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PRESENTER

Ethan Chen

Director, Division of Data Management Services and Solutions,
Office of Business Informatics | CDER | US FDA

Ethan Chen provides overall leadership to CDER in streamlining electronic and traditional submissions and delivering solutions to enable rapid adoption of emerging electronic data standards. Since joining the FDA in 2012, Mr. Chen has led several critical initiatives as the CDER Informatics Architect, including Data Management and Business Intelligence programs. While leading the CDER Division of Data Management Service and Solution, Ethan had successfully implemented the eCTD electronic submission mandate.

FDA Study Data Technical Rejection Update

PharmaSUG 2021

May 26, 2021

Agenda

- ❖ Technical Rejection Criteria for Study Data (TRC)
- ❖ Tools to Help Industry Pass TRC Validation
- ❖ TRC Validation Overview
- ❖ Addressing Common TRC Errors:
 - Error 1734
 - Error 1789
 - Error 1735
- ❖ Summary

Technical Rejection Criteria for Study Data (TRC)

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).

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

Stay Connected

If you have study data questions for CDER, please contact the CDER eDATA Team at cdere-data@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.

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*	High	
	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*		
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	


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: NDA444493
eCTD Sequence Number: 0006
CoreID: ci1613111075001_2641324_Test@fdsvr08654_tel

CDER Warning sent from the CDER-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

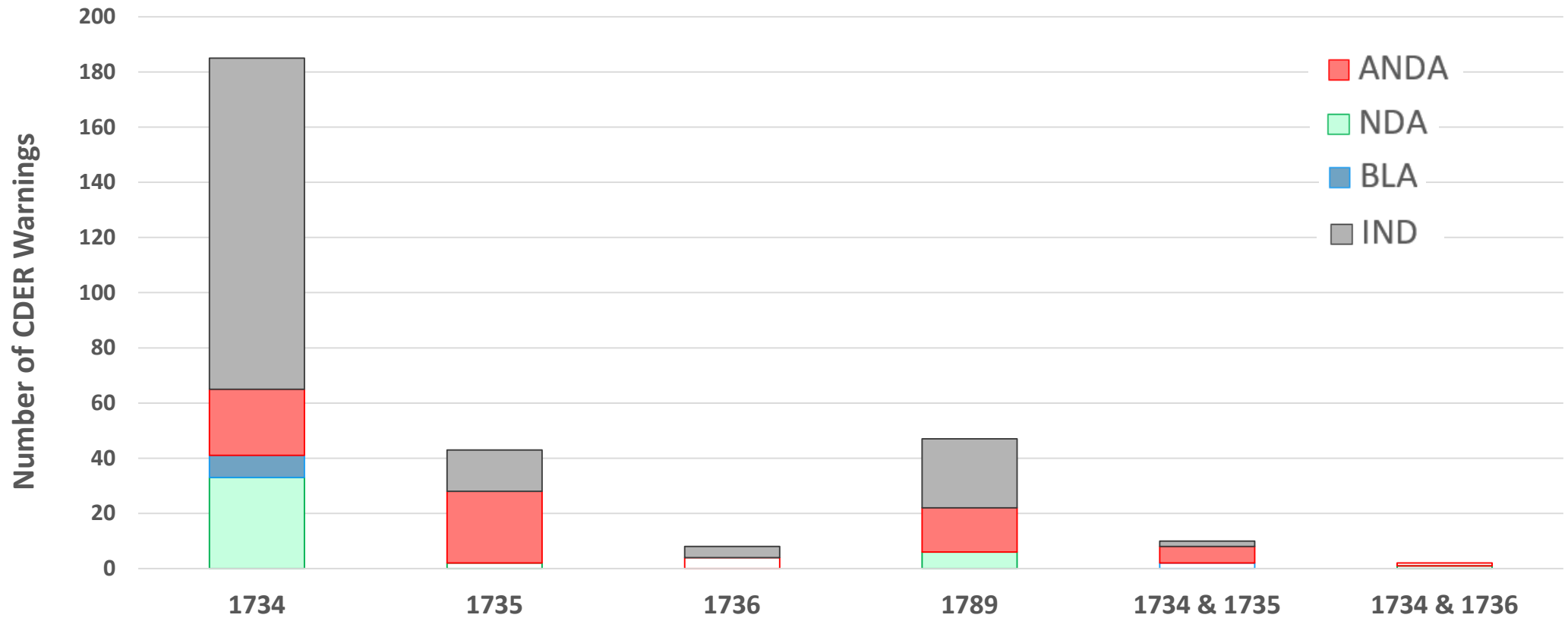
[1789 Template Table](#)

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 [N4765450c17914e3fa2e5314c71db14595STF]
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-rm2222-001.xml [N4765450c17914e3fdfd45dfgd5314c71db14595STF]

