U.S. FOOD & DRUG ADMINISTRATION

FDA Conformance Analysis and Upcoming Implementation of Technical Rejection Criteria for Study Data

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FDA Disclaimer

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

Agenda

- Technical Rejection Criteria for Study Data (TRC)
- TRC Conformance Statistics and Trends
- Tools to Help Industry Pass TRC Validation
- TRC Validation Overview
- Addressing Common TRC Errors
- Summary

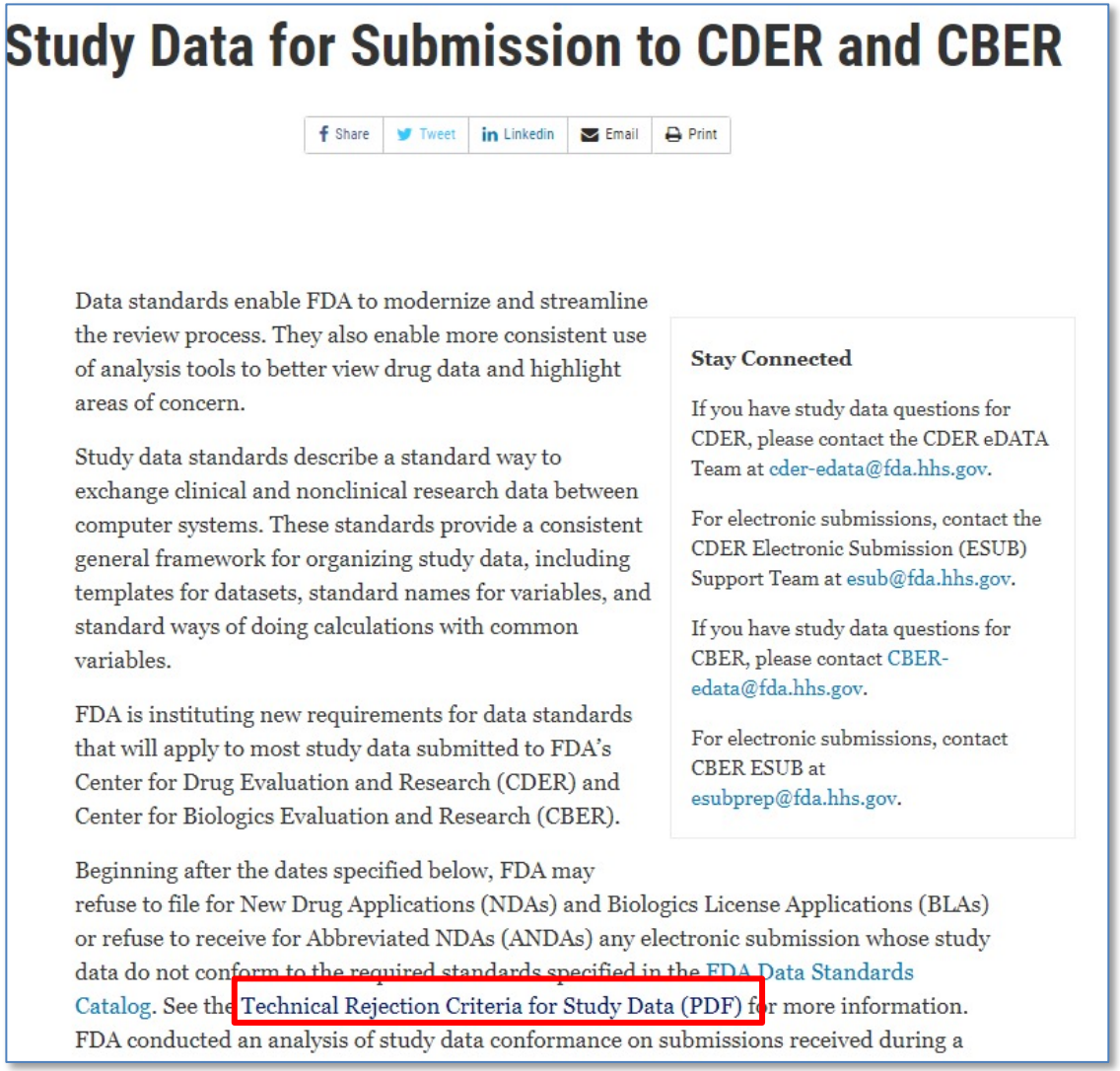
Technical Rejection Criteria for Study Data (TRC) – What's New

Technical Rejection Criteria for Study Data (TRC) – What's New

- **Starting Sept 15th, 2021, if a submission contains study information and fails eCTD validations in TRC, CDER and CBER will reject**

- Details on the TRC effective date can be found online:
  - FDA's *Electronic Common Technical Document (eCTD)* web page
  - FDA's *Study Data for Submission to CDER and CBER* web page
  - *Technical Rejection Criteria (Revised 03/15/21)*

- Warning notices are sent if a submission containing study information fails eCTD validations in TRC
  - CDER sending notices in ESG 3rd acknowledgement
  - CBER sending notices from CBER-edata account



Study Data for Submission to CDER and CBER

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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).

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.

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

Overview of TRC Errors

- Study Data Technical Conformance Guide provides technical recommendations for submitting study data according to CDISC standards

- Technical Rejection Criteria for Study Data provides the conditions under which FDA will not accept submissions with study data

Error	Description (Reference to FDA Study Data Technical Rejection Criteria March 2021 version)	Severity Level	Effective Date
1734	A dataset named ts.xpt with information on study start date must be present for each study in required sections*	High	Sept. 15, 2021
1735	The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*	High	
1736	For Standard for Exchange of Nonclinical Data (SEND) data, a Demographic (DM) dataset and define.xml must be submitted in Module 4 required sections* For Study Data Tabulation Model (SDTM) data, a DM dataset and define.xml must be submitted in Module 5 required sections* For Analysis Data Model (ADaM) data, an ADaM Subject level analysis dataset (ADSL) dataset and define.xml must be submitted in Module 5 required sections*	High	
1789	A file has been submitted in a study section without providing an STF file. STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports	High	

** Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4*
Module 5 sections: 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

Where to Find the TRC Effective Date

The Effective Dates for validation criteria 1734, 1735, 1736, and 1789 have been added to the "Technical Rejection Criteria for Study Data" and the "Specifications for eCTD Validation Criteria" documents.

Number:	1734
Group:	General
Description:	A dataset named ts.xpt with information on study start date must be present for each study in Module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4, and in Module 5, sections 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
Severity Description:	High
US DTD Version	2.01 and 3.3
Effective Date:	9/15/2021

Number:	1735
Group:	STF
Description:	The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in Module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4, and in Module 5, sections 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
Severity Description:	High
US DTD Version	2.01 and 3.3
Effective Date:	9/15/2021

Number:	1736
Group:	General
Description:	For Standard for Exchange of Nonclinical Data (SEND) data, a Demographic (DM) dataset and define.xml must be submitted in Module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4 For Study Data Tabulation Model (SDTM) data, a DM dataset and define.xml must be submitted in Module 5, sections 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 For Analysis Data Model (ADaM) data, an ADaM Subject level analysis dataset (ADSL) dataset and define.xml must be submitted in Module 5, sections 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
Severity Description:	High
US DTD Version	2.01 and 3.3
Effective Date:	9/15/2021

Number:	1789
Group:	STF
Description:	A file has been submitted in a study section without providing an STF file. STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports
Severity Description:	High
US DTD Version	2.01 and 3.3
Effective Date:	9/15/2021

TRC Warnings

- Sponsors will receive warnings from FDA when a TRC error is identified in submissions received between March 15 and September 15, 2021

CDER Notice included in the ESG 3rd Acknowledgement

ASR Successful and 3rd Acknowledgement PDF notification with
SPECIAL WARNING

Your submission has been successfully processed, however, during eCTD validation it was noted that this submission contains the following error information listed in the table below:

Warning: Per the 'Specifications for eCTD Validation Criteria', the severity level of the following error codes will be effective as a High error as of 09/15/2021

Error Code	STF Study ID	eCTD section	Error Reason
1734	uat	m4-2-3-1-single-dose-toxicity	No ts.xpt found for this study

Note: If a study for this submission received validation error code 1734, the given study was not validated for other error codes 1735 and 1736

Warning: Per the 'Specifications for eCTD Validation Criteria', the severity level of the following error codes will be effective as a High error as of 09/15/2021

Error Code	Reason	Findings
1789	Files in study sections without STF reference	m5/53-clin-stud-rep/535-rep-effic-safety-stud/confusion/5351-stud-rep-contr/uat-1/rptamnd-1.pdf [a5]

This is an informational notice that after 09/15/2021 submissions with an error code, where the error code corresponds to a particular study data format requirement, will be rejected per the published Technical Rejection Criteria for Study Data/Specifications for eCTD Validation Criteria (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd), as discussed in the eCTD guidance, Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.

