

FDA DISCLAIMER



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- ❖ eCTD and Study Data Requirements
- ❖ Study Data Conformance Analysis (CY2020 Q1-Q2)
- ❖ Top Error Reasons for TRC Rules 1734 and 1736
- ❖ FDA Tools - Study Data Self-Check Worksheet & Instructions (Revised Nov. 2019)
- ❖ Summary

eCTD AND STUDY DATA REQUIREMENTS

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 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 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

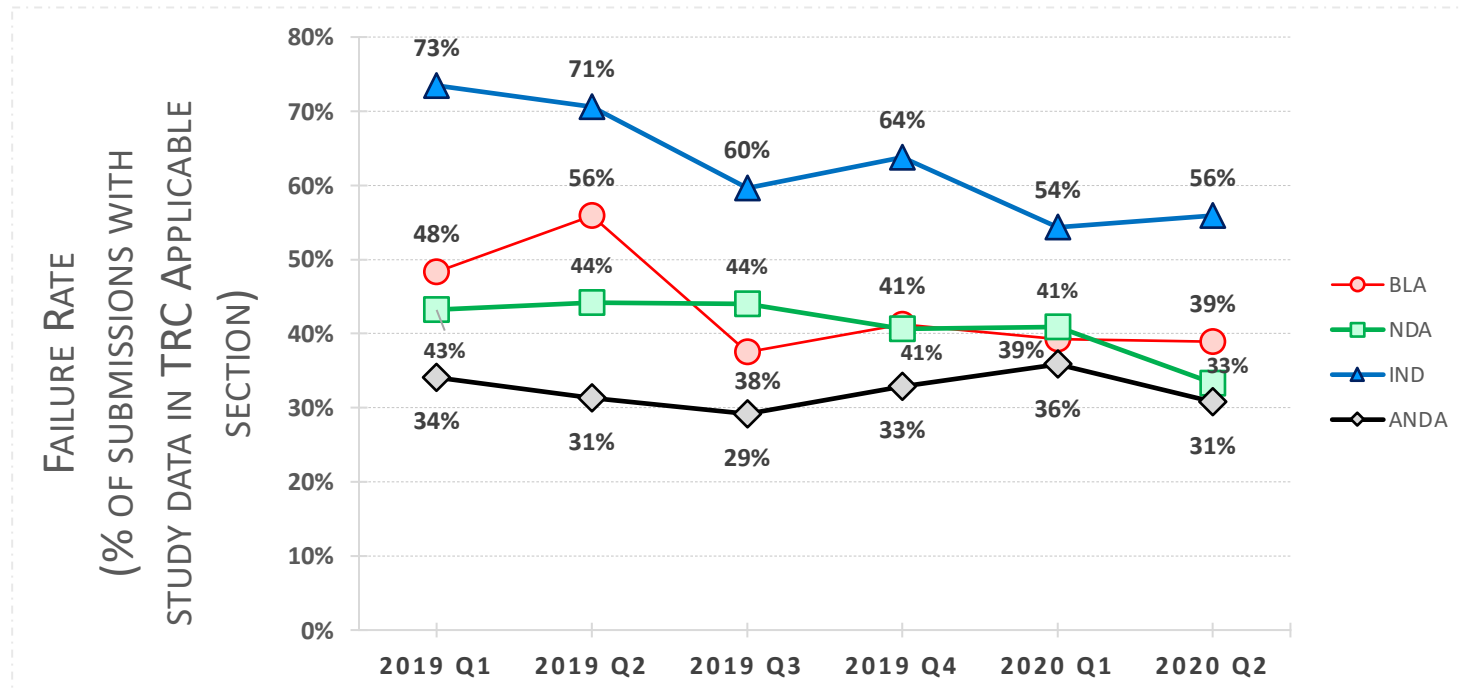
- Per FD&C Act Section 745A(a), drug application sponsors must use the standards defined in the FDA Data Standards Catalog starting 24 months after final guidance for a specific submission type.
- FDA issued “Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for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

STUDY DATA CONFORMANCE ANALYSIS (CY2019 TO CY2020 Q1-Q2)

QUARTERLY TREND - 1734 & 1736 FAILURE RATE



Analysis includes NDA, BLA, ANDA and commercial IND submissions received by CDER between 1/1/2019 and 6/30/2020



