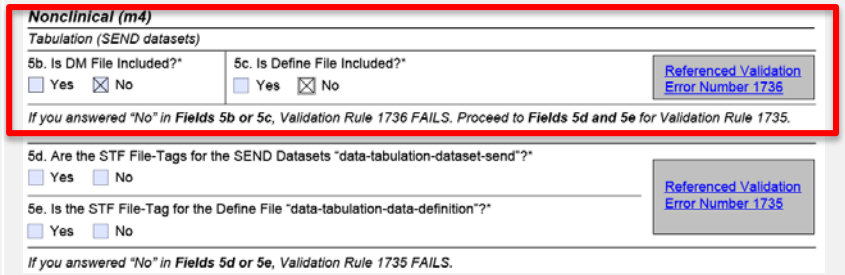
IND m4 Non-Clinical

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 1736	36
Error Rate (% among submissions with Study Data in TRC Applicable Sections)	**17%**



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

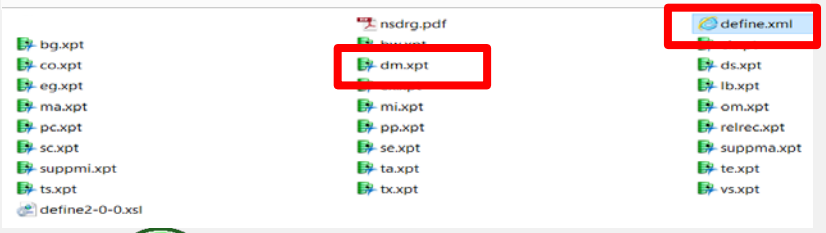
Example	Self-Check Worksheet
Study Files and/or datasets submitted in **m4-2-3-2 (non-clinical)** **Study Start Date:** 2018-01-01 **Dataset Type:** Tabulation (SEND)  **Fail Rule 1736**	 **dm.xpt and define.xml are not included** ❖ **80%** of studies with 1736 error are because of missing define.xml file

TRC Validation Rule 1735 and 1736 (Section 5b-5c)

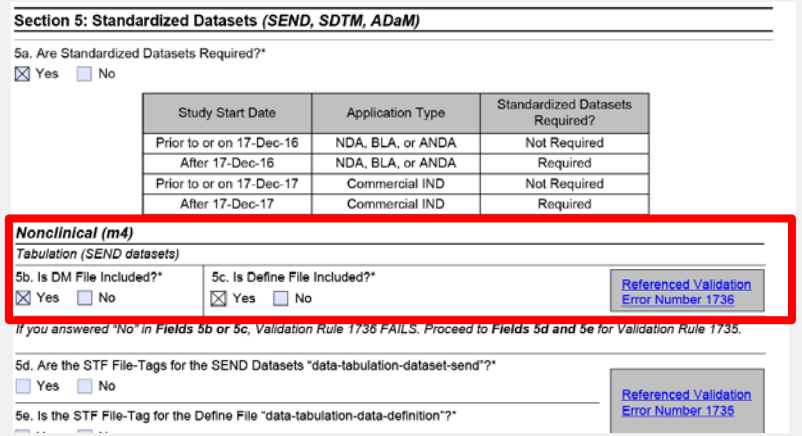
- Rule 1735: Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections
- Rule 1736: For SEND data, a DM dataset and define xml must be submitted in required sections
  - For SDTM data, a DM dataset and define.xml must be submitted in required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

Example	Self-Check Worksheet
Study Files and/or datasets submitted in **m4-2-3-2 (non-clinical)** **Study Start Date**: 2018-01-01 **Dataset Type:** Tabulation (SEND)	

Dataset Folder



Pass Rule 1736



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

Nonclinical (m4)
Tabulation (SEND datasets)

5b. Is DM File Included?* ☒ Yes ☐ No
5c. Is Define File Included?* ☒ Yes ☐ No
Referenced Validation Error Number 1736

*If you answered "No" in **Fields 5b or 5c**, Validation Rule 1736 FAILS. Proceed to **Fields 5d and 5e** for Validation Rule 1735.*