Application Type/Number:

eCTD Sequence Number:

CoreID:

CBER Warning sent from the CBER-edata account

Dear XXXXX,

Your submission below was successfully processed on MM/DD/YYYY.

Application Type/Number: **BLA XXXXXX**
eCTD Sequence Number: **XXXX**

However, during eCTD validation it was noted that this submission contains the following error information listed in the table below:

Warning: future High error for study data as specified in the Study Data Technical Rejection Criteria

1734, 1735, 1736 Template Table

Error Code	STF Study ID	eCTD section	Error Reason
1734	YHTEST1	5.3.5.2	Invalid Start Date format in ts.xpt

Note: If a study for this submission received validation error code 1734, the given study was not validated for other error codes such as 1735 and 1736

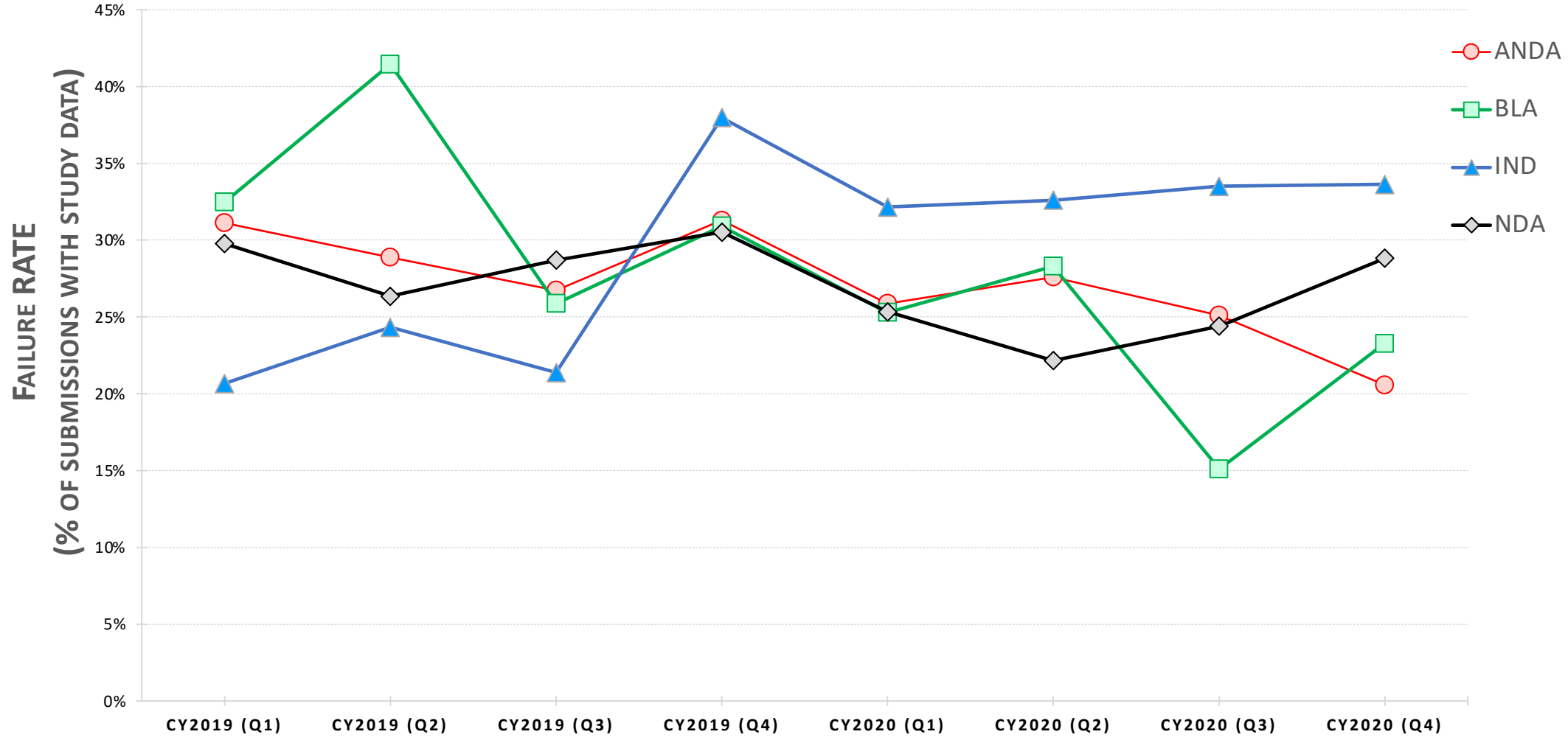
1789 Template Table

Error Code	Reason	eCTD section	Findings
1789	A file has been submitted in a study section without providing an STF file.	5.3.5.1	m5/53-clin-stud-rep/531-rep-biopharm-stud/5312-compar-ba-be-stud-rep/ome-rm02-001/stf-ome-rm02-001.xml [N4765450c17914e3fa2e5314c71db1459STF]
1789	A file has been submitted in a study section without providing an STF file.	5.3.5.1	m5/53-clin-stud-rep/531-rep-biopharm-stud/5312-compar-ba-be-stud-rep/ome-rm02-001/stf-ome-rm22222-001.xml [N4765450c17914e3fdfdfg45dfgdgd5314c71db1459STF]

This is an informational notice that after September 15, 2021 submissions with an error code, where the error code corresponds to a particular study data format requirement, will be rejected per the published Technical Rejection Criteria for Study Data/Specifications for eCTD Validation Criteria (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd), as discussed in the eCTD guidance, Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.

TRC Conformance Statistics and Trends

CDER CY2019 & CY2020 Conformance Trend:
TRC Validation Errors 1734 & 1736



Notes:

1) CY2019 and CY2020 analysis was conducted according to the TRC (Revised Oct. 2019)
2) Analysis includes NDA, BLA, ANDA and Commercial IND Sequence received by CDER between 1/1/2019 and 12/31/2020
3) Validation of error 1736 is not performed if a study has error 1734
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 eCTD module 4
5) M5 Definition of Study Data - .xpt files present in eCTD module 5

CDER CY2020 Submission Level Conformance:
Validation Errors 1734 & 1736

ANDA, NDA, BLA, and Commercial IND Submissions received by CDER between 1/1/2020 and 12/31/2020, were assessed for conformance to the two high-level errors as revised in the Technical Rejection Criteria for Study Data (Revised March 2021)

		ANDA	BLA	NDA	Comm. IND**	All
a	**Total Number of Submissions**	61,525	19,808	55,817	95,222	232,372
b	**Total Number of Submissions with Study Data***	704	388	1073	3291	5456
c	**Total Number of Submissions with Study Data* in TRC Applicable Sections**	635	268	693	1907	3503
d	**Total Number Submissions with Critical Errors (e or f)**	**175**	**90**	**271**	**1086**	**1622**
e	**Error 1734**	164	87	263	1045	1559
f	**Error 1736**	28	7	21	62	118
g	**Failure Rate (% among submissions with Study Data* in TRC Applicable Sections) [d/c]**	27.56%	33.58%	39.11%	56.95%	46.30%
h	**Failure Rate (% among submissions with Study Data*) [d/b]**	**24.86%**	**23.20%**	**25.26%**	**33.00%**	**29.73%**
I	**Failure Rate (% among all submissions) [d/a]**	0.28%	0.45%	0.49%	1.14%	0.70%

Notes:

1) CY2020 analysis was conducted according to the TRC (Revised Oct. 2019)
2) Analysis includes NDA, BLA, ANDA and Commercial IND Sequence received by CDER between 1/1/2020 and 12/31/2020
3) Validation of error 1736 is not performed if a study has Error 1734
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 eCTD module 4
5) * M5 Definition of Study Data - .xpt files present in eCTD module 5
6) **Comm. IND Clinical studies are included in this analysis which constitutes a very small fraction of the total submissions with critical errors. Comm. IND clinical studies are not subject to errors 1734, 1735, 1736, or 1737