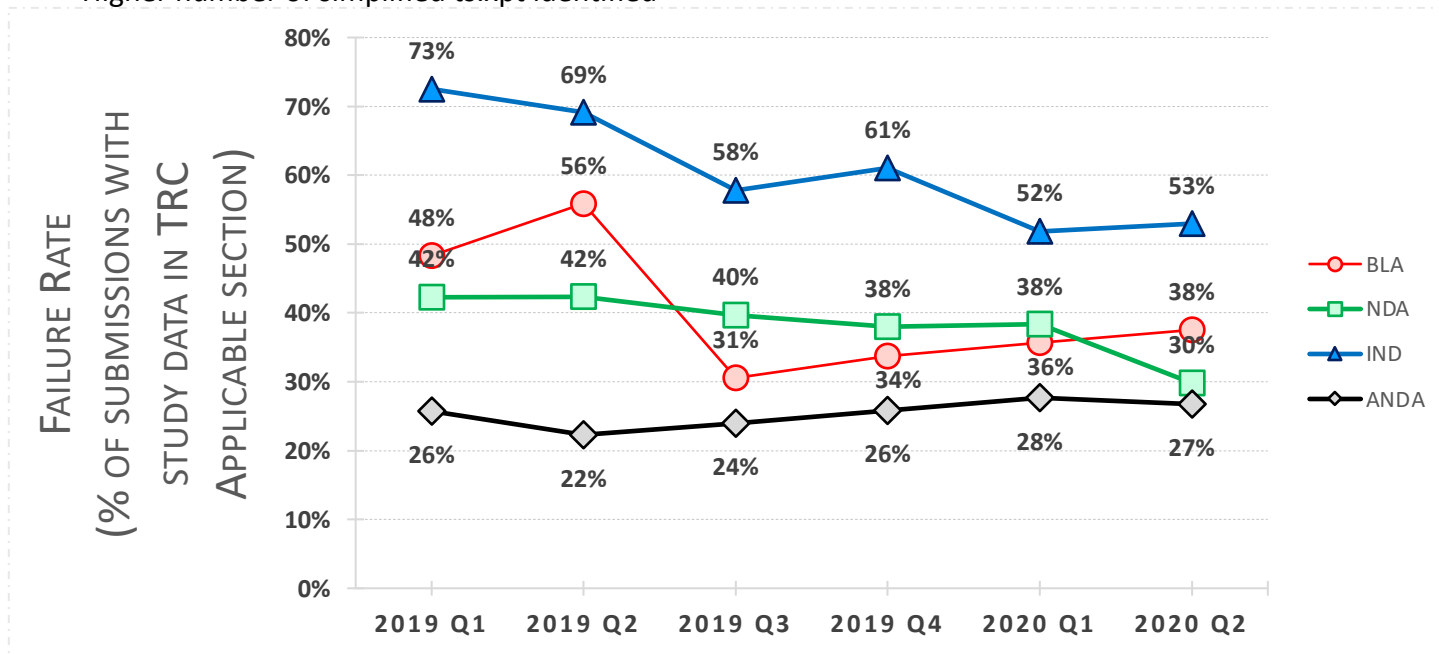
Notes:

- 1) Submission with multiple studies can report both 1734 and 1736 failure
- 2) 1736 is not analyzed if the study fails 1734
- 3) Analysis is conducted according to the revised TRC (Revised Oct. 2019)

QUARTERLY TREND - 1734 FAILURE RATE



- IND applications shows most significant decline in the 1734 failure rate over the time period (CY2019 Q1 through CY2020 Q2)
- NDAs also show the significant decline between CY2020 Q1 and Q2 due to:
 - Lower number of M4 (non-clinical) missing ts.xpt
 - Higher number of simplified ts.xpt identified