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 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				
<p>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.</p>				
<p>*Required Field</p>				
Section 1: Application & Submission Information				
1a. FDA Center* <input type="checkbox"/> CDER <input type="checkbox"/> CBER		1b. Application Type* <input type="checkbox"/> NDA <input type="checkbox"/> BLA <input type="checkbox"/> ANDA <input type="checkbox"/> Commercial IND		1c. Application Number* <input type="text"/>
1d. eCTD Sequence Number <input type="text"/>	1e. eCTD Submission Type <input type="text"/>		1f. eCTD Submission Sub Type <input type="text"/>	
<p>Note: Repeat Sections 2 through 5 for each study included in the submission.</p>				
Section 2: Study Information				
2a. Study ID* <input type="text"/>				
<p><i>(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.)</i></p>				
2b. Is This the First Time Study Data is Being Submitted for This Study as Part of This Application?* <input type="checkbox"/> Yes <input type="checkbox"/> No				
<p><i>If you answered "No" in Field 2b, do not proceed. This self-check worksheet is designed for newly submitted study data.</i></p>				
2c. Title of the Study <input type="text"/>				
2d. Study Section - eCTD Heading (Example: m4-2-1-1)* <input type="text"/>				
2e. Module* <input type="checkbox"/> Nonclinical (m4) <input type="checkbox"/> Clinical (m5)				
2f. Study Dataset Type(s)* <input type="checkbox"/> Tabulation <input type="checkbox"/> Analysis <input type="checkbox"/> Other				
<p><i>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.</i></p>				
FORM FDA 4061 (11/19) Page 1 of 3 PSC Publishing Services (301) 443-6740 EIP				

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 \(https://geotiger.shinyapps.io/07_genTS/\)](https://geotiger.shinyapps.io/07_genTS/)

3. If a Study Start Date is not available or applicable, delete "YYYY-MM-DD", keeping the question marks and next to "TSVALNF", enter "NA"

Please Note – While editing Study ID, TRTSEQ, and TRTSEQID, drop the question marks around the values; you enter.

Step 4 – After updating the code, run the code by selecting "Run All" from the Edit Menu. A Simplified TS File in .xpt format will be saved in the folder location you provided.

The file path, i.e. where the Simplified TS File will be saved, can be changed to your preferred location by replacing "C:\Simplified TS Files\" with a different location where you would like to save the file.

Please Note – When adding a new file path, be sure the slash marks are forward (/). Backward slashes will result in an error when running the code.

b) Option 2: Use Python

i) Pre-Requirement: Install Python and IDLE

To install Python and IDLE, please refer to www.python.org/downloads/ and follow installation instructions.

Please Note – IDLE is an integrated development environment for Python, which has been installed with the default installation of Python.

Launch Command Prompt in Windows (Windows Key+R) and type "cmd"

1. At the CMD use command line interface, type in the following command and press ENTER: `cd C:\Program Files\Python37\Scripts`
- Please Note – This path may vary depending upon the directory where python was installed.
2. Type in: `python -m pip install --upgrade pip` (to ensure pip is at the latest version).
- Please Note – This step is optional.
3. Type in: `pip install xport` (to install the xport module)

