U.S. FOOD & DRUG ADMINISTRATION

FDA Update on Technical Rejection Criteria for Study Data

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Disclaimer

The views and opinions presented here represent those of the speakers and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

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

Study Data Conformance from Previous Analysis

- **Study Data was assessed for:**
  - NDA, BLA, and ANDA Submissions received from 12/18/2016 to 3/31/2018
  - Commercial IND Submissions received from 12/18/2017 to 3/31/2018
  - No duplicates

- **Conformance was checked against the existing two high-level validation rules as described in the Technical Rejection Criteria for Study Data**
  - 1734 – TS Dataset & Correct Study Start Date must be present
  - 1736 – DM Dataset, ADSL Dataset and define.xml must be present

Reference: FDA Study Data Technical Rejection Criteria (Revised May 2018)

Overall Conformance Statistics from Previous Analysis

Error	Description
1734	Trial Summary (TS) dataset must be present for each study in eCTD section 4.2 and 5.3
1736	Demographic dataset (DM) and the define.xml must be submitted in Module 4 for nonclinical data; DM dataset, the subject-level analysis dataset (ADSL) and define.xml must be submitted in Module 5 for clinical data

	NDA	ANDA	BLA	Comm. IND	All
Total Number of Submissions with Study Data	1,126	1,446	473	176	3,221
Total Number Submissions with Critical Errors	302	551	138	41	1,032
Error 1734	290	506	137	35	968
Error 1736	14	63	1	6	84
Failure Rate (% among submissions with Study Data)	26.8%	38.1%	29.2%	23.3%	32.0%

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, and ANDA submissions received by CDER between 12/18/2016 and 3/31/2018, and commercial IND submissions received by CDER between 12/18/2017 and 3/31/2018

(3) Validation of error 1736 of a study is not performed if a study has Error 1734

(4) 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

Reference: FDA Study Data Technical Rejection Criteria (Revised May 2018)

CY2018 Conformance Analysis for Validation Errors 1734 & 1736

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

** Refer to the latest Technical Rejection Criteria for Study Data*

	NDA	ANDA	BLA	Comm. IND	All
Total Number of Submissions with Study Data	877	1078	291	649	2895
Total Number Submissions with Critical Errors	195	266	50	113	624
Error 1734	185	186	48	96	515
Error 1736	16	88	2	18	124
Failure Rate (% among submissions with Study Data)	22.2%	24.7%	17.2%	17.4%	21.6%

Notes:

(1) Analysis includes NDA, BLA, ANDA and Commercial IND submissions received by CDER between 1/1/2018 and 12/31/2018

(2) Validation of error 1736 is not performed if a study has Error 1734

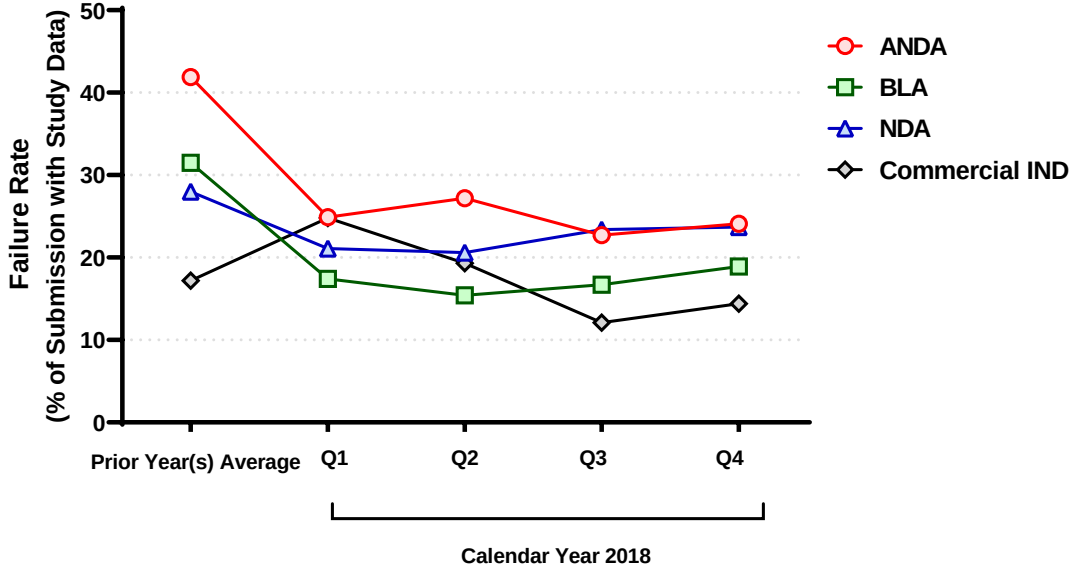
(3) A submission with multiple studies can report both Errors 1734 and 1736. In this instance, the submission is counted only once at the submission level when calculating failure rate