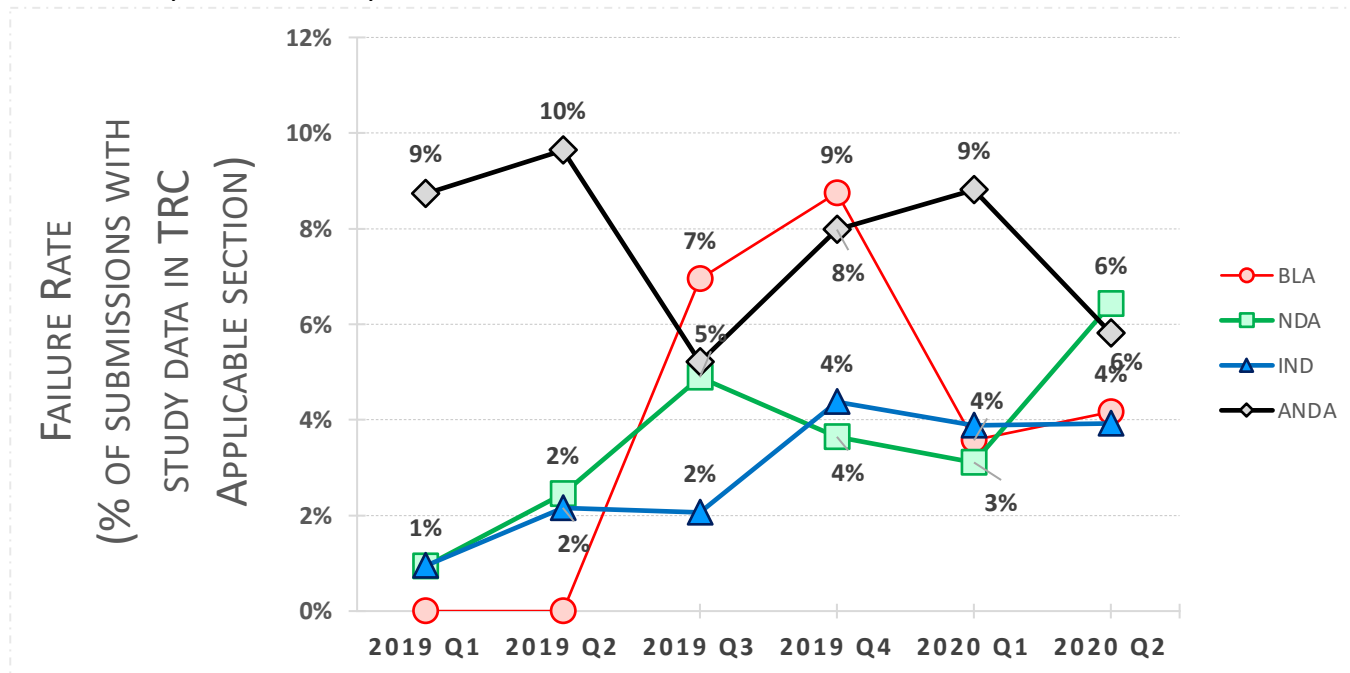
Notes:

- 1) Analysis includes NDA, BLA, ANDA and commercial IND submissions received by CDER between 1/1/2019 and 6/30/2020
- 2) Submission with multiple studies can report both errors 1734 and 1736
- 3) Analysis is conducted according to the revised TRC (Revised Oct. 2019)

QUARTERLY TREND - 1736 FAILURE RATE



- 1736 errors continue to have a failure rate less than 10%
- 1736 is not analyzed if the study fails 1734



Notes:

- 1) Analysis includes NDA, BLA, ANDA and commercial IND submissions received by CDER between 1/1/2019 and 6/30/2020
- 2) Submission with multiple studies can report both Errors 1734 and 1736
- 3) 2020 Q2 Analysis is conducted according to the revised TRC (Revised Oct. 2019)

CY2020 TECHNICAL REJECTION CRITERIA CONFORMANCE RESULTS



- 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.
- The entire submission will be rejected if there is at least one error.

