

Study Data Technical Rejection Criteria

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FDA Disclaimer



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Learning Objectives

- Review the importance of eCTD and CDISC Standards to streamlining FDA's review processes
- Share the latest metrics of sponsors' conformance rates to Technical Rejection Criteria (TRC) for ANDA submissions
- List the most common TRC errors and underlying root causes
- Illustrate how the Self-Check Worksheet and other FDA tools can help sponsors correct common TRC errors



Poll Question #1

How familiar are you with FDA's Self-Check Worksheet for Study Data preparation?

- A. Used it multiple times to prepare study data submissions
- B. Read through it or only used it once
- C. Heard of it, but have not used it
- D. Never heard of it

Topics



- ❖ **eCTD and Study Data Requirements**
- ❖ **Study Data Conformance Analysis (CY2019 Q4)**
- ❖ **Top Error Reason for TRC Rule 1734, 1735 and 1736**
- ❖ **FDA Tools - Study Data Self-Check Worksheet & Instructions (Revised Nov. 2019)**
- ❖ **Summary**

Purpose of eCTD and Study Data Requirements

- ❖ Reviewing study data in a timely manner is critical for FDA's review process (e.g. Reviewers have 30 days to review an IND application)
- ❖ When sponsors/applicants submit data to the FDA in a reliable and accessible format, it improves efficiency and consistency of review decisions
- ❖ CDISC Standards enable FDA to streamline the review process:
 - Reduce time for reviewers to locate and identify study data
 - Reduce the burden on sponsors/applicants and reviewers from IRs (Information Requests)
 - Reduce review time by enabling the use of COTS reviewer's tools such as JReview, JMP Clinical, etc. to automate review analyses
 - Support data driven decisions by applying data mining and data analytic techniques

“The agreement to assemble all the Quality, Safety and Efficacy information in a common format (called CTD - Common Technical Document) has revolutionized the regulatory review processes, led to harmonized electronic submission that, in turn, enabled implementation of good review practices. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities.”

