Study Data Technical Rejection Criteria

Heather Crandall
Division of Data Management Services & Solutions,
Office of Business Informatics
CDER | US FDA

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Topics

- ❖ **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**

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

"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."

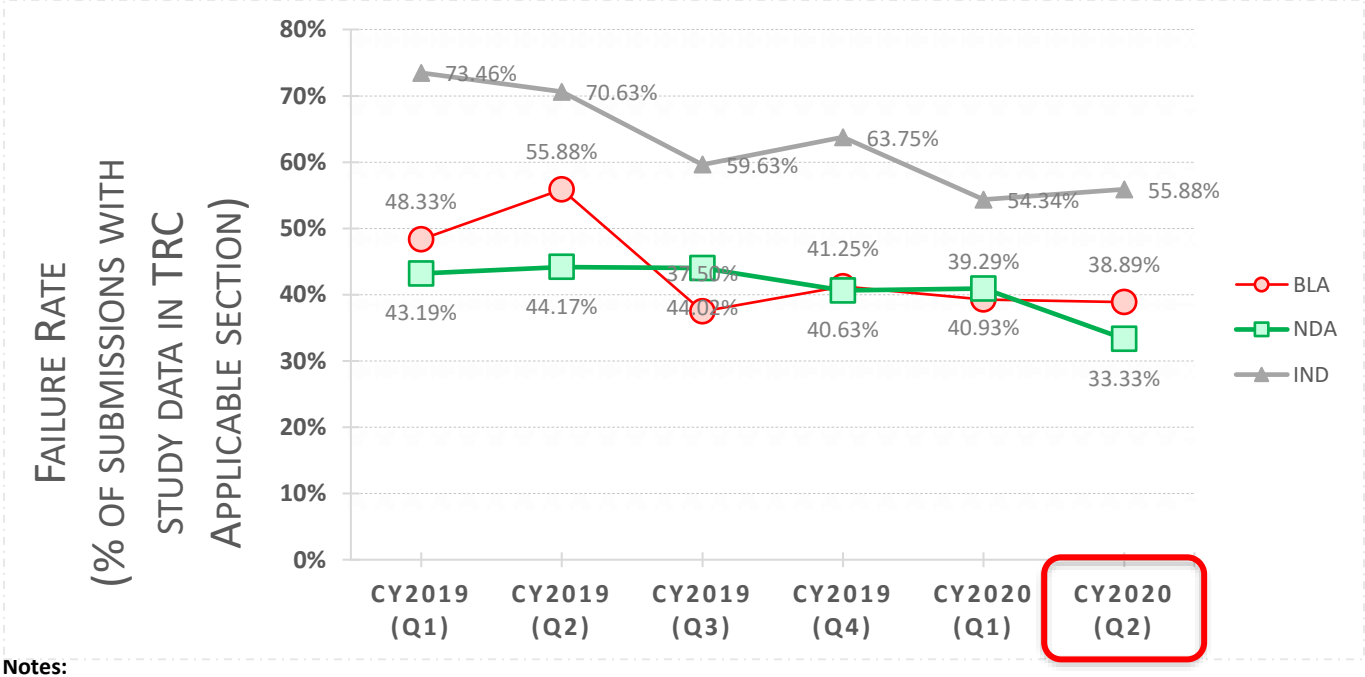
Source: https://www.ich.org/products/ctd.html

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 "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**

TRC Conformance Trend

- There is a significant decrease in NDA Failure Rate between CY2020 Q1 and CY2020 Q2
- There is a slight increase in IND Failure Rate between CY2020 Q1 and CY2020 Q2



Notes:

1) Analysis includes NDA submissions received by CDER between 4/1/2020 to 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 Conformance Analysis for Validation Errors 1734 & 1736