Submission Level		ANDA		BLA		NDA		Comm IND		Total	
		Q1	Q2	Q1	Q2	Q1	Q2	Q1	Q2	Q1	Q2
a	Total Number of Submissions	14,019	15,258	4,093	5,181	12,479	13,819	22,682	23,871	53,273	58,073
b	Total Number of Submissions with Study Data or Study Reports*	170	192	87	99	292	258	740	832	1289	1381
c	Total Number of Submissions with Study Data or Study Reports* in TRC Applicable Sections	159	172	56	72	193	171	438	485	846	900
d	Total Number Submissions with Critical Errors (e or f)	44	53	22	28	74	57	238	271	378	409
e	Error 1734	44	46	20	27	74	51	227	257	365	381
f	Error 1736	14	10	2	3	6	11	17	19	39	43
g	Failure Rate (% among submissions with Study Data in TRC Applicable Sections [d/c])	27.7%	30.8%	39.3%	38.9%	38.3%	33.3%	54.3%	55.9%	44.7%	45.4%
h	Failure Rate (% among submissions with Study Data*) [d/b]	25.9%	27.6%	25.3%	28.3%	25.3%	22.1%	32.2%	32.6%	29.3%	29.6%
i	Rejection Rate [d/a]	0.3%	0.4%	0.5%	0.5%	0.6%	0.4%	1.0%	1.1%	0.7%	0.7%

Notes:

- (1) One drug application could contain multiple submissions throughout its review life-cycle, such as original, supplements, and amendments
- (2) Analysis includes NDA, BLA, ANDA and commercial IND submissions received by CDER between 1/1/2020 and 6/30/2020
- (3) *Definition of Study Data: submissions with .xpt files (m5) and/or Study Report (m4) in TRC Applicable section

CY2020 TECHNICAL REJECTION CRITERIA CONFORMANCE RESULTS



Most of the 1734 errors are observed for non-clinical (m4) studies submitted in NDA and commercial IND applications.

Study Level		ANDA		BLA		NDA		Comm IND		All	
		m4	m5	m4	m5	m4	m5	m4	m5	m4	m5
a	Studies with Study Data	20	414	294	209	1932	748	8050	73	10,296	1444
b	Studies with Study Data* in Data in TRC Applicable Sections	9	347	45	128	279	499	1364	66	1697	1040
c	Studies with Critical Error	6	97	30	35	108	85	812	22	911	239
d	1734 Error	6	78	30	32	108	72	767	22	911	204
e	1736 Error	0	19	0	3	0	13	45	0	45	35
f	Error Rate (% among failed studies with Study Data* Data in TRC Applicable Sections) [c/b]	66.7%	28.0%	66.7%	27.3%	38.7%	17.0%	59.5%	33.3%	53.7%	23.0%
g	Error Rate - (% among failed studies with Study Data*) [c/a]	30.0%	23.4%	10.2%	16.8%	5.6%	11.4%	10.1%	30.1%	8.9%	16.6%

Notes:

- (1) One drug application could contain multiple submissions throughout its review life-cycle, such as original, supplements, and amendments
- (2) Analysis includes NDA, BLA, ANDA and commercial IND submissions received by CDER between 1/1/2020 and 6/30/2020
- (3) *Definition of Study Data: submissions with .xpt files and/or Study Report (m4) in TRC Applicable section

TOP ERROR REASONS FOR TRC RULE 1734 FAILURE

1734 COMMON ERROR REASON – A MISSING TS FILE



Submitting a simplified ts.xpt for all these non-clinical studies will greatly reduce the 1734 error rate.

703 IND non-clinical studies are missing a ts.xpt file

	Commercial IND 2020 Q2 Count
Submissions with 1734 errors	257
Studies in submissions with a 1734 error	789
Studies with a 1734 error in a nonclinical section	767
Received a 1734 error in a nonclinical section due to missing ts.xpt file	703

	Count
Studies with study data or reports	703
Studies with only study reports	691
Studies with study data and study reports	8
Studies with only study data	4

97% of the 703 IND non-clinical studies are toxicology

Toxicology Sections	Count
Repeat dose toxicology (m4.2.3.2)	517
Single dose toxicology (m4.2.3.1)	122
Carcinogenicity (m4.2.3.4)	44

Notes:

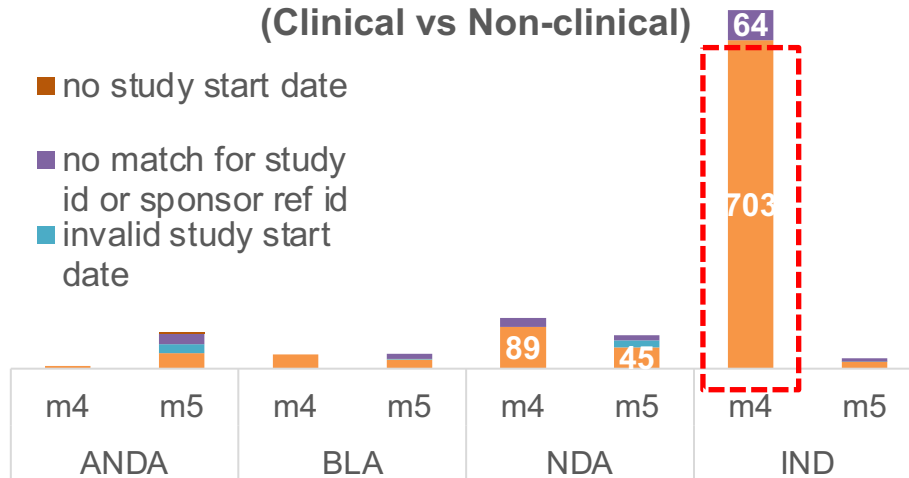
(1) Analysis includes commercial IND submissions received by CDER between 3/1/2020 and 6/30/2020

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*

- Submitting a simplified ts.xpt for all these non-clinical studies will greatly reduce the 1734 error rate.
- Common error reasons for all application types:
 - A missing ts.xpt file
 - Study ID Mismatch between TS and STF
- In Q2 2020, out of 8050 studies that have study data or study reports, 7283 passed 1734

1734 Error Reason for Q2 2020 Studies (Clinical vs Non-clinical)



Notes:

(1) Analysis includes ANDA, BLA, NDA and commercial IND submissions received by CDER between 3/1/2020 and 6/30/2020

IMPORTANT REMINDERS



For CDER/OND, the following nonclinical study types are required to have SEND datasets as defined by study initiation date:

SEND Requirement Dates for Nonclinical Studies Modelled in SEND (Studies started after these dates require SEND datasets)		
Study Types Modelled in SEND	NDA/BLAs	Commercial INDs
Single Dose Toxicity, Repeat Dose Toxicity, and Carcinogenicity Studies	December 17, 2016 (SENDIG v3.0)	December 17, 2017 (SENDIG v3.0)
	March 15, 2019 (SENDIG v3.1)	March 15, 2020 (SENDIG v3.1)
Cardiovascular and Respiratory Safety Pharmacology Studies	March 15, 2019 (SENDIG v3.1)	March 15, 2020 (SENDIG v3.1)

HOW TO IDENTIFY AND CREATE A SIMPLIFIED TS.XPT



- **Sponsors should submit a simplified ts.xpt even if datasets are not submitted for a non-clinical study**
- To understand if a simplified ts.xpt file is required, please review the TRC Self-check worksheet.
- FDA has created a step-by-step [Simplified ts.xpt Creation Guide](#) on how to create a simplified ts.xpt using free and open source tools such as R or Python.
 - There's also a PHUSE Utility to assist in generating a simplified ts.xpt file

SELF-CHECK WORKSHEET 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/Applicant 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 provide more guidance to sponsors/applicants to check for the expectation from a Simplified TS file



Study ID in TS =
S107



Date =

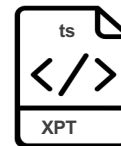
Simplified TS File	
4l. Study ID (STUDYID) in TS File*: S107	
4m. Does Study ID (study-id) in STF (Field 3d) and TS Files Match?*	Referenced Validation Error Number 1734
☒ Yes ☐ No	
If you answered "No" in Field 4m , Validation Rule 1734 FAILS. Do not proceed.	
4n. Is there a Value in TSVALNF?	
☐ Yes ☒ 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"?	Referenced Validation Error Number 1734
☐ Yes ☐ No	
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)?	Referenced Validation Error Number 1734
☒ Yes ☐ No	
If you answered "No" in Field 4q , Validation Rule 1734 FAILS. Do not proceed.	

EXAMPLE - SIMPLIFIED TS.XPT WITH AND WITHOUT STUDY START DATE



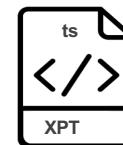
Example of a Simplified TS file submitted for a non-clinical study with study-id “S107” in the STF file

STUDYID	TSPARMCD	TSVAL	TSVALNF
S107	STSTDTC	2020-01-26	



Example of a Simplified TS file submitted for a non-clinical study with study-id “S108” in the STF file without a study start date. Review the [Technical Conformance Guide](#) for study data to understand the requirements.