CDER CY2020 Study Level Conformance for Validation Errors 1734 & 1736

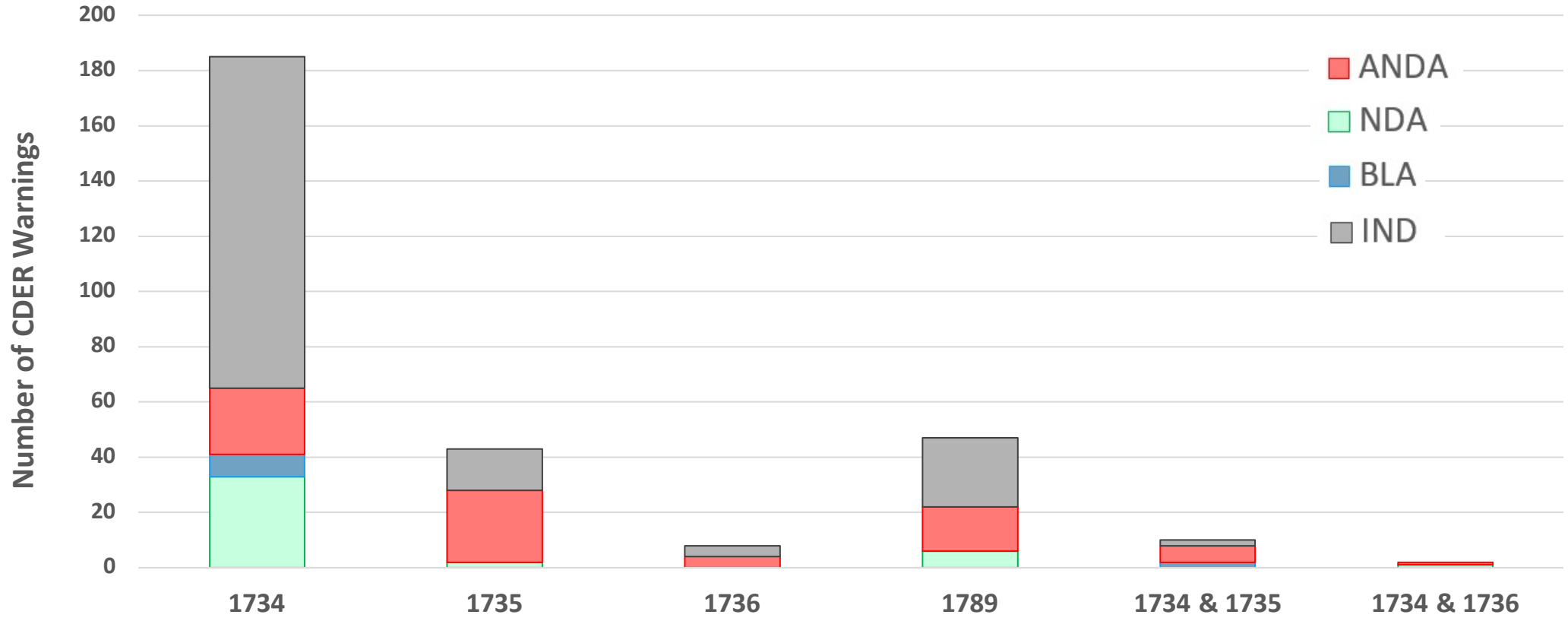
- A high number of non-clinical (m4) studies fail Validation Rule 1734 because of a missing trial summary dataset
- A trial summary dataset (ts.xpt) is required when a non-clinical study report is submitted (TRC Revised March 2021)

		ANDA		BLA		NDA		Comm. IND	Total	Total
		m4	m5	m4	m5	m4	m5	m4	m4	m5
a	Total Number of Studies*	45	1398	1041	796	5477	2556	33534	40097	4750
b	Total Number of Studies* in TRC Applicable Sections	15	1222	136	453	868	1645	5619	6638	3320
c	Total Number Studies with Critical Errors (d or f)	**12**	**342**	**82**	**109**	**349**	**334**	**3272**	3715	785
d	Error 1734	12	277	82	104	348	333	3173	3615	714
f	Error 1736	0	65	0	5	1	24	99	100	94
g	Error Rate (% among failed studies with Study Data* Data in TRC Applicable Sections**) [c/b]	80.0%	28.0%	60.3%	24.1%	40.2%	20.3%	58.2%	55.97%	23.64%
h	Error Rate (% among Total Number of Studies) [c/a]	**26.7%**	**24.5%**	**7.9%**	**13.7%**	**6.4%**	**13.1%**	**9.8%**	9.27%	16.53%

Notes:
(1) CY2020 analysis was conducted according to the TRC (Revised Oct. 2019)
(2) Validation of errors 1736 is not performed if a study has Error 1734
(3) *M4 Definition of Study - .xpt files and/or a Study Report tagged as pre-clinical-study-report, legacy-clinical-study-report, or study-report-body present in TRC applicable sections
(4) *M5 Definition of Study - .xpt files present in TRC applicable sections

TRC Warning Notices (March 15 – April 30, 2021)

- 1734 is the most common failure reason, especially for Commercial IND submissions
- 1789 is the second largest failure reason and is particularly high for Commercial IND submissions
- 1735 is the most common failure reason for ANDA submissions



Note: Warnings generated by CDER between March 15th and April 30th, 2021

Tools to Help Industry Pass TRC Validation

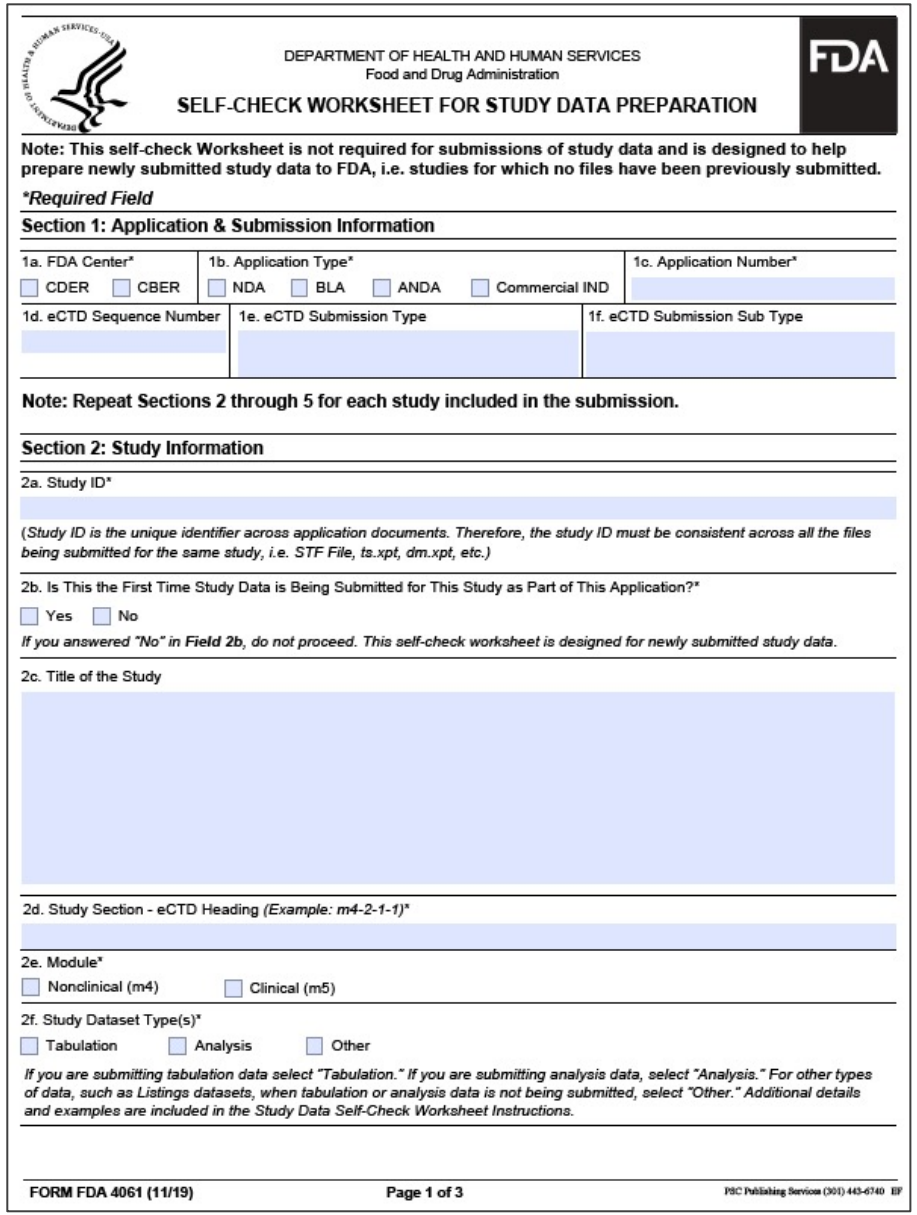
The Self-Check Worksheet

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

[Demonstration Videos & Other Supporting Material]

[Technical Rejection Criteria Self-Check Worksheet]

[Self-Check Worksheet Instructions]



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*	1b. Application Type*	1c. Application Number*
☐ CDER ☐ CBER	☐ NDA ☐ BLA ☐ ANDA ☐ Commercial IND	