Source: <https://www.ich.org/products/ctd.html>

FDA Guidance and Data Standards Catalog

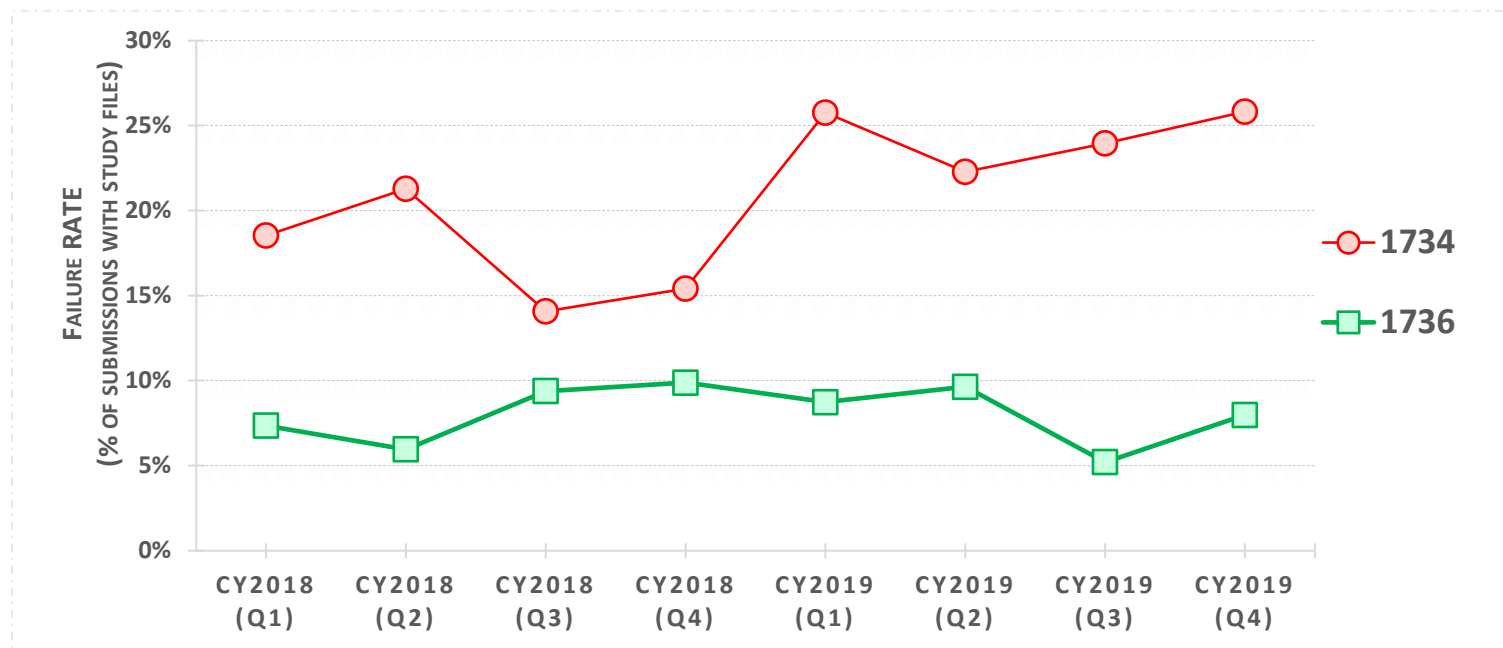


- ❖ **Per FD&C Act Section 745A(a), drug application sponsors must use the standards defined in the FDA Data Standards Catalog starting 24 months after final guidance for a specific submission type.**
- ❖ **FDA issued the Final Guidance “Providing Regulatory Submissions in Electronic Format - Standardized 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
- ❖ **Sponsors are obligated to meet Technical Rejection Criteria for Study Data which determine whether a submission complies with FDA’s standards for study data**

2018 and 2019 ANDA TRC Conformance Trend



- ❖ CY2019 TRC Conformance analysis shows that there are no significant improvement in the submission failure rate over each quarter



Notes:

1. Q1-Q3 2019 Analysis is conducted according to the revised TRC (Revised Jan. 2019)
2. Q4 2019 Analysis is conducted according to the revised TRC (Revised Oct. 2019)

CY2019 Conformance Analysis for Validation Errors 1734 & 1736



	ANDA
a Total Number of Submissions with Study Data and/or Study Report	862
b Total Number of Submissions with Study Data and/or Study Report in TRC Applicable section	800
c Total Number of Submissions with 1734 or 1736 Errors	256
d Error 1734	197
e Error 1736	63
f Failure Rate (% among submissions with Study Data and/or study Report) [c/a]	29.69%
g Failure Rate (% among submissions with Study Data and/or study Report in TRC Applicable sections) [c/b]	32%

Notes:

- (1) One drug application could contain multiple submissions throughout its review life-cycle, such as original, supplements, and amendments;
- (2) Analysis includes ANDA submissions received by CDER between 1/1/2019 and 12/31/2019
- (3) A submission with multiple studies can report both Errors 1734 and 1736. In this instance, the submission is counted only once at the submission level when calculating failure rate
- (4) M4 Definition of Study Data - .xpt files and/or a Study Report tagged as pre-clinical-study-report, legacy-clinical-study-report, or study-report-body present in submission
- (5) M5 Definition of Study Data - .xpt files present in the submission
- (6) Analysis is conducted according to the revised TRC (Revised Oct. 2019)



ANDA Original Application – First Applicant Analysis

- FDA analyzed CY2019 ANDA application to determine the potential impact on **Original ANDA Submissions with First Filer Status** when subjected to FDA's Technical Rejection Criteria for Study Data (TRC):
 - When TRC rules are enforced, **submissions with study data that fail validation will be rejected and could lose First Applicant status**
 - Rejecting an Original ANDA Submission with First Applicant Status may cause a sponsor/applicant to lose eligibility for the 180-day generic drug exclusivity

CY2019 Conformance Analysis for ANDA First Filers



- Based on CY2019 analysis
 - **15%** of all **original ANDA applications with First Filer status would be subject to rejection**