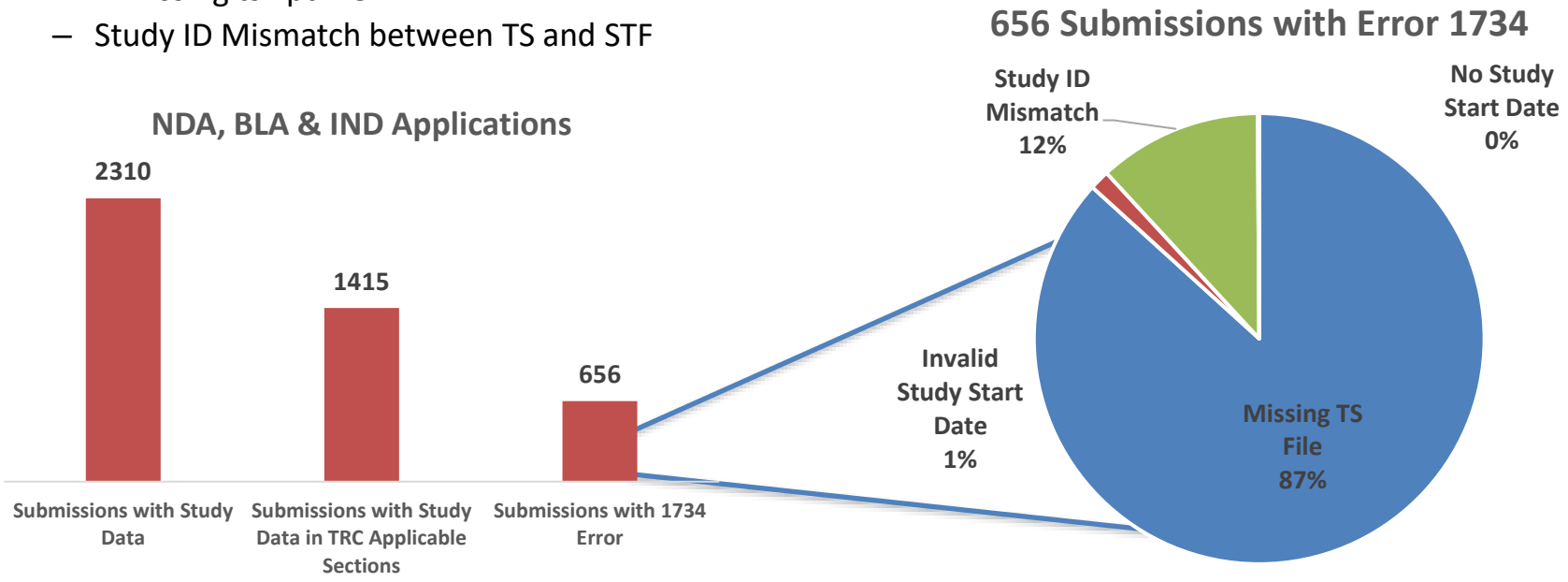
		BLA		NDA		IND	
		Q1	Q2	Q1	Q2	Q1	Q2
a	Total Number of Submissions	4,093	5,181	12,479	13,819	22,682	23,815
b	Total Number of Submissions with Study Data and/or Study Reports	87	99	292	258	740	832
c	Total Number of Submissions with Study Data and/or Study Reports in TRC Applicable Sections	56	72	193	171	438	485
d	Total Number Submissions with 1734 or 1736 Errors	**22**	**28**	**79**	**57**	**238**	**271**
e	Error 1734	20	27	74	51	227	257
f	Error 1736	2	3	6	11	17	19
g	Failure Rate (% among submissions with Study Data and/or Study Reports) [d/b]	25.29%	28.28%	27.05%	22.09%	32.16%	32.57%
h	Failure Rate (% among submissions with Study Data and/or Study Reports in TRC Applicable Sections) [d/c]	**39.29%**	**38.89%**	**40.93%**	**33.33%**	**54.34%**	**55.88%**