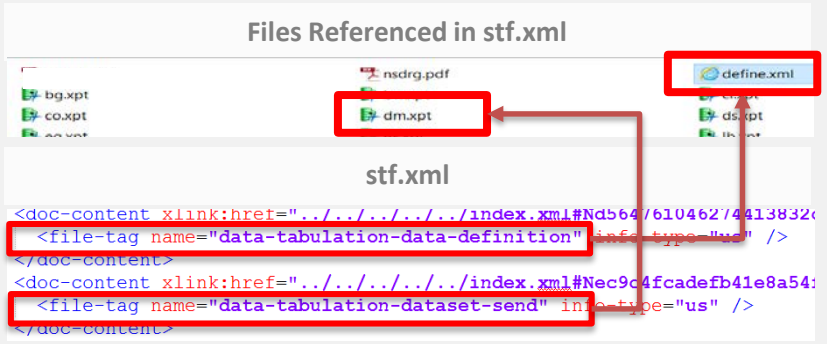
5d. Are the STF File-Tags for the SEND Datasets "data-tabulation-dataset-send"?* ☐ Yes ☐ No
5e. Is the STF File-Tag for the Define File "data-tabulation-data-definition"?*
Referenced Validation Error Number 1735

- **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
- Rule 1736: For SEND data, a DM dataset and define xml must be submitted in required sections
  - For SDTM data, a DM dataset and define.xml must be submitted in required sections
  - For ADaM data, an ADSL dataset and define.xml must be submitted in required sections

Example	Self-Check Worksheet
Study Files and/or datasets submitted in **m4-2-3-2 (non-clinical)** **Study Start Date:** 2018-01-01 **Dataset Type:** Tabulation (SEND)	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.*



Pass Rule 1735

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

FDA U.S. FOOD & DRUG ADMINISTRATION

Study Data for Submission to CDER and CBER

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Study Data Standards Resources

- Study Data for Submission to CDER and CBER
- Study Data Research and Collaborations
- Janus Data Repository
- Study Design Standard
- Study Participation Standard
- Subject Data Standard

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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 cder-edata@fda.hhs.gov.

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

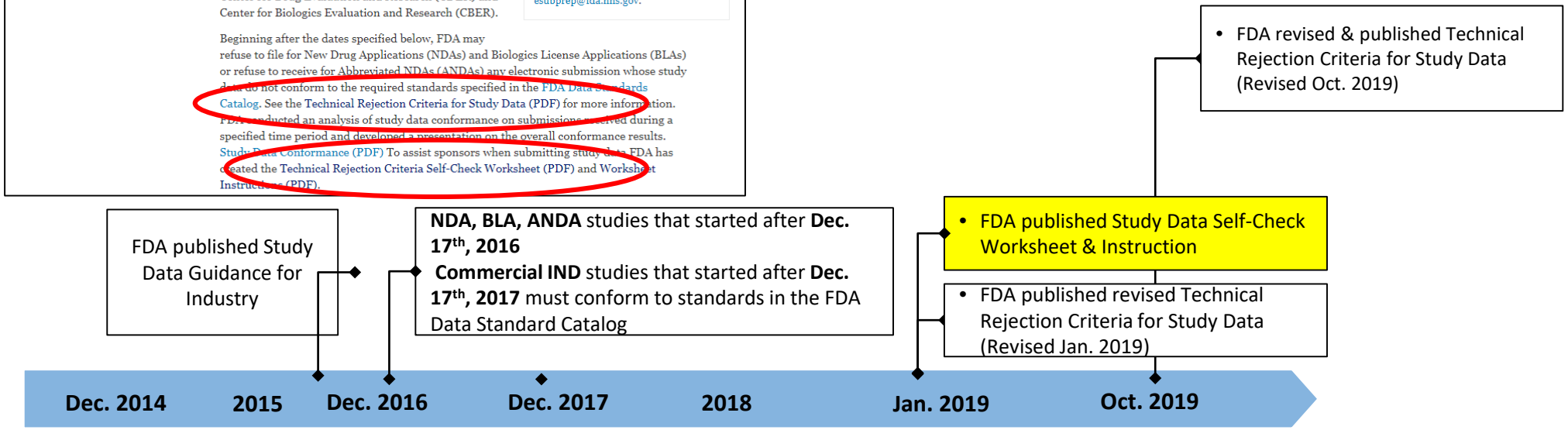
If you have study data questions for CBER, please contact CBER-edata@fda.hhs.gov.