(4) Analysis is conducted according to the revised TRC (Revised Jan. 2019)

Reference: FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

Overall Conformance Trend for Validation Errors 1734 & 1736

- Submissions with study data received during CY2018 showed overall decreases in failure rate of Validation Errors 1734 and 1736 compared to prior years' average failure rate



Notes:

(1) Prior year(s) average uses data from the previous analysis, but excludes any submissions received in 2018

(2) CY2018 analysis is conducted according to the revised TRC (Revised Jan. 2019)

Summary of 1734 and 1736 Conformance Trend

- The failure rate for Errors 1734 and 1736 for all application types received in CY2018 is 21.6%
- Overall conformance for Errors 1734 and 1736 improved compared to the previous analysis (previous years' average of 68.0% vs. CY2018's average of 78.4%)
- FDA has identified the need to provide additional clarifications on TRC to help Industry meet study data requirements and continue to improve the conformance trend over time
  - **Revision to TRC**
    - Details on 1734 and 1736
    - Emphasis on Error 1735
    - Inclusion of Error 1789
    - Inclusion of **Table 1** eCTD Technical Rejection Criteria for Study Data Expectation
    - Inclusion of **Appendix 1** Examples of Validation Findings in Study Data
    - Inclusion of **Appendix 2** Examples of ts.xpt datasets
  - **Additional Tools**: Self-Check Worksheet and Instructions for Study Data

Summary of Latest Revisions to the Technical Rejection Criteria for Study Data (Revised Jan. 2019)

- **Technical Rejection Criteria for Study Data (Revised 05/01/2018)**
  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.

- **Technical Rejection Criteria for Study Data (Revised 01/22/2019)**
  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.

Reference:
FDA Study Data Technical Rejection Criteria (Revised May 2018)
FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

Summary of Latest Revisions to the Technical Rejection Criteria for Study Data (Revised Jan. 2019)

Error	Description (Reference to FDA Study Data Technical Rejection Criteria May 2018 version)	Severity Level
1734	Trial Summary (TS) dataset must be present for each study in eCTD section 4.2 and 5.3	High
1736	Demographic dataset (DM) and the define.xml must be submitted in Module 4 for nonclinical data; DM dataset, the subject-level analysis dataset (ADSL) and define.xml must be submitted in Module 5 for clinical data	High

Error	Description (Reference to FDA Study Data Technical Rejection Criteria Jan. 2019 version)	Severity Level
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**	STF Files must be submitted for required study sections*	High

** Refer to the latest Technical Rejection Criteria for Study Data*

*** From Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specification, Section J: Datasets must only be provided in modules 3, 4, or 5 and not in modules 1 or 2*

Reference:
FDA Study Data Technical Rejection Criteria (Revised May 2018)
FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

CY2018 Conformance Analysis of IND, NDS, BLA and ANDA Submission Studies: Errors 1734, 1735 & 1736