STUDYID	TSPARMCD	TSVAL	TSVALNF
S108	STSTDTC		NA

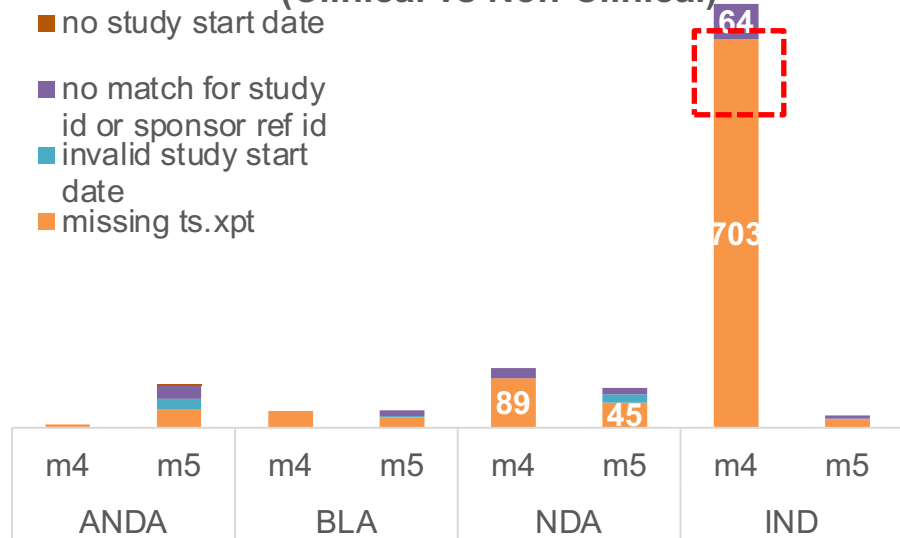


1734 COMMON ERROR REASON – STUDY ID MISMATCH



1734 Error Reason for Q2 2020 Studies

(Clinical vs Non-Clinical)



64 IND non-clinical studies have a Study ID mismatch

	Count
Studies with study data or reports	64
Studies with only study reports	56
Studies with study data and study reports	8
Studies with only study data	4

94% of the 64 IND non-clinical studies are toxicology studies

Toxicology Sections	Count
Repeat dose toxicology (m4.2.3.2)	43
Single dose toxicology (m4.2.3.1)	17
Carcinogenicity (m4.2.3.4)	4

Notes:

(1) Analysis includes ANDA, BLA, NDA and commercial IND submissions received by CDER between 3/1/2020 and 6/30/2020

1734 COMMON ERROR REASON – STUDY ID MISMATCH



- 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).

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		SPLNAM	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
</>
XPT

TS STUDYID

STF STUDYID

SPREFID

```
<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>
```

1734 COMMON ERROR REASON – STUDY ID MISMATCH

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

- Question 4m will help Sponsors/Applicant ensure that the study-ID in the STF and simplified TS match

✓ Study ID in STF = pqr-456

3d. Study ID (study-id) in STF File

pqr-456

Simplified TS File

✓ Study ID in TS = pqr-456

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

pqr-456

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.*

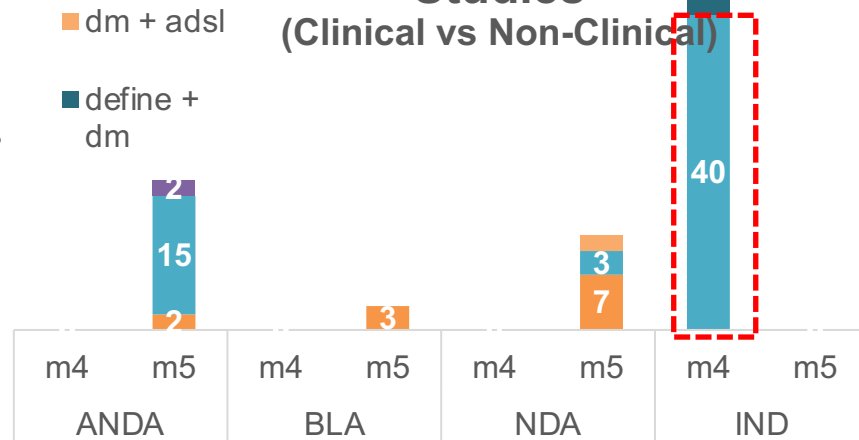
TOP ERROR REASONS FOR TRC RULE 1736 FAILURE