TOP ERROR REASON FOR TRC RULE 1734

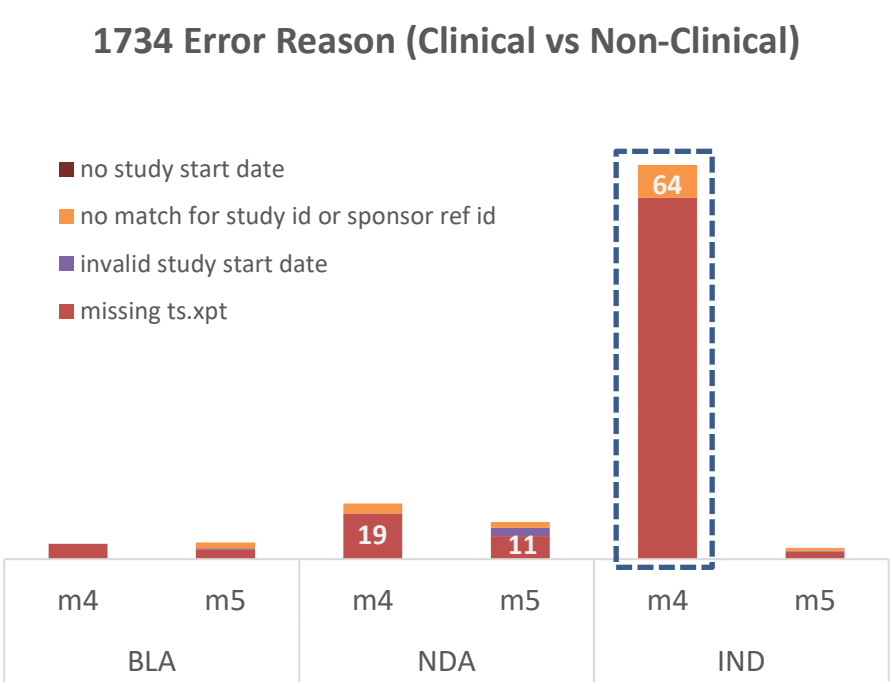
CY2020 Error Reasons for Validation Rule 1734

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



CY2020 Q2 1734 Common error reason – A missing TS file



- Out of 8050 studies that have study data or reports, 7283 (90%) do not have a 1734 error (pass)
- 703 IND non-clinical studies are missing a ts.xpt file

	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 studies

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

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

Important Reminders

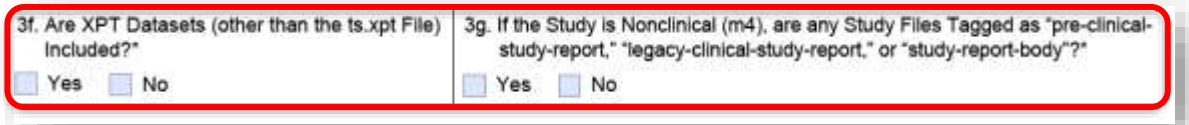
For CDER/OND, the following nonclinical study types are required to have SEND datasets as defined by study initiation date:

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

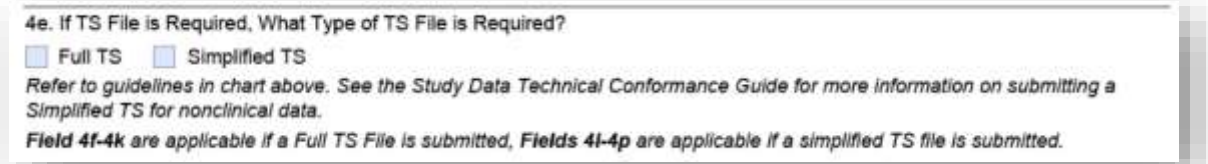
Self-Check Worksheet Revisions and Examples

❖ 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/Applicant clarify the requirement about expectation of ts.xpt, question 3f and 3g is introduced