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)*

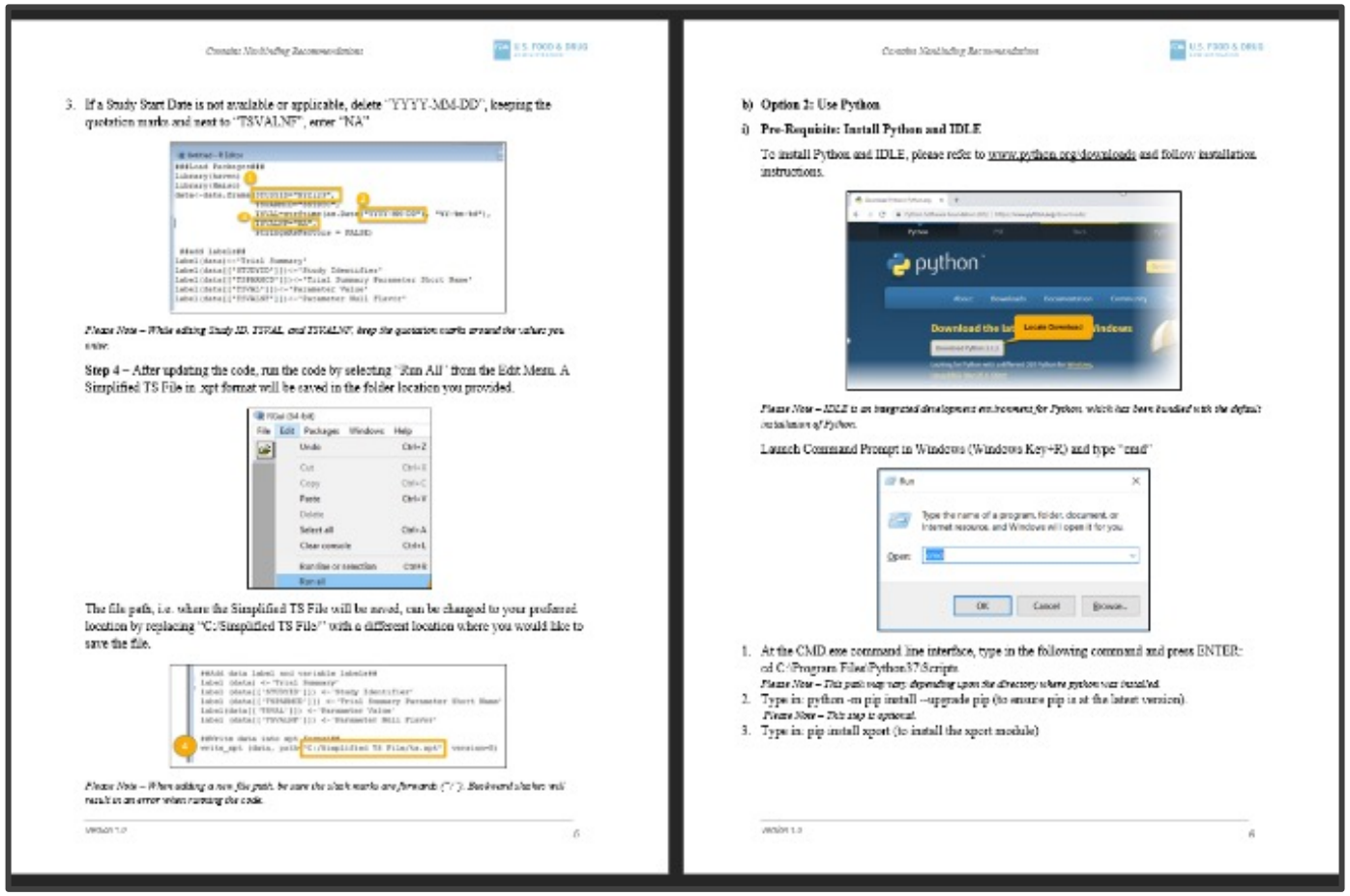
☐ Tabulation ☐ Analysis ☐ Other

If you are submitting tabulation data select "Tabulation." If you are submitting analysis data, select "Analysis." For other types of data, such as Listings datasets, when tabulation or analysis data is not being submitted, select "Other." Additional details and examples are included in the Study Data Self-Check Worksheet Instructions.

FORM FDA 4061 (11/19) **Page 1 of 3** PSC Publishing Services (301) 443-6740 EF

The Simplified ts.xpt Creation Guide

- Helps industry create simplified TS files using free and open-source software, R and Python
- Provides step by step instructions to install the necessary software
- Users can copy and paste code samples from the guide into R or Python
- Available on FDA's web page, *Study Data for Submission to CDER and CBER*
- Demonstration video also available at *Study Data for Submission to CDER and CBER*
- Additionally, a publicly available tool was developed by PHUSE:
  Simplified ts.xpt File Generator (*https://geotiger.shinyapps.io/07_genTS/*)

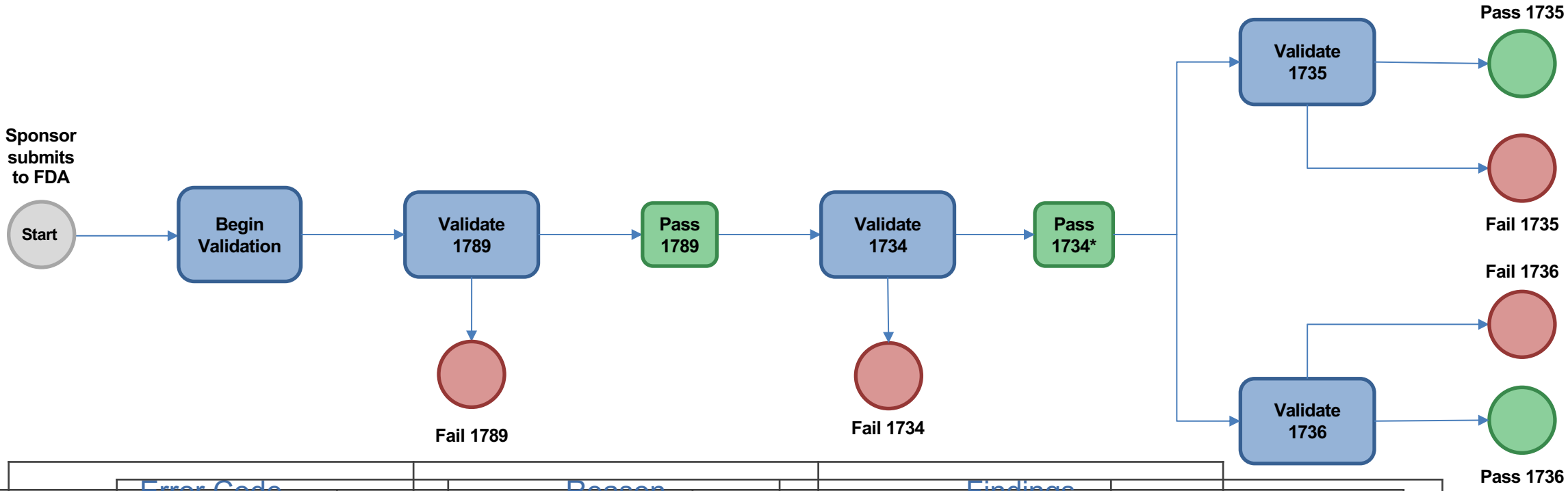


TRC Validation Overview

TRC Validation Rule Flow

Legend

- Validation errors lead to rejection of the submission
- When no validation errors occur, the submission is not rejected



Error Code	STF Study ID	eCTD section	Error Reason
1734 1789	STUDY ID	M4-2-3 toxicity	No tx xpt found for this study
1735	STUDY ID Example 1	m5-3-5-clinical-study-rep/585-rep-effect-safety-study/confusion/55511	Incorrect file tag for define.xml
1735	STUDY ID Example 2	m5-3-1-2-comparative-ba-and-bioequivalence-study-reports	Incorrect file tag for define.xml

Files in study sections without STF reference

1789, 1734, 1735, and 1736 warnings include the relative file path for the file

Multiple errors are returned when more than one study fails TRC validation

* *Not every submission will proceed beyond 1734 to 1735 and 1736, depending on the Study Start Date (SSD)*