		ANDA	ANDA Original First Filers
a	Total Number of Submissions with Study Data	862	116
b	Total Number of Submissions with Study Data in TRC Applicable Sections	800	113
c	Error 1734	197	13
d	Error 1736	63	8
e	Study Data Rejection Rate	32%	18.58%

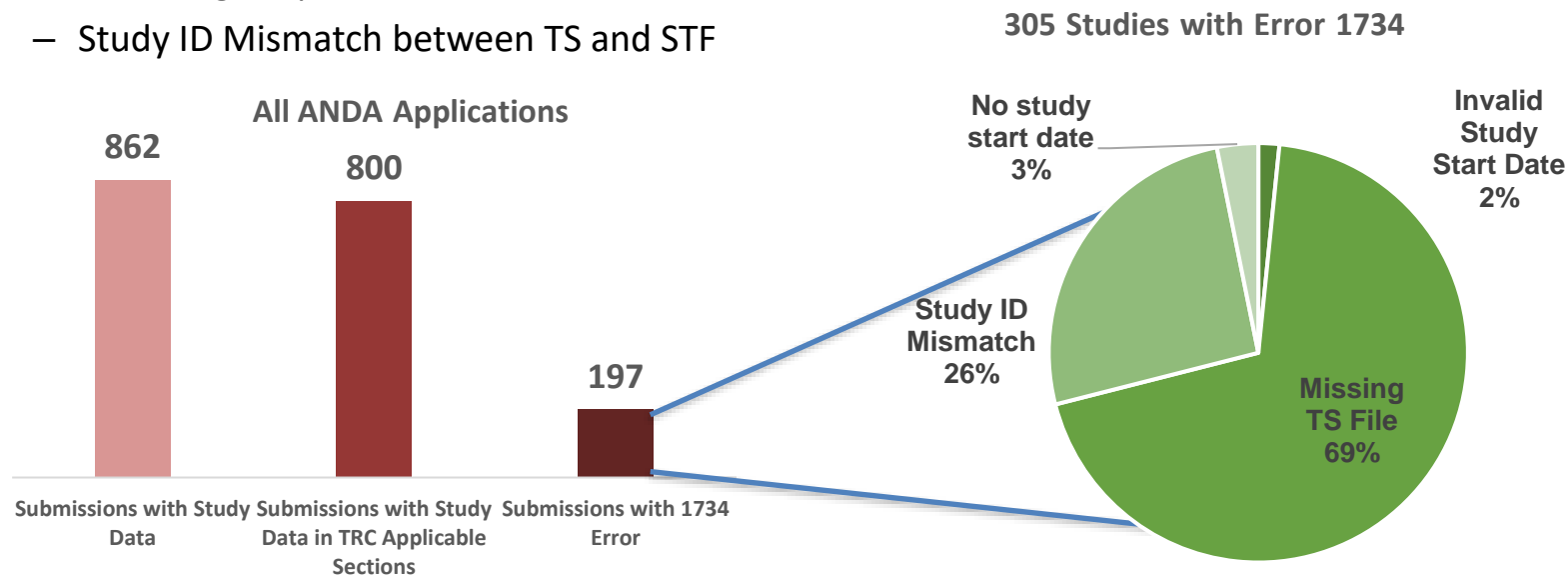
TOP ERROR REASON FOR TRC RULE 1734

CY2019 Error Reasons for Validation Rule 1734



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

- Common error reason for all application type:
 - A missing ts.xpt file
 - Study ID Mismatch between TS and STF



1734 Common error reason – A missing TS file

- A Simplified ts.xpt file would be expected in cases in which a clinical study report submitted is not required to include accompanying standardized datasets
- **Simplified ts.xpt**
 - Sponsors/applicants should submit a dataset named ‘ts.xpt’ with four variables: STUDYID, TSPARMCD, TSVAL, and TSVALNF. Exempted clinical studies should submit a simplified ts.xpt file with TSVALNF value as “NA”
- **Example of Simplified ts.xpt Dataset**