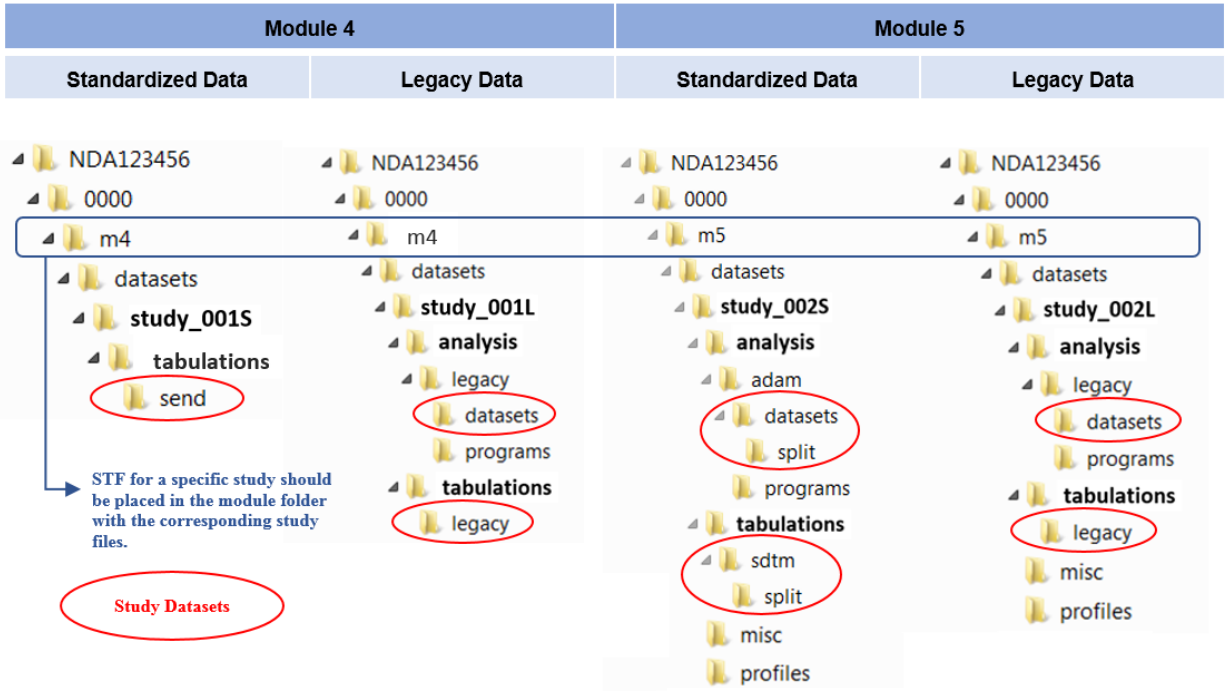
Error	Description
1734	Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections*
1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*
1736	For SEND data, a DM dataset and define 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*

** Refer to the latest Technical Rejection Criteria for Study Data*

	IND		NDA		BLA		ANDA	
	Nonclin (m4)	Clin (m5)	Nonclin (m4)	Clin (m5)	Nonclin (m4)	Clin (m5)	Nonclin (m4)	Clin (m5)
Total Number of Studies	883	288	403	1810	12	206	N/A	1004
Total Number Studies with Critical Errors	105	98	38	390	3	51	N/A	673
Error 1734	65	85	33	321	2	46	N/A	186
Error 1735	36	2	6	53	0	5	N/A	497
Error 1736	11	13	1	35	1	1	N/A	88
Error Rate (% among Total Number of Studies)	11.9%	34.0%	9.7%	21.6%	25.0%	24.8%	N/A	67.0%

Folder Structure for Module 4 and Module 5

❖ STF files and their associated datasets should be organized into a specific file directory structure and a specific headings and hierarchy structure



References:
FDA Study Data Technical Conformance Guide (Appendix E; Version 4.2, October 2018)
ICH M2 EWG: The eCTD Backbone File Specification for Study Tagging Files

Additional Details for Error 1734

❖ **Full ts.xpt**

Sponsors should submit a dataset named ‘ts.xpt’ following published CDISC Standard and FDA Study Data Technical Conformance Guide

❖ **Simplified ts.xpt**

Sponsors should submit a dataset named ‘ts.xpt’ with four variables: STUDYID, TSPARMCD, TSVAL, AND TSVALNF)

Example of ts.xpt Datasets

STUDYID	TSPARMCD	TSVAL	TSVALNF
•Study ID in STF File	•SSTDTC for a clinical study •STSTDTC for a nonclinical study	•Format: yyyy-mm-dd •Left blank when study start date is not available	• Left blank when study start date is provided in TSVAL • Exception code as specified in the ISO 21090 Standard when study start date is not available