- 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

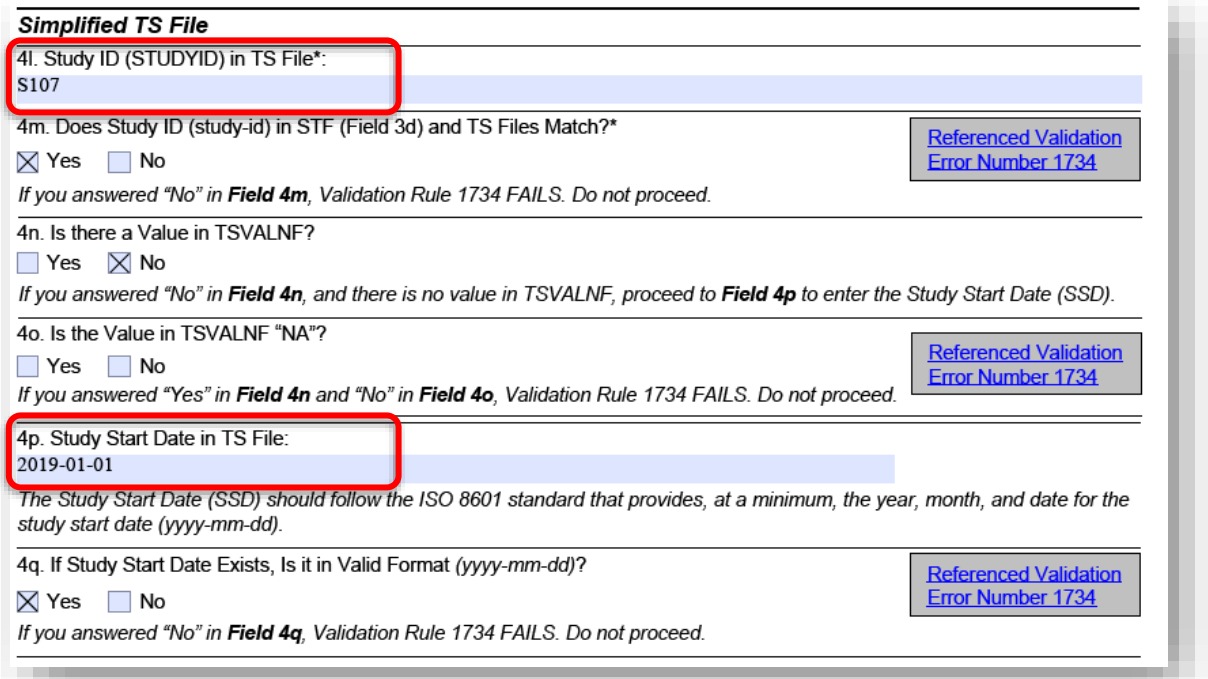


Self-Check Worksheet Example for Simplified TS

- 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

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.*

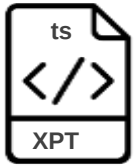
4p. Study Start Date in TS File:
2019-01-01
The Study Start Date (SSD) should follow the ISO 8601 standard that provides, at a minimum, the year, month, and date for the study start date (yyyy-mm-dd).

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

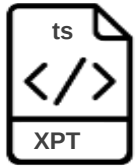
- Example of a Simplified TS file submitted for a clinical study with study-id “S107” in the STF file

STUDYID	TSPARMCD	TSVAL	TSVALNF
S107	SSTDTC	2014-10-26	

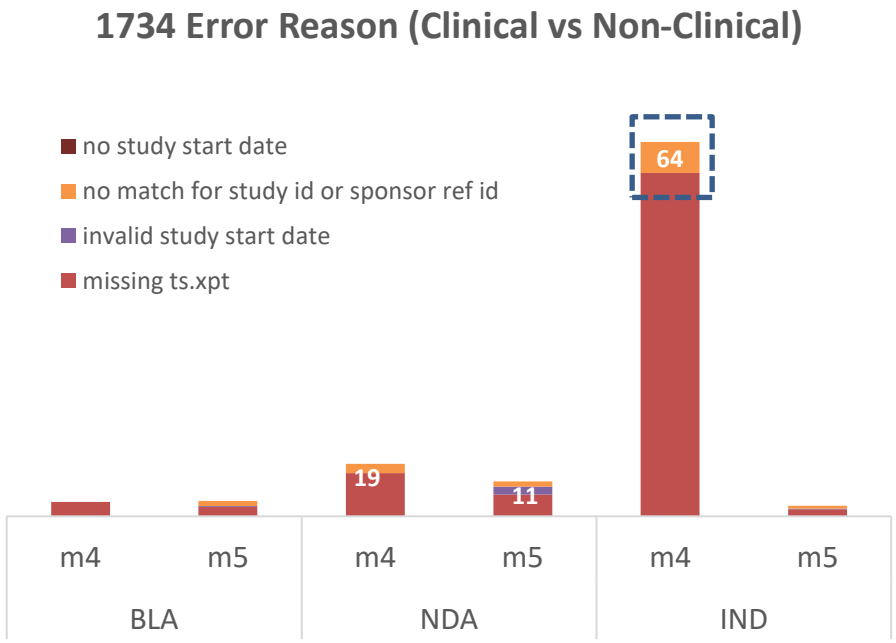


- Example of a Simplified TS file submitted for a clinical study with study-id “S108” in the STF file without a study start date. Review the Technical Conformance Guide for study data to understand the requirements.