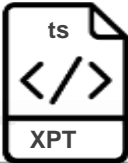
STUDYID	TSPARMCD	TSVAL	TSVALNF
<ul style="list-style-type: none"> • Study ID in STF File 	<ul style="list-style-type: none"> • SSTDC for a clinical study 	<ul style="list-style-type: none"> • Format: yyyy-mm-dd • Left blank when study start date is not available or irrelevant 	<ul style="list-style-type: none"> • Left blank when study start date is provided in TSVAL • “NA”

References:

FDA Study Data Technical Conformance Guide (Section 8 and Appendices C Version 4.4, Oct 2019)
 FDA Study Data Technical Rejection Criteria (Revised Oct. 2019)

1734 Common Error Reason – Study ID Mismatch

- This is an example of a Full TS file submitted for a clinical study with study-id “S107” in the STF file
- The variable STUDYID does not match with STF study-id but SPREFID parameter “S107” is provided to determine the match



	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

TS STUDYID

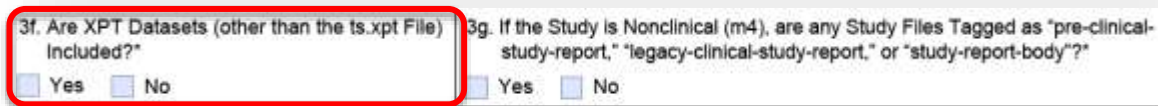
Study Start Date

SPREFID

Self-Check Worksheet Revisions and Examples

❖ Addressing common 1734 Error Reason – Missing TS File

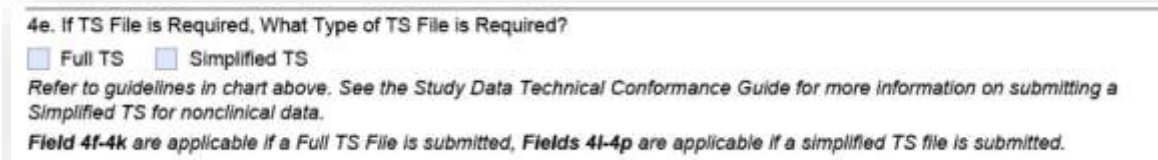
- Self-Check worksheet was revised in Nov 2019 to accommodate all the updates to the published TRC (Oct 2019)
- To help Sponsors/Applicants clarify the requirement about expectation of ts.xpt, question 3f and 3g is introduced



3f. Are XPT Datasets (other than the ts.xpt File) Included?
☐ Yes ☐ No

3g. If the Study is Nonclinical (m4), are any Study Files Tagged as "pre-clinical-study-report," "legacy-clinical-study-report," or "study-report-body"?"
☐ Yes ☐ No

- Based on subsequent selections in the self-check worksheet Sponsors/Applicant can verify if a Simplified or a Full TS is required (question 4e) for a study as seen below



4e. If TS File is Required, What Type of TS File is Required?
☐ Full TS ☐ Simplified TS

Refer to guidelines in chart above. See the Study Data Technical Conformance Guide for more information on submitting a Simplified TS for nonclinical data.

Field 4f-4k are applicable if a Full TS File is submitted, Fields 4l-4p are applicable if a simplified TS file is submitted.

Self-Check Worksheet Example for Simplified TS

- A new sub-section (4f-4K) will be dynamically added in the Self-Check Worksheet to provides more guidance to sponsors/applicants to check for the expectation from a Simplified TS file



Study ID in TS = S107



Study Start Date=
2019-01-01

Simplified TS File

4l. Study ID (STUDYID) in TS File*:
S107

4m. Does Study ID (study-id) in STF (Field 3d) and TS Files Match?*

☒ Yes ☐ No

[Referenced Validation
Error Number 1734](#)

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

4n. Is there a Value in TSVALNF?

☐ Yes ☒ No

If you answered "No" in **Field 4n**, and there is no value in TSVALNF, proceed to **Field 4p** to enter the Study Start Date (SSD).

4o. Is the Value in TSVALNF "NA"?