References:
FDA Study Data Technical Conformance Guide (Appendices F & G; Version 4.2, October 2018)
FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

Emphasis on Errors 1735 and Inclusion of 1789

- Each submission typically contains many studies, an STF file is necessary to process study files into their corresponding studies; Accepting a submission where CDER cannot process the study tagging file will result in the reviewer seeing a list of files for which they do no not know the study they belong to
- If a study data file (e.g. define.xml) is not properly tagged in the STF file, it cannot be identified and located, resulting in Error 1736 being reported

Error	Description	Severity Level
1789	STF Files must be submitted in a study section. STF s are not required 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**

** Refer to the latest Technical Rejection Criteria for Study Data*

Additional Details for Error 1734

❖ **STUDYID in STF.xml and ts.xpt should match**

Based on the FDA Study Data TCG and the ICH STF Specification the Study ID uniquely and unambiguously identifies a particular study

ICH M2 EWG: The eCTD Backbone File Specification for Study Tagging Files (June 2008)

II. STUDY-IDENTIFIER ELEMENT

Information describing the study is contained in the *study-identifier* element of the STF. There are three elements contained in the *study-identifier* element: *title*, *study-id*, and *category*.

A. Title Element

The *title* element provides the full title of the study, not the title of each individual document.

B. study-id Element

The *study-id* is the internal alphanumeric code used by the sponsor to unambiguously identify this study.

CDISC Submission Metadata Model

The following variables are considered core selection variables for use in all CDISC domain models. These variable roles may also be defined with other roles (such as Key), and roles may differ from dataset to dataset.

Variable Name	Variable Label	Comments	Included in:
STUDYID	Study ID	Uniquely identifies a study within a particular submission.	All files
SITEID	Site ID	Some sponsors may use INVID instead of or in addition to a SITEID.	At least one of these variables must be included in all files
INVID	Investigator ID		
USUBJID	Unique Subject ID	Must be unique subject identifier within a submission (previously defined as PID; should be consistent with PID references used elsewhere in the submission)	All files

References:

- ICH M2 EWG: The eCTD Backbone File Specification for Study Tagging Files (June 2008) (http://estri.ich.org/STF/STFV2-6-1.pdf)
- CDISC Submission Metadata Model (https://www.cdisc.org/system/files/all/reference_material_category/application/pdf/submissionmetadatamodelv2.pdf)

Study Data Requirements for Submissions

Study Start Date	Application Type	Data Type	Study Sections	Expectation by Center	
				CDER	CBER
Prior to or on 17-Dec-2017	Commercial INDs	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	Rejection criteria will not be applied
		Clinical	5.3.1.1, 5.3.1.2, 5.3.3.1z, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	Rejection criteria will not be applied	
After 17-Dec-2017	Commercial INDs	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; submit a full TS	Rejection criteria will not be applied
		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	Rejection criteria will not be applied	
Prior to or on 17-Dec-2016	NDA, BLA, ANDA	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	Rejection criteria will not be applied
		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	Rejection criteria will be applied; submit a simplified TS if the study contains an xpt dataset (other than the ts.xpt)	
After 17-Dec-2016	NDA, BLA, ANDA	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; submit a full TS	Rejection criteria will not be applied
		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	Rejection criteria will be applied; submit a full TS	

Reference: FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

Tools for Industry

FDA has developed tools to help sponsors meet updated study data standard requirements and provide more transparency on the validation process

www.fda.gov

Sponsor reviews Study Data Standard Resources:

- **Revised Study Data Technical Rejection Criteria with eCTD Validation Table**
- **Study Data Self-Check Worksheet & Instruction**

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

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

Purpose: To clarify the requirements for eCTD Validation of submissions with study data and to provided examples (**Appendix 1 and 2**) to illustrate the requirements

2. TRC Self-Check Worksheet & Instruction

Purpose: To help sponsors understand criteria for submissions with study data to pass the updated TRC

3. eCTD and/or Standardized Data Sample Validation

Purpose: To help sponsors validate their sample submissions and receive feedback with identified errors