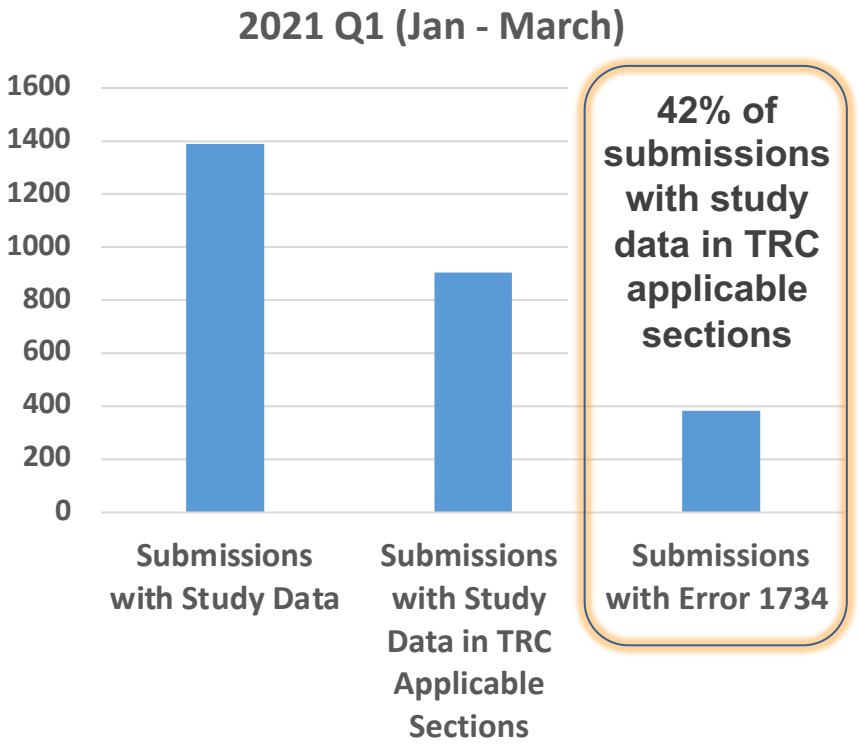
Addressing Common TRC Errors

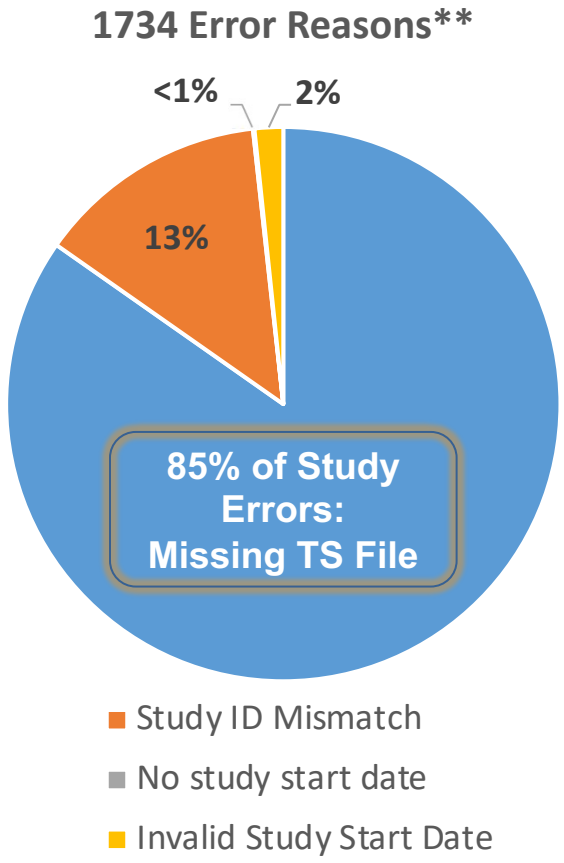
Error 1734

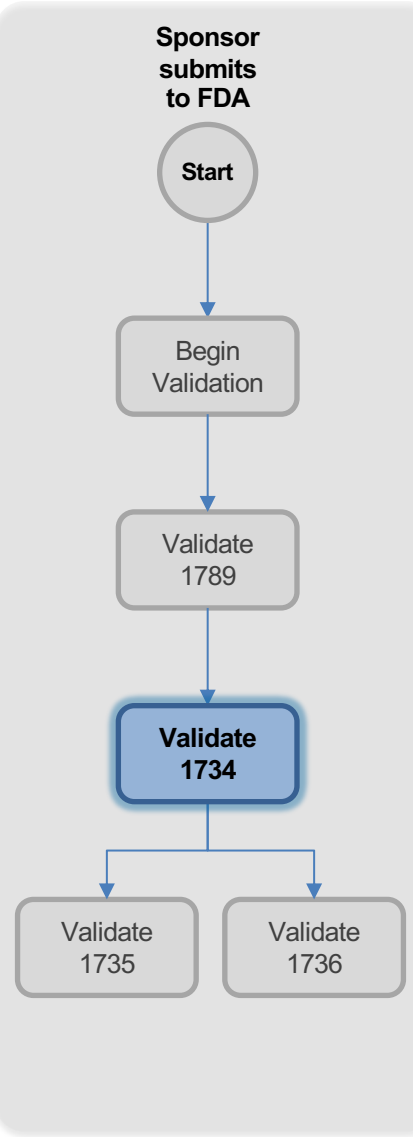
Validation Rule 1734

A dataset named ts.xpt with information on study start date must be present for each study in required sections*

- ✓ Trial Summary Dataset (ts.xpt) is present
- ✓ Study ID (or SPREFID) matches STF Study ID
- ✓ Study start date is provided (or TSVALNF = NA)
- ✓ Study start date is in a valid format







* *Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4*
Module 5 sections: 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

** *1,140 Studies in 384 Submissions with Error 1734 2021 Q1*

Verifying Rule 1734 Using Self-Check Worksheet

✓ Trial Summary Dataset (ts.xpt) is present

Section 3 helps check if non-clinical studies without .xpt datasets require a TS file:

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

Section 4 helps check if a Full or Simplified TS file is required:

Section 4: TS File Information

4a. If the Study is for a Commercial IND Application, Is the Study Start Date:

☐ Prior to or on **17-Dec-2017** ☒ After **17-Dec-2017**

4b. If the Study Is for an NDA, BLA, or ANDA Application, Is the Study Start Date:

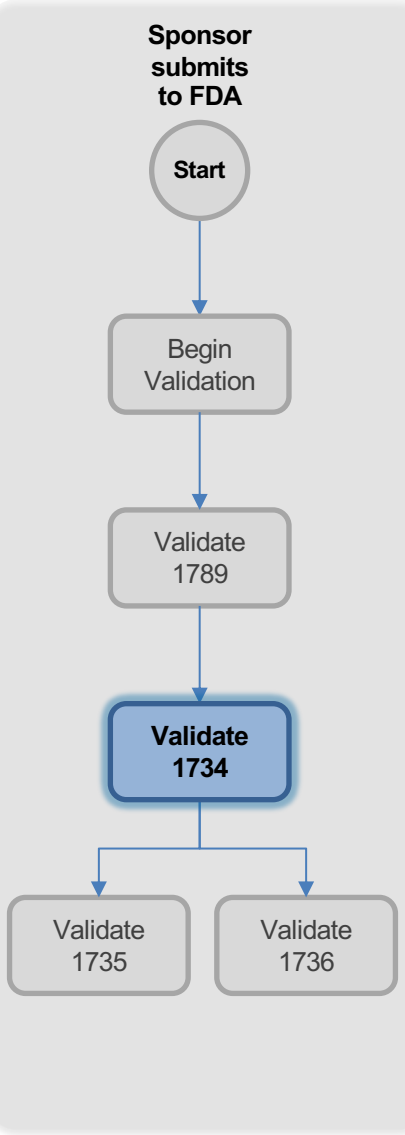
☐ Prior to or on **17-Dec-2016** ☐ After **17-Dec-2016**

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.*



Note: TS files must be named *ts.xpt* and cannot be customized or changed (other standardized datasets, such as dm.xpt and adsl.xpt, must also be named correctly)

Addressing 1734 Errors for Missing TS File

Providing a TS File for non-clinical studies which require a Simplified TS will address the biggest root cause of Error 1734.

86% of Missing TS File Errors are for non-clinical studies with study reports and no .xpt datasets*

	M4	M5
Studies with only study reports	831	N/A
Studies with only study data	5	112
Studies with study data and reports	18	NA

Option 1

Use the Simplified ts.xpt Creation Guide to generate a simplified ts.xpt in R or Python:

Option 2

Use publicly available tool developed by PHUSE to generate simplified ts.xpt files:

Example of a Simplified TS file for a non-clinical study:

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	S107	STSTDTC	2014-10-26	

*831 of 966 studies missing ts.xpt 2021 Q1

Option 1: Simplified ts.xpt Creation Guide

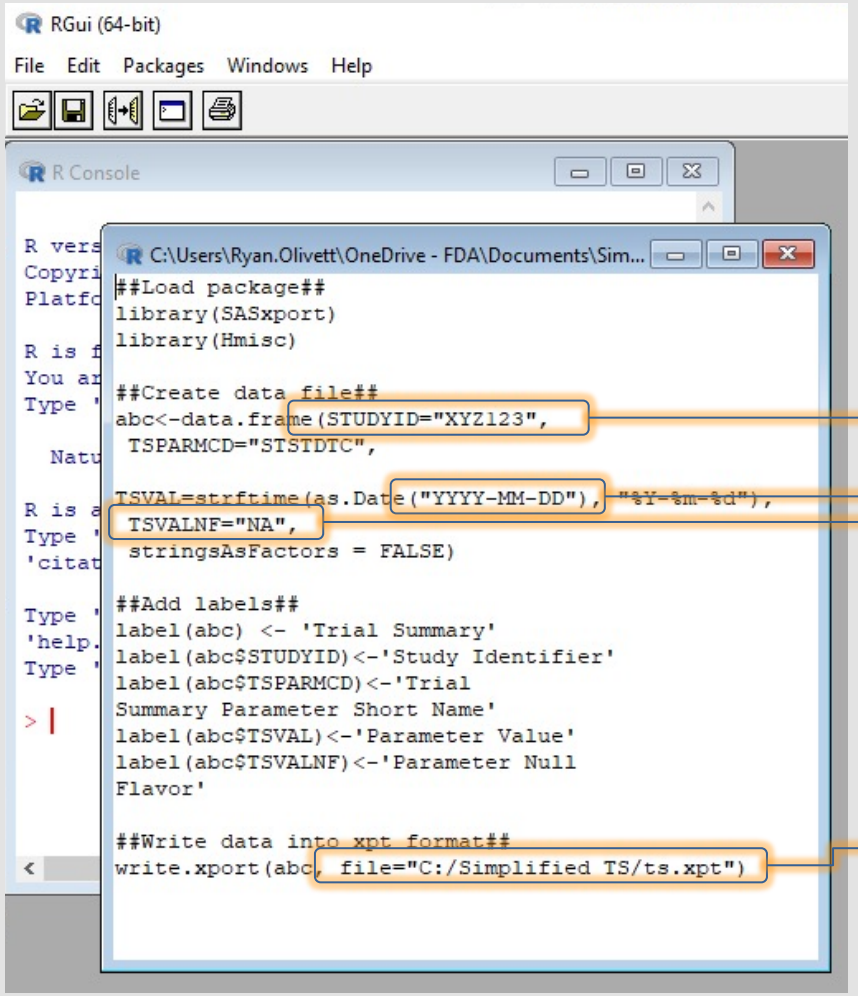
Example using R to generate a Simplified TS File:

1. Copy and paste code from the Guide into R Editor to create a script

Table 2: Code for Creating ts.xpt Using R : Option B - Using the SASxport Package

R Package	Clinical Study	Non-clinical Study
Option B: Using the SASxport Package	##Load package## library(SASxport) library(Hmisc) ##Create data file## abc<-data.frame(STUDYID="XYZ123", TSPARMCD="SSTDTC", TSVAL=strftime(as.Date("YYYY-MM-DD"), "%Y-%m-%d"), TSVALNF="NA", stringsAsFactors = FALSE) ##Add labels## label(abc) <- 'Trial Summary' label(abc$STUDYID)<-'Study Identifier' label(abc$TSPARMCD)<-'Trial Summary Parameter Short Name' label(abc$TSVAL)<-'Parameter Value' label(abc$TSVALNF)<-'Parameter Null Flavor' ##Write data into xpt format## write.xport(abc, file="C:/Simplified TS File/ts.xpt")	##Load package## library(SASxport) library(Hmisc) ##Create data file## abc<-data.frame(STUDYID="XYZ123", TSPARMCD="STSTDTC", TSVAL=strftime(as.Date("YYYY-MM-DD"), "%Y-%m-%d"), TSVALNF="NA", stringsAsFactors = FALSE) ##Add labels## label(abc) <- 'Trial Summary' label(abc$STUDYID)<-'Study Identifier' label(abc$TSPARMCD)<-'Trial Summary Parameter Short Name' label(abc$TSVAL)<-'Parameter Value' label(abc$TSVALNF)<-'Parameter Null Flavor' ##Write data into xpt format## write.xport(abc, file="C:/Simplified TS File/ts.xpt")

Simplified TS File Creation Guide



2. Edit the Study ID

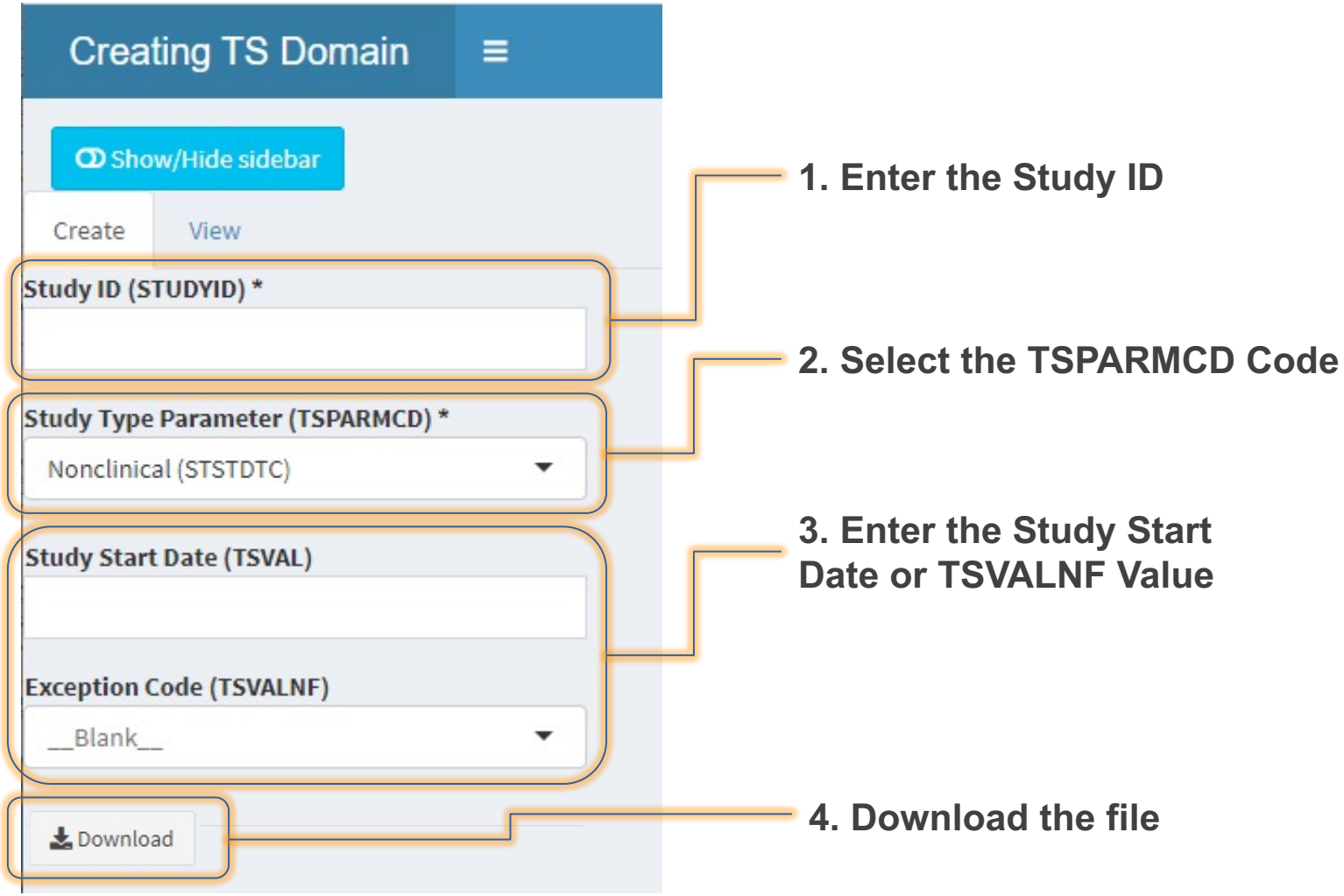
3. Edit the Study Start Date and TSVALNF Value

4. Edit where to save the file

R Application

Option 2: PHUSE Utility

Example using the online PHUSE Utility to generate a Simplified TS File:



PHUSE Utility

Verifying Other Sources of Error 1734

The Self-Check Worksheet can also be used to verify other sources of Error 1734:

- ✓ **Study ID (or SPREFID) matches STF Study ID**

  13% of 1734 Errors*

- ✓ **Study start date is in a valid format**

  2% of 1734 Errors*

- ✓ **Study start date is provided (or TSVALNF = NA)**

  <1% of 1734 Errors*

Simplified TS File

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

xyz-123

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:

2014-07-01

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.*

*Out of 1,140 studies with Error 1734 2021 Q1

Addressing Common TRC Errors

Error 1789

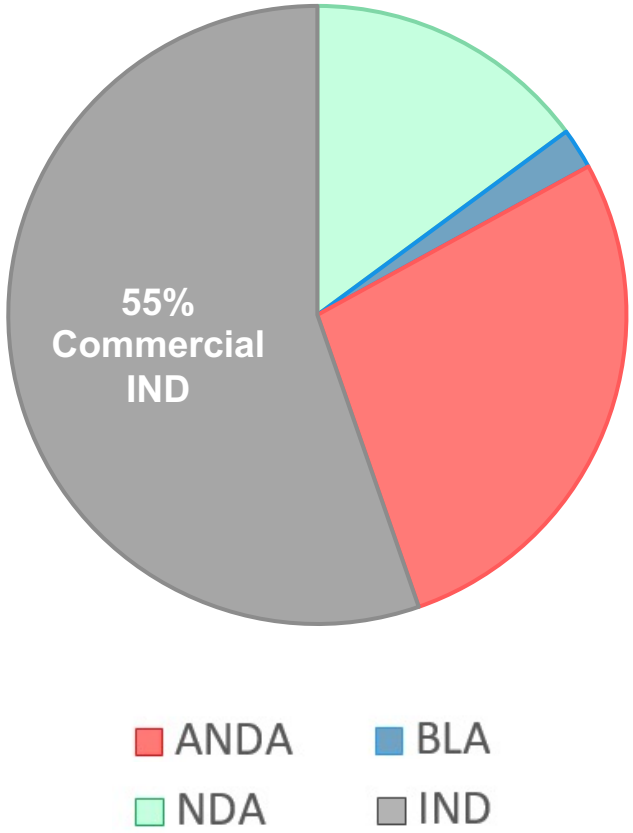
Validation Rule 1789

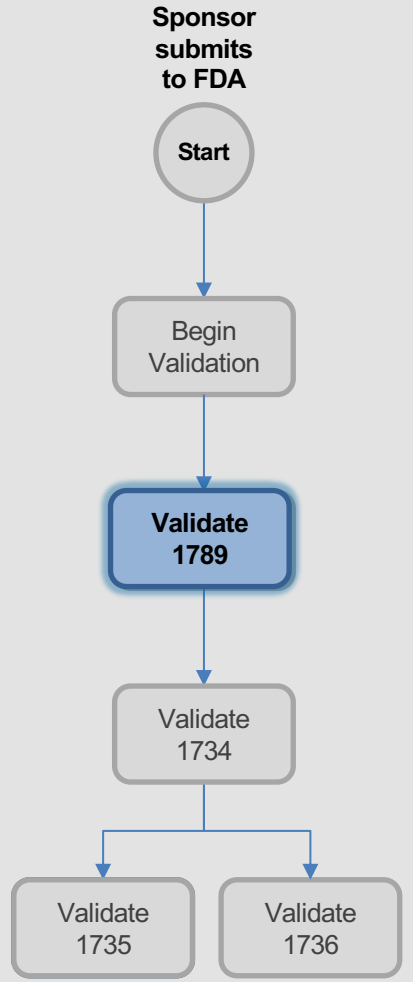
A file has been submitted in a study section without providing an STF file (STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports).

✓ All study files are included in a Study Tagging File (STF)

1789 errors are the second largest source of TRC failures*

Submission Types for 1789 Errors*





*147 1789 failures out of 283 total warning notices March 15 – April 30, 2021

Verifying Error 1789 Using Self-Check Worksheet

Section 3 helps check if all study files in applicable eCTD sections are referenced in a Study Tagging File:

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.*

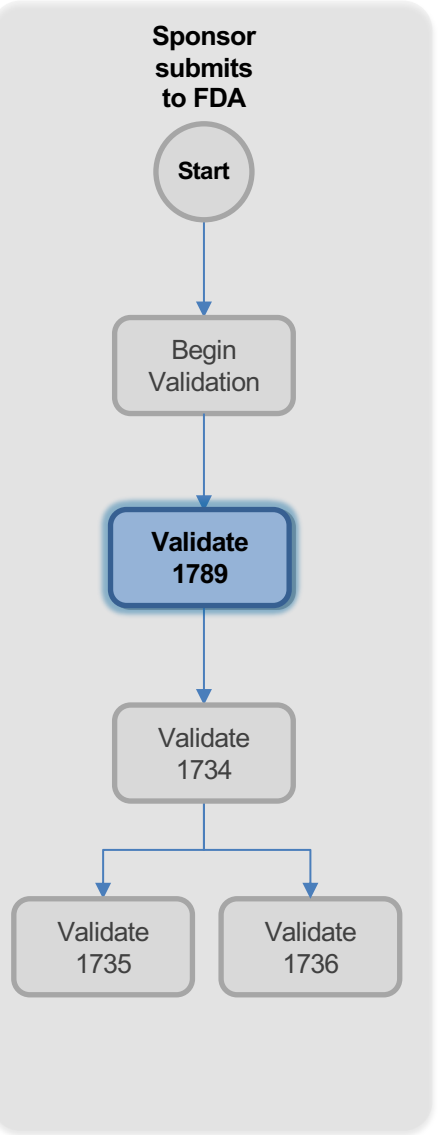
3b. Is STF File Included?*	3c. Does STF File Reference all Associated Study Files?*	Referenced Validation Error Number 1789
☒ Yes ☐ No	☒ Yes ☐ No	

*If you answered "No" in **Fields 3b or 3c**, Validation Rule 1789 FAILS. Do not proceed.*

3d. Study ID (study-id) in STF File*	3e. Does the Study ID in the STF File Match Field 2a?
xyz-123	☐ 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.*

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



Addressing 1789 Errors

When placing files in applicable sections within Modules 4 and 5, they should also be referenced within an STF for the study to which they belong.

Applicable eCTD Section*

Example Index.xml:

```
<m4-2-3-2-repeat-dose-toxicity>
    <leaf xlink:href="m4/datasets/[redacted]/tabulations/send/datasets/bg.xpt" operation="replace"
    modified-file="../0005/index.xml#id6390013" checksum-type="md5" ID="id7897938" checksum=
    "0109c0548f4e8ee9f0674dafc9c4b794">
        <title>bg</title>
    </leaf>
    <leaf xlink:href="m4/datasets/[redacted]/tabulations/send/datasets/bw.xpt" operation="replace"
    modified-file="../0005/index.xml#id6390014" checksum-type="md5" ID="id7897939" checksum=
    "fa912b85feabfdbc2ffa643f237f297b">
        <title>bw</title>
    </leaf>
    <leaf xlink:href="m4/datasets/[redacted]/tabulations/send/datasets/cl.xpt" operation="replace"
    modified-file="../0005/index.xml#id6390015" checksum-type="md5" ID="id7897940" checksum=
    "9094a213cc464f686bf9cdf608cff6f3">
        <title>cl</title>
    </leaf>
    <leaf xlink:href="m4/datasets/[redacted]/tabulations/send/datasets/co.xpt" operation="replace"
    modified-file="../0005/index.xml#id6390016" checksum-type="md5" ID="id7897941" checksum=
    "2684210bca6cdc9f83846041685caec6">
        <title>co</title>
    </leaf>
```

The file, bw.xpt, is included in the Index.xml but not referenced in the STF for the study.

Example STF:

```
<doc-content xlink:href="../../../../../index.xml#id7897938" xlink:type="simple">
  <file-tag name="data-tabulation-dataset-send" info-type="us" />
</doc-content>
<doc-content xlink:href="../../../../../index.xml#id7897940" xlink:type="simple">
  <file-tag name="data-tabulation-dataset-send" info-type="us" />
</doc-content>
<doc-content xlink:href="../../../../../index.xml#id7897941" xlink:type="simple">
  <file-tag name="data-tabulation-dataset-send" info-type="us" />
</doc-content>
```

The other 3 datasets are properly referenced in the STF for the study.

Correction: Add missing file reference to the STF file for the study

*STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports.