STUDYID	TSPARMCD	TSVAL	TSVALNF
S108	SSTDTC		NA



CY2020 Q2 1734 Common error reason – Study ID Mismatch



- 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

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

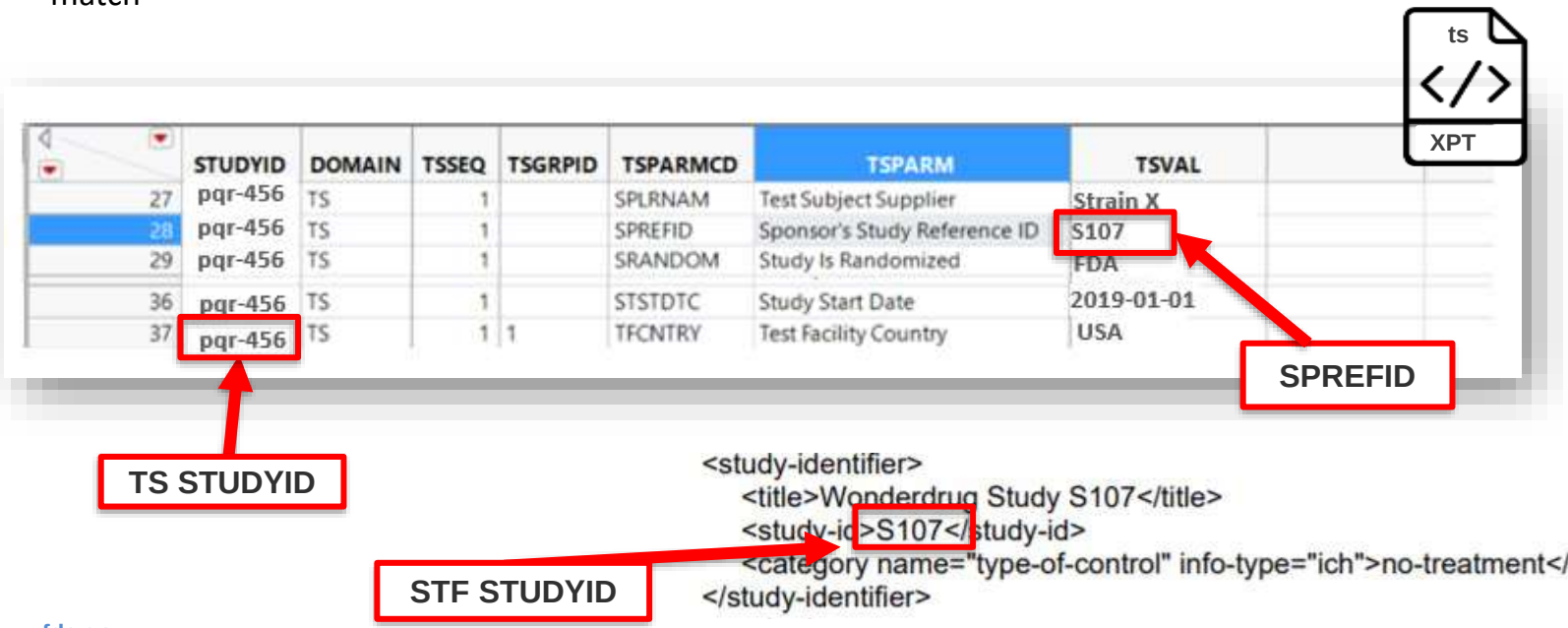
TRC Introduced SPREFID to Match STF Study ID with ts.xpt

- 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).