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

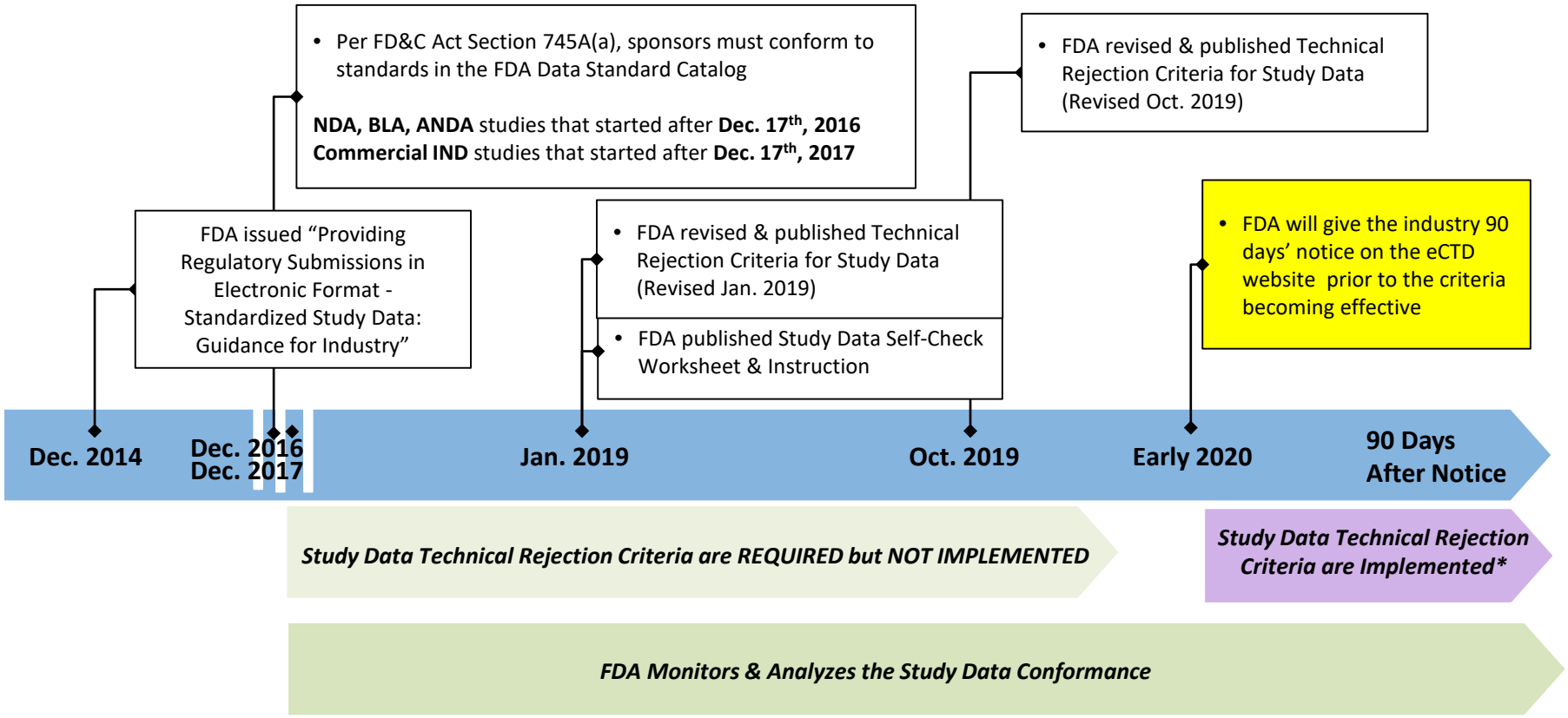
"Technical Rejection Criteria Self-Check Worksheet Instructions"
https://www.fda.gov/media/123099/download



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/

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