☐ Yes ☐ No

[Referenced Validation
Error Number 1734](#)

If you answered "Yes" in **Field 4n** and "No" in **Field 4o**, Validation Rule 1734 FAILS. Do not proceed.

4p. Study Start Date in TS File:
2019-01-01

The Study Start Date (SSD) should follow the ISO 8601 standard that provides, at a minimum, the year, month, and date for the study start date (yyyy-mm-dd).

4q. If Study Start Date Exists, Is it in Valid Format (yyyy-mm-dd)?

☒ Yes ☐ No

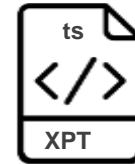
[Referenced Validation
Error Number 1734](#)

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

Example - Simplified ts.xpt with and without Study Start Date

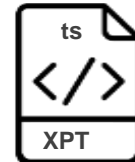
- Example of a Simplified TS file submitted for a clinical study with study-id “S107” in the STF file

STUDYID	TSPARMCD	TSVAL	TSVALNF
S107	SSTDTC	2014-10-26	



- Example of a Simplified TS file submitted for a clinical study with study-id “S107” in the STF file without a study start date

STUDYID	TSPARMCD	TSVAL	TSVALNF
S108	SSTDTC		NA



TRC Introduced SPREFID to Match STF Study ID with ts.xpt

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

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).

Self-Check Worksheet Example for Full TS

❖ **Section 4** in the Self-Check Worksheet Provides more guidance to sponsors/applicants to check for the expectation from a full TS file.

- Question 4h will help Sponsors/Applicant to determine alternate way to match STF study ID in ts.xpt SPREFID



Study ID in TS =
pqr-456



Study ID in
SPREFID= S107

Full TS File

4f. Study ID (STUDYID) in TS File*:
pqr-456

4g. Does Study ID (study-id) in STF (Field 3d) and TS Files Match?*

☐ Yes ☒ No

[Referenced Validation
Error Number 1734](#)

4h. If Study ID does Not Match, What is the Value of SPREFID in TS File?
S107

4i. Does Study ID (study-id) in STF (Field 3d) and SPREFID Match?

☒ Yes ☐ No

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

[Referenced Validation
Error Number 1734](#)

4j. Study Start Date in TS File:
2019-01-01

*If you do not have a Study Start Date in **Field 4j**, Validation Rule 1734 FAILS. Do not proceed.*

[Referenced Validation
Error Number 1734](#)

4k. If Study Start Date Exists, Is it in Valid Format (yyyy-mm-dd)?

☒ Yes ☐ No

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

The Study Start Date (SSD) should follow the ISO 8601 standard that provides, at a minimum, the year, the month, and the day for the study start date (yyyy-mm-dd).

TOP ERROR REASON FOR TRC RULE 1736

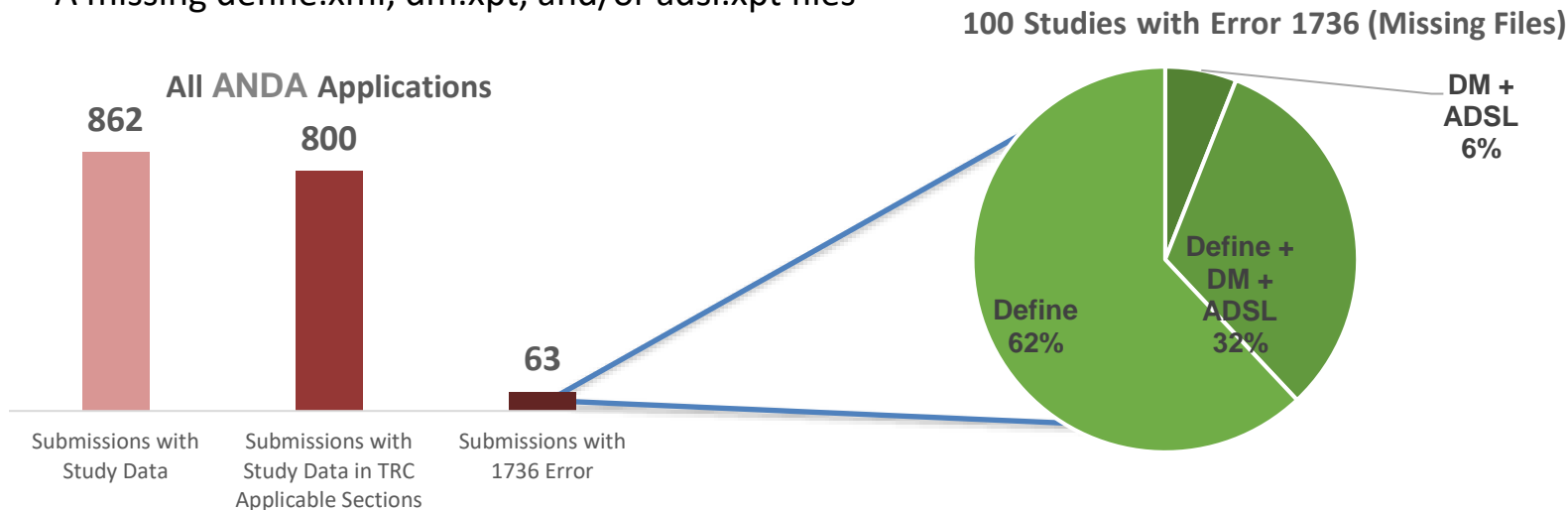
CY2019 CDER Error Reasons for Validation Rule 1736