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



Self-Check Worksheet Example for Simplified TS

- **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

✓ Study ID in TS = pqr-456

Simplified TS File

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

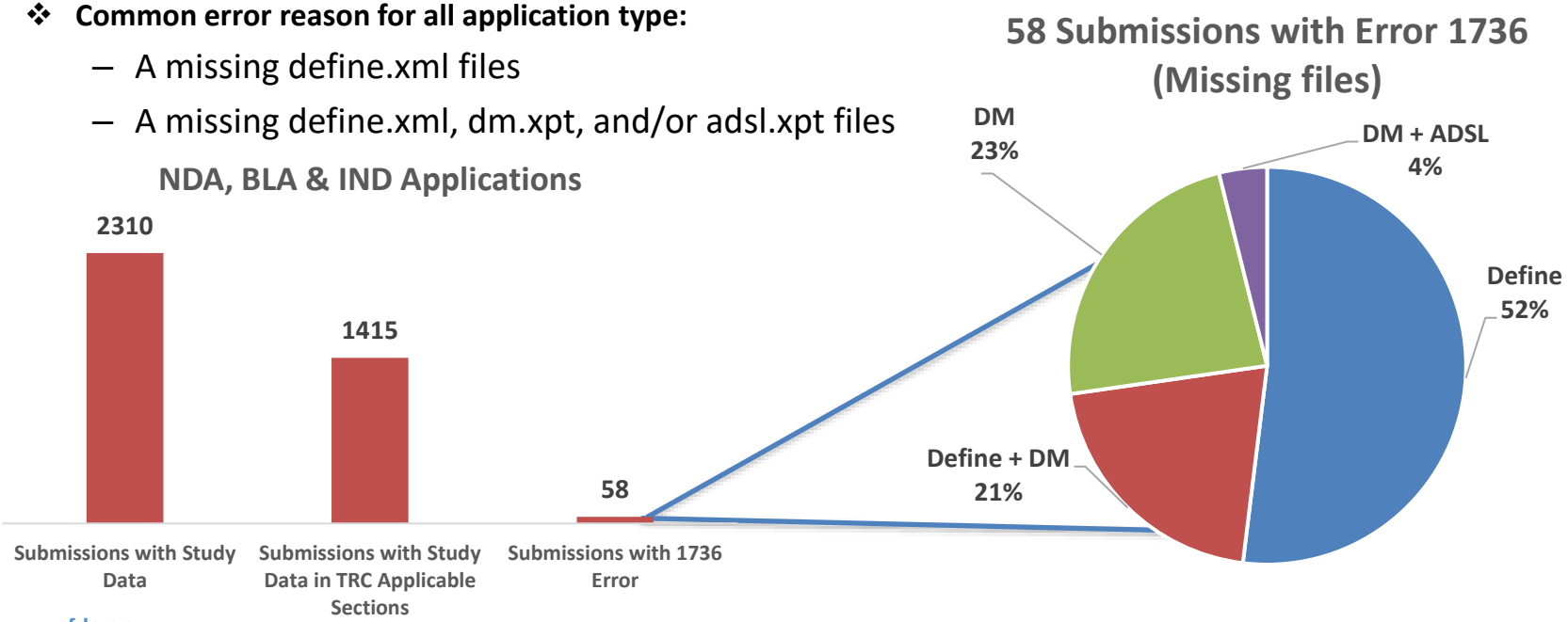
*If you answered "No" in **Field 4m**, Validation Rule 1734 FAILS. Do not proceed.*

TOP ERROR REASON FOR TRC RULE 1736

CY2020 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*

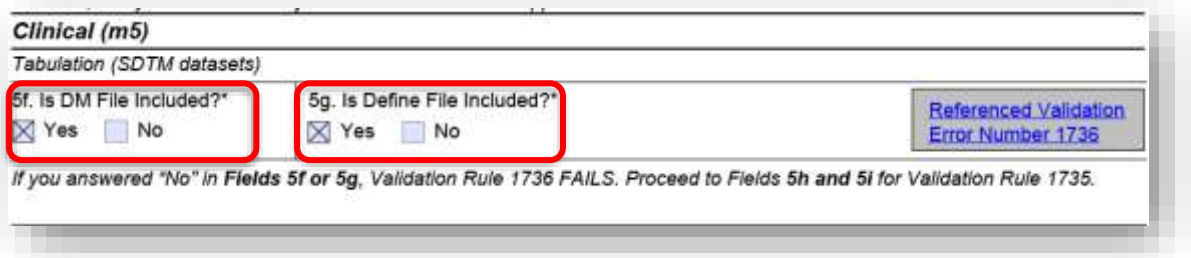
- **Common error reason for all application type:**
  - A missing define.xml files
  - A missing define.xml, dm.xpt, and/or adsl.xpt files