Published Technical Rejection Criteria for Study Data & Self-Check Worksheet

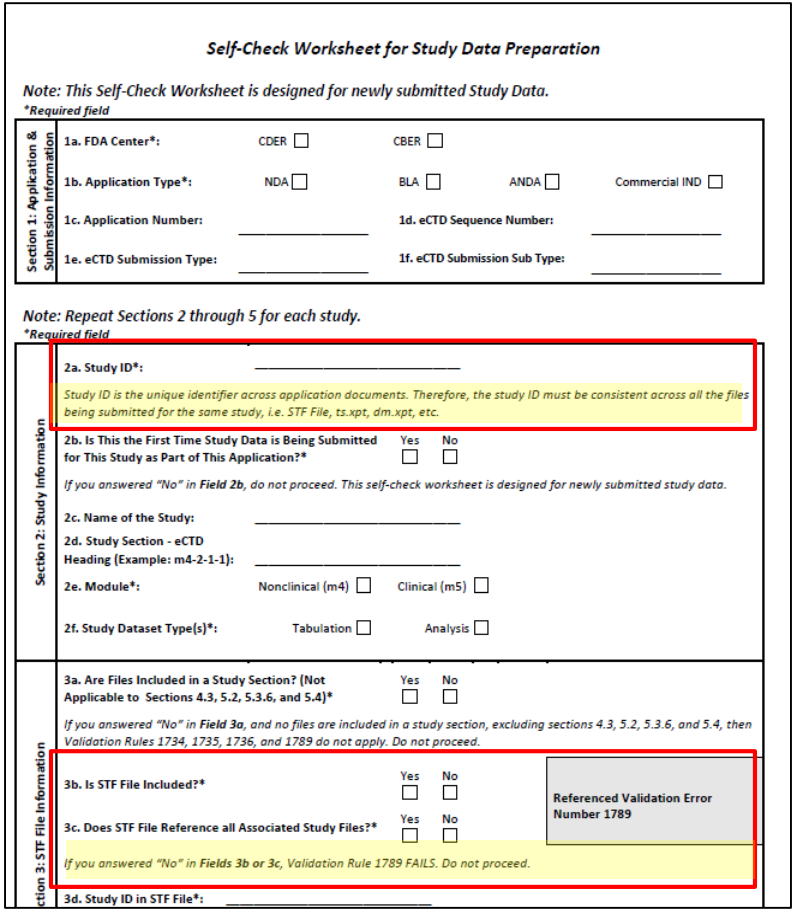
"Technical Rejection Criteria for Study Data"
https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm630740.pdf"

"Technical Rejection Criteria Self-Check Worksheet"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630732.pdf

"Technical Rejection Criteria Self-Check Worksheet Instructions"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630733.pdf

Overview of the Self-Check Worksheet

- Designed to walk sponsors through each step of TRC validation process
- Dynamically guides sponsors through study data requirements based on study information entered
- Designed to help the sponsors when they prepare study data to submit to the FDA for the first time



Self-Check Worksheet for Study Data Preparation

Note: This Self-Check Worksheet is designed for newly submitted Study Data.

**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.

**Required field*

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. Name 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 ☐

Section 3: STF File 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*: _____

Reference: "Technical Rejection Criteria Self-Check Worksheet"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630732.pdf
"Technical Rejection Criteria Self-Check Worksheet Instructions"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630733.pdf