1736 COMMON ERROR REASON – MISSING DEFINE FILE

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*

- **1736 is not analyzed if the study fails 1734**
- **Common error reasons for all application types:**
 - A missing define.xml files
 - A missing define.xml, dm.xpt, and/or adsl.xpt files
- **Missing define.xml is the largest reason for 1736 errors for IND Non-clinical studies**

1736 Error Reason for Q2 2020 Studies (Clinical vs Non-Clinical)



Notes:

(1) Analysis includes ANDA, BLA, NDA and commercial IND submissions received by CDER between 3/1/2020 and 6/30/2020

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
SEND

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.

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.

FDA TOOLS AND SUMMARY

FDA TOOLS - STUDY DATA SELF-CHECK WORKSHEET & INSTRUCTIONS



The screenshot shows the FDA website's 'Study Data Standards' page. The header includes the FDA logo, 'U.S. FOOD & DRUG ADMINISTRATION', and navigation links like 'A to Z Index', 'Follow FDA', and 'En Español'. A search bar is also present. The main navigation bar lists various FDA categories: Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, and Tobacco Products. The page title is 'Study Data for Submission to CDER and CBER'. A sidebar on the left lists 'Study Data Standards' with links to 'Study Data for Submission to CDER and CBER', 'Study Data Research and Collaborations', 'Janus', 'Study Design Standard', 'Study Participation Standard', and 'Subject Data Standard'. The main content area includes social media sharing options (Share, Tweet, LinkedIn, Print, Email, Print), a link to 'Sign up for email updates', and a 'Stay Connected' section with contact information for CDER eDATA and CBER eSUB teams. The text explains that study data standards enable FDA to modernize and streamline the review process and provide a consistent framework for organizing study data. It also mentions that 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). The page concludes with a note about the FDA's refusal to file or receive certain electronic submissions that do not conform to the required standards, and a link to the 'Technical Rejection Criteria for Study Data (pdf)'. A final note states that CDER and CBER strongly encourage Investigational New Drug (IND) sponsors and NDA applicants to consider the implementation and use of study data standards as early as possible in the product development life cycle so that data standards are accounted for in the design, conduct, and analysis of studies. A bullet point at the bottom states that sponsors whose studies start after Dec. 17, 2016, must submit data in the data formats supported by FDA and listed in the 'FDA Data Standards Catalog'. This applies to NDAs, BLAs, ANDAs, and subsequent submissions to the FDA.

- Technical Rejection Criteria for Study Data (Oct 2019)
- Technical Rejection Criteria Self-Check Worksheet (Nov 2019)
- Technical Rejection Criteria Self-Check Worksheet Instructions (Nov 2019)

- ❖ Overall conformance for Errors 1734 and 1736 have decreased in Q2 since Q1 2020, especially NDA
- ❖ **FDA requires the submission of standardized Study Data as defined in the FDA Data Standard Catalog**
- ❖ 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
- ❖ FDA will provide a Public Notice on the Technical Rejection Criteria effective date
 - ❖ After the Public Notice announcement, FDA plans to provide TRC validation error warning message as part of 3rd acknowledgement
 - ❖ TRC will be enforced after six months of the Public Notice



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.

- ❖ **Study Data Standards Resources**

- ❖ **Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry**

- ❖ **Study Data Technical Conformance Guide**

- ❖ **FDA Data Standards Catalog**

- <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>

- ❖ **Study Data for Submission to CDER and CBER**

- ❖ **Technical Rejection Criteria For Study Data**

- ❖ **Technical Rejection Criteria Self-Check Worksheet**

- ❖ **Technical Rejection Criteria Self-Check Worksheet Instructions**

- <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

- ❖ **Providing Regulatory Submissions In Electronic Format - Submissions Under Section 745a(a) Of The FD&C Act: Guidance For Industry**

- <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>

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*Thank
You*

For Questions Please Contact:

Study Data Questions:
edata@fda.hhs.gov

eCTD Questions:
esub@fda.hhs.gov



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