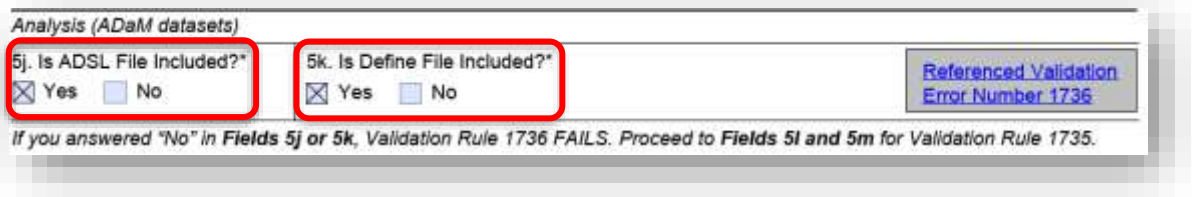
Self-Check Worksheet Example

- **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

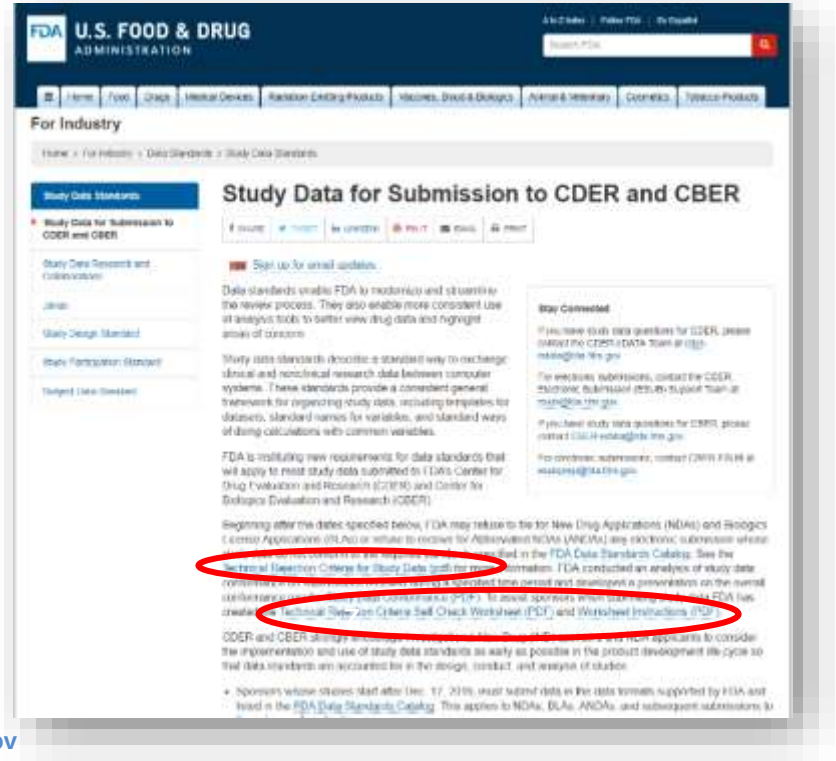
Verify DM and Define for SDTM



Verify DM and Define for ADaM



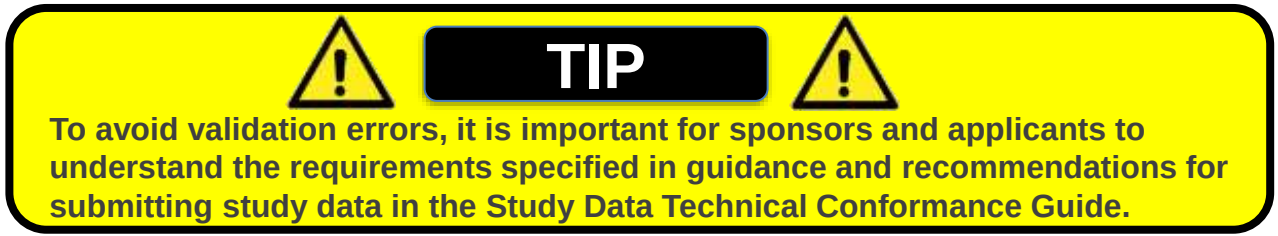
FDA Tools - Study Data Self-Check Worksheet & Instructions (Revised Nov. 2019)



- **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)**

Summary

- 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 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



References

- **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

Acknowledgments

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