Sections of the Study Data Self-Check Worksheet

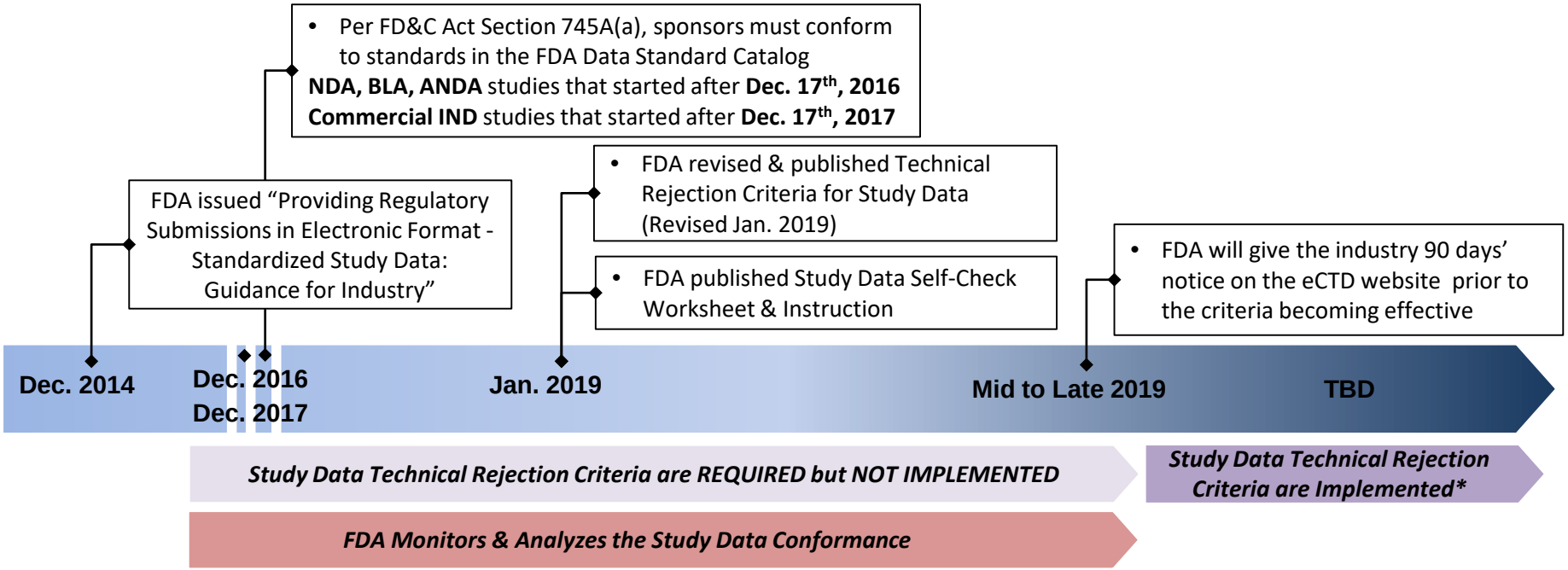
Section	Contents	Example(s)
1	**Application & Submission Information** • Provides high level information about the application and submission	1a. FDA Center*: CDER ☐ CBER ☐
2	**Study Information** • Provides more detailed information about the specific study	2a. Study ID*: 2f. Study Dataset Type(s)*: Tabulation ☐ Analysis ☐
3	**STF File Information** (1789 Validation Error) • Provide information about STF file	3b. Is STF File Included?* Yes ☐ No ☐ 3c. Does STF File Reference all Associated Study Files?* Yes ☐ No ☐
4	**TS File Information** (1734 Validation Error) • Provide information about ts.xpt file with study start date	4c. Study ID in TS File*: _____ 4d. Does Study ID in STF & TS Files Match?* Yes ☐ No ☐
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	5f. Is DM File Included?* Yes ☐ No ☐ 5g. Is Define File Included?* Yes ☐ No ☐ 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 ☐

Note: Sections 2 through 5 are repeated for each study.

Reference: "Technical Rejection Criteria Self-Check Worksheet"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630732.pdf
"Technical Rejection Criteria Self-Check Worksheet Instructions"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630733.pdf

Implementation Timeline

FDA published Revised Study Data Technical Rejection Criteria (Revised Jan. 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*

Summary

- Based on the revised TRC, about 21.6% all submissions were received with non-critical errors for 1734 and 1736
- FDA published Study Data Self-Check Worksheet to help sponsors to follow the revised TRC
- 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

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

- **“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/122913/DOWNLOAD
- **“FDA Data Standards Catalog”**
  HTTPS://WWW.FDA.GOV/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/DEFAULT.HTM
- **“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
- **For FDA instruction of Study Data submission, 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
- **For the full list of Study Data standards, see the FDA “Study Data Standards Resources” page at:**
  HTTP://WWW.FDA.GOV/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS

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