Error	Description
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*

❖ Common error reason for all application type:

- A missing define.xml files
- A missing define.xml, dm.xpt, and/or adsl.xpt files



Self-Check Worksheet Example

- ❖ **Section 5** in the Self-Check Worksheet Provides more guidance to sponsors/applicants to check for the DM and/or ADSL for standardized dataset as well as the associated Define file

Verify DM and Define for SDTM

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.

Verify DM and Define for ADaM

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.

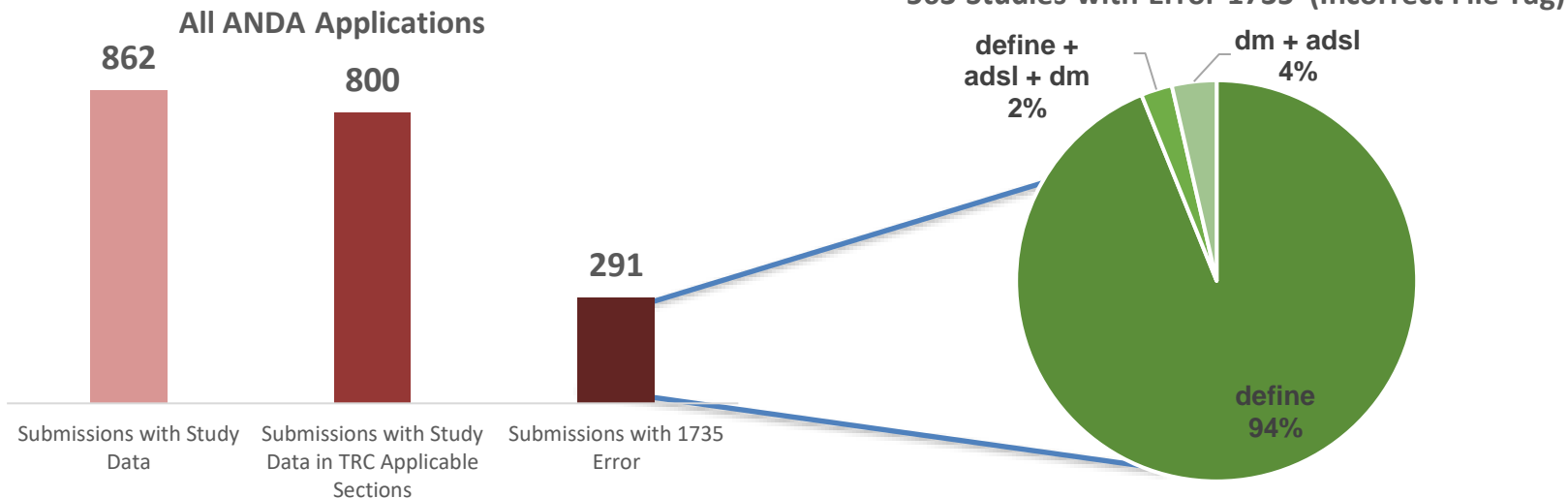
TOP ERROR REASON FOR TRC RULE 1735

CY2019 Error Reasons for Validation Rule 1735

Error	Description
1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*

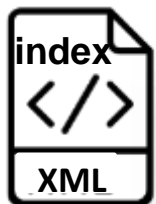
❖ **Common error reason for all application type:**

- An incorrect file tag for a define.xml file
- An incorrect file tag for a DM and ADSL file

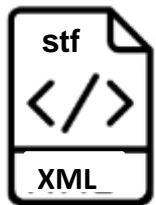