Addressing Common TRC Errors

Error 1735

Validation Rule 1735

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

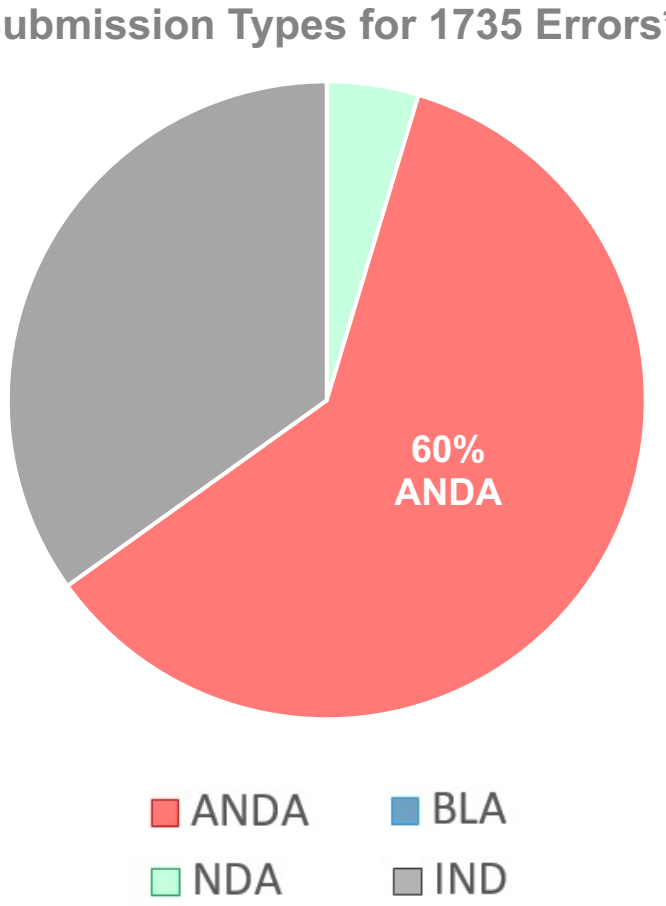
- ✓ Standardized dataset domains

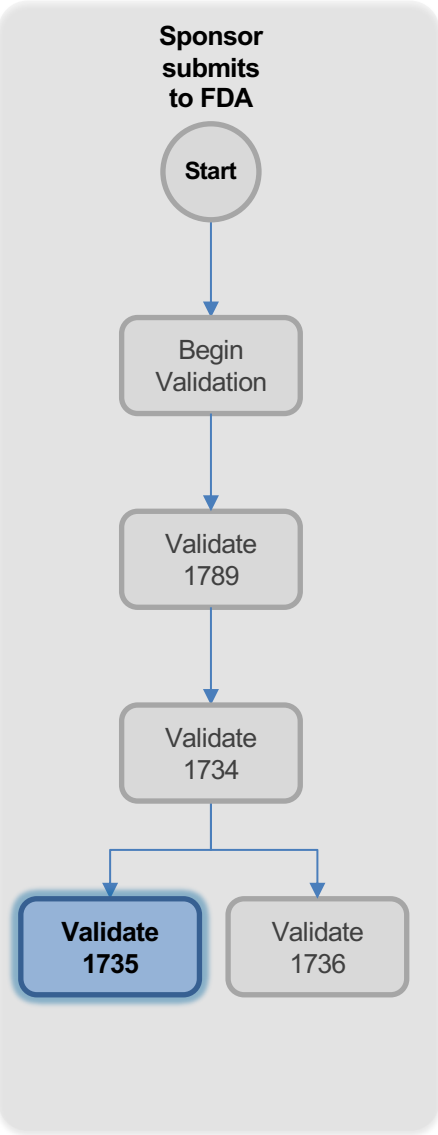
  (e.g., adsl.xpt, dm.xpt) are tagged as:

  - "data-tabulation-dataset-sdtm" for SDTM
  - "analysis-dataset-adam" for ADaM
  - "data-tabulation-dataset-send" for SEND
- ✓ Define.xml files are tagged as:
  - "data-tabulation-data-definition"

    for SDTM & SEND
  - "analysis-data-definition" for ADaM

ANDA submissions have the highest number of 1735 errors*





*43 1735-only failures out of 283 total warning notices March 15 – April 30, 2021

Verifying Rules 1735 & 1736 Using Self-Check Worksheet

Section 5 helps check—when standardized data is required—if standardized datasets are tagged correctly in the STF and if required datasets are included:

Clinical (m5)

Tabulation (SDTM datasets)

5f. Is DM File Included?*	5g. Is Define File Included?*	
☐ Yes ☐ No	☐ 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?*	5k. Is Define File Included?*	
☐ Yes ☐ No	☐ 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.*

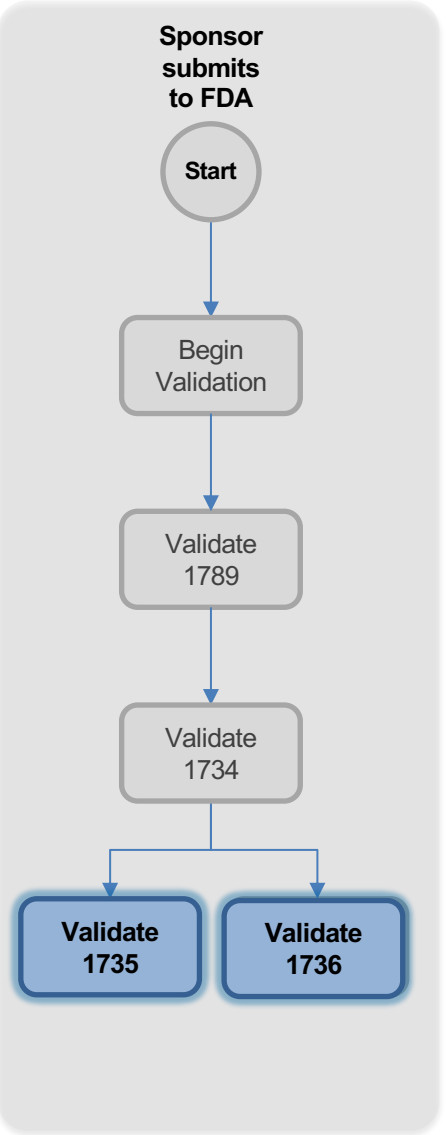
5l. Are the STF File-Tags for the ADaM Datasets "analysis-dataset-adam"?* ☐ Yes ☐ No
5m. Is the STF File-tag for the Define File "analysis-data-definition"?* ☐ Yes ☐ No

Referenced Validation Error Number 1735

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

✓ **Correct File Tags**

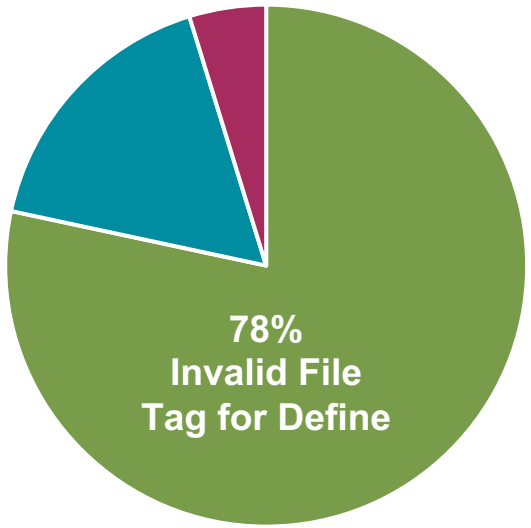
✓ **Required Files/Datasets**



Addressing the Most Common 1735 Error

- **The most common cause of 1735 errors is incorrectly tagged define.xml files**
- **When preparing STF files, ensure files are tagged properly**

1735 Error Reasons*



Example Study Tagging File (STF) for SDTM:

Sponsors commonly apply the same file tags as datasets or other files for all files submitted, including define.xml files

Standardized dataset domains (e.g. dm.xpt)

Define.xml

```
<doc-content
    xlink:href="../../../../../../0001/index.xml#adf5f97a527ef1507a6db8fca2f8b4867" xlink:type="simple">
    <file-tag info-type="us" name="data-tabulation-dataset-sdtm"/>
</doc-content>
<doc-content
    xlink:href="../../../../../../0001/index.xml#ab54f98276616b94d1d30fa071ffffc36" xlink:type="simple">
    <file-tag info-type="us" name="data-tabulation-dataset-sdtm"/>
</doc-content>
<doc-content
    xlink:href="../../../../../../0001/index.xml#a7794eaba0442a7c66cbf122fb66ff932" xlink:type="simple">
    <file-tag info-type="us" name="data-tabulation-dataset-sdtm"/>
</doc-content>
<doc-content
    xlink:href="../../../../../../0001/index.xml#a57bb2ed13e2d2feb7606e65d59586355" xlink:type="simple">
    <file-tag info-type="us" name="data-tabulation-dataset-sdtm/>
```

Correct File Tags

File tag for define.xml needs to be corrected to: "data-tabulation-data-definition"

www.fda.gov

**231 studies with Error 1735 2021 Q1*

Summary

Summary: Addressing Top 3 Causes of TRC Errors

	1734		1789	1735
Impact	**All 1734** 65% of Warning Notices	**Comm. IND** 42% of Warning Notices	17% of Warning Notices	15% of Warning Notices
Rule Summary	A dataset named ts.xpt with information on study start date must be present for each study in required sections		A submitted file in a study section must be included in an accompanying STF file	The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files
1. Check if your study has an error	Self-Check Worksheet Sections 3 & 4		Self-Check Worksheet Section 3	Self-Check Worksheet Section 5
2. Correct the errors	If a Simplified TS file is required, utilize the *Simplified ts.xpt Creation Guide* or online PHUSE Utility		Ensure that all files included in applicable eCTD sections in the Index.xml are referenced in an STF	Ensure the correct STF file-tags for standardized datasets and define.xml files are used

Note: Warnings generated by CDER between March 15th and April 30th, 2021

References

❖ Study Data Standards Resources

- Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [Oct 2020]
- Study Data Technical Conformance Guide [Nov 2020]
- FDA Data Standards Catalog [March 2021]
- Link: 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 [March 2021]
- Technical Rejection Criteria Self-Check Worksheet
- Technical Rejection Criteria Self-Check Worksheet Instructions
- Link: 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

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

CDER eData Mailbox: cder-edata@fda.hhs.gov
CBER eData Mailbox: cber-edata@fda.hhs.gov