TRC Validation Rule 1735 Typical Error

- Rule 1735: Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections



```
<leaf ID="PR95201" operation="new" checksum="5ce625fb017ce290de6ad2a214ba0cf5" checksum-type="MD5" xlink:href="m5/datasets/abc123/tabulations/sdtm/define.xml">
<title>define</title>
```



```
<doc-content xlink:href="../../../0002/index.xml#PR95201">
  <file-tag name="data-tabulation-dataset-sdtm" info-type="us" />
</doc-content>
```

**define.xml is tagged as
"data-tabulation-data-definition"**

Self-Check Worksheet Example

- ❖ **Section 5** in the Self-Check Worksheet Provides more guidance to sponsors/applicants to check for the proper file tags for standardized dataset as well as the associated define.xml file

Verify SDTM
Dataset File Tag

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.

Verify ADaM
Dataset File Tag

5l. Are the STF File-Tags for the ADaM Dataset "analysis-dataset-adam"?

☒ Yes ☐ No

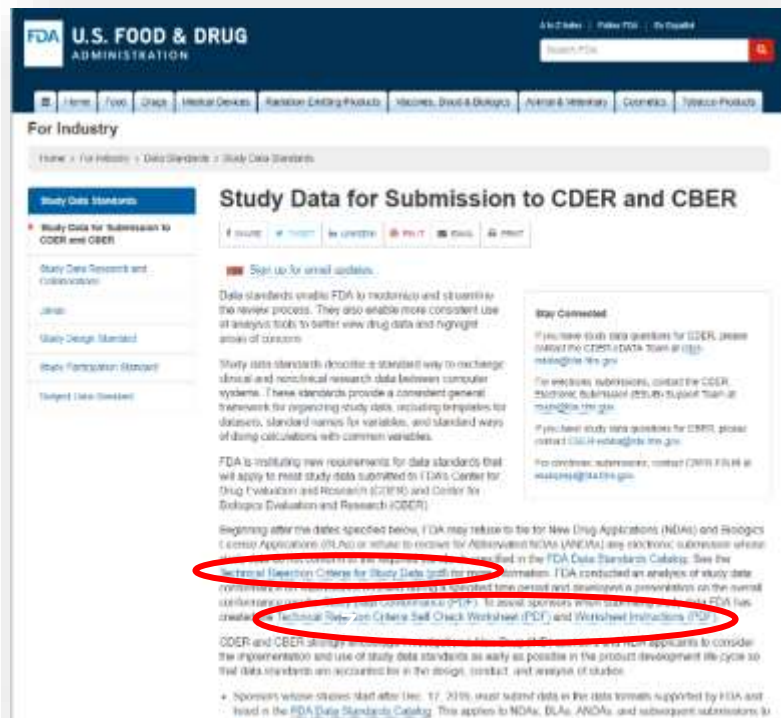
5m. Is the STF File-tag for the Define File "analysis-data-definition"?

☒ Yes ☐ No

[Referenced Validation
Error Number 1735](#)

If you answered "No" in Fields 5l or 5m, Validation Rule 1735 FAILS

FDA Tools - Study Data Self-Check Worksheet & Instructions (Revised Nov. 2019)



“Technical Rejection Criteria for Study Data” (Oct 2019)

<https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm630740.pdf>

“Technical Rejection Criteria Self-Check Worksheet” (Nov 2019)

<https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630732.pdf>

“Technical Rejection Criteria Self-Check Worksheet Instructions” (Nov 2019)

<https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630733.pdf>

Summary



- ❖ Overall conformance for Errors 1734 and 1736 have slightly increased
- ❖ FDA requires the submission of standardized Study Data as defined in the FDA Data Standard Catalog
- ❖ FDA has not rejected any submission that contains errors as reflected in this analysis
- ❖ FDA plans to use technical rejection criteria to identify applications that are not fulfilling this requirement
- ❖ FDA published Study Data Self-Check Worksheet to help sponsors to follow the revised TRC
- ❖ FDA published Simplified TS file creation guide and utility to Generate Simplified TS file



TIP



To avoid validation errors, it is important for sponsors and applicants to understand the requirements specified in guidance and recommendations for submitting study data in the Study Data Technical Conformance Guide.

References



- ❖ **Guidance for industry *Providing Regulatory Submissions In Electronic Format - Standardized Study Data***
[HTTPS://WWW.FDA.GOV/DOWNLOADS/DRUGS/GUIDANCECOMPLIANCEREGLATORYINFORMATION/GUIDANCES/UCM292334.PDF](https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292334.pdf)
- ❖ **Guidance for industry *Providing Regulatory Submissions In Electronic Format - Submissions Under Section 745a(a) Of The FD&C Act***
[HTTPS://WWW.FDA.GOV/DOWNLOADS/DRUGS/GUIDANCECOMPLIANCEREGLATORYINFORMATION/GUIDANCES/UCM384686.PDF](https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm384686.pdf)
- ❖ **Technical Rejection Criteria For Study Data**
[HTTPS://WWW.FDA.GOV/MEDIA/100743/DOWNLOAD](https://www.fda.gov/media/100743/download)
- ❖ **Study Data Technical Conformance Guide**
[HTTPS://WWW.FDA.GOV/MEDIA/131872/DOWNLOAD](https://www.fda.gov/media/131872/download)
- ❖ **FDA Data Standards Catalog**
[HTTPS://WWW.FDA.GOV/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/DEFAULT.HTM](https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm)
- ❖ **Technical Rejection Criteria Self-Check Worksheet**
[HTTPS://WWW.FDA.GOV/MEDIA/123098/DOWNLOAD](https://www.fda.gov/media/123098/download)
- ❖ **Technical Rejection Criteria Self-Check Worksheet Instructions**
[HTTPS://WWW.FDA.GOV/MEDIA/123099/DOWNLOAD](https://www.fda.gov/media/123099/download)

Recommended Readings

- ❖ For FDA instruction of Study Data submission, Self-Check Worksheet and Simplified TS file creation guide see the FDA “Study Data for Submission to CDER and CBER” page at:
[HTTPS://WWW.FDA.GOV/INDUSTRY/STUDY-DATA-STANDARDS-RESOURCES/STUDY-DATA-SUBMISSION-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” page at:
[HTTPS://WWW.FDA.GOV/INDUSTRY/FDA-RESOURCES-DATA-STANDARDS/STUDY-DATA-STANDARDS-RESOURCES](https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources)

Challenge Question #1

A study submitted in an ANDA that has a study start of 2012-02-28 should not contain a ts.xpt file

- A. Yes, a full ts.xpt is expected
- B. Yes, a simplified ts.xpt is expected
- C. No, it should not contain a ts.xpt file

Challenge Question #2

Which of the following statements is **NOT** true?

- A. A clinical study that follows CDISC format is expected to contain a define.xml file
- B. Standardized clinical study files should be tagged with “data-tabulation-dataset-sdtm”
- C. The study start date should be in the format “MM-DD-YYYY”

Questions?

Closing Thought

The Study Data Guidance is in effect and requires the submission of standardized study data. Please utilize the available tools to ensure conformance to the Study Data Technical Rejection Criteria.

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*Thank
You*



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