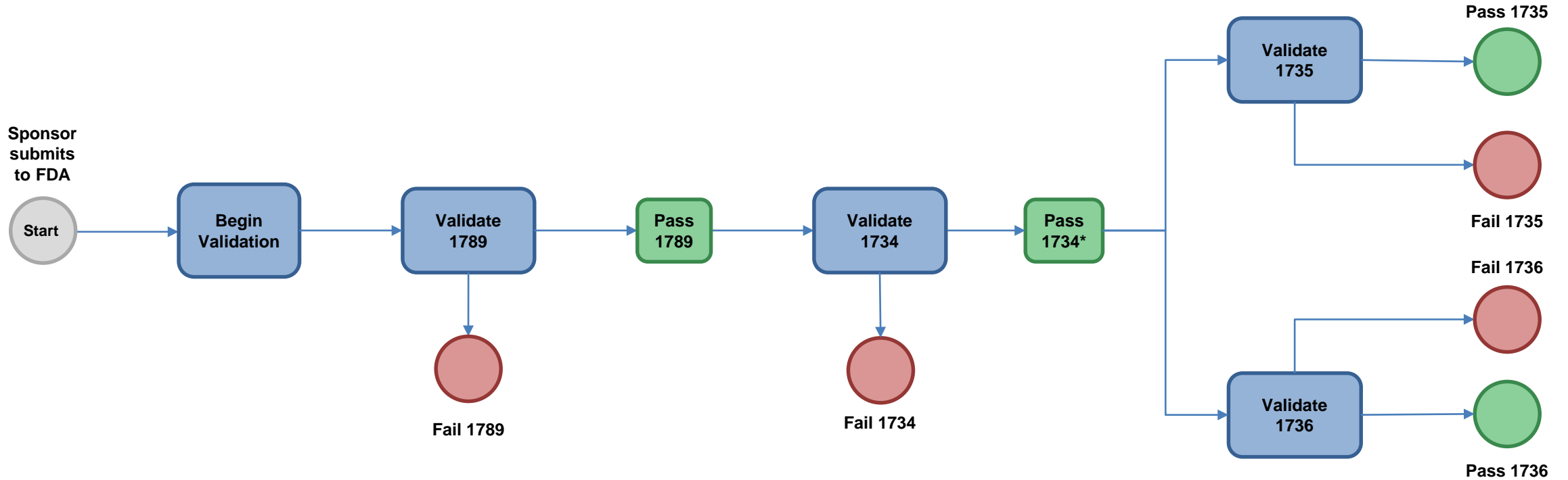
TRC Validation Overview

TRC Validation Rule Flow



Legend



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

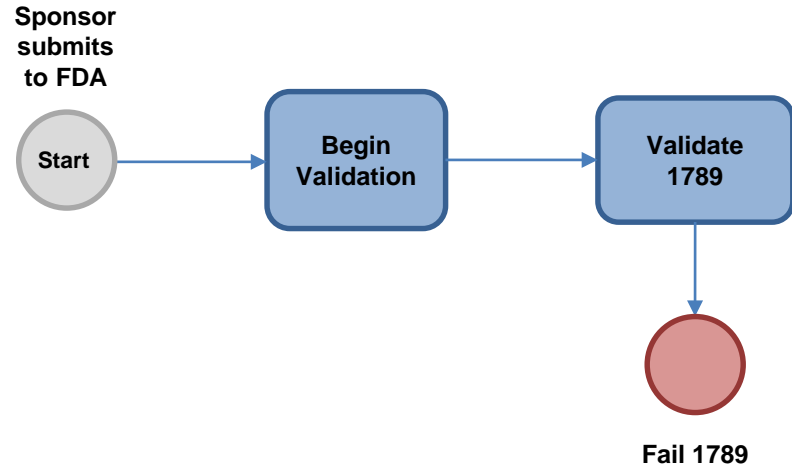


* Not every submission will proceed beyond 1734 to 1735 and 1736, depending on the Study Start Date (SSD)

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	Reason	Findings
1789	Files in study sections without STF reference	M5/53-clin-stud-rep/535-rep-effic-safety-study/confusion/5351-stud-rep-contr/report.pdf



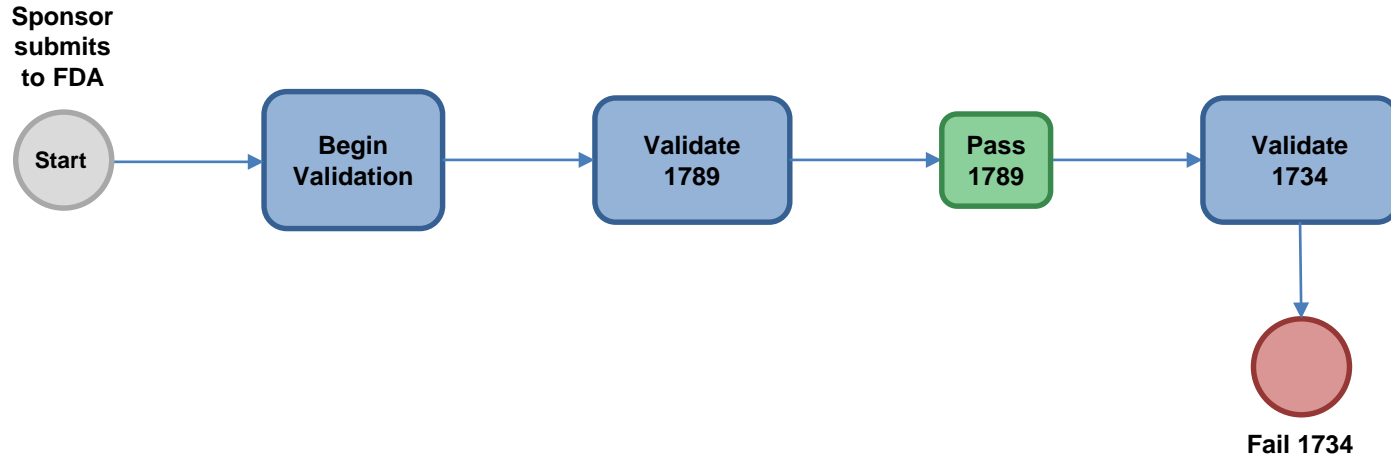
1789 warnings include the relative file path for the file causing the error

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	STUDY ID	M4-2-3-1-single-dose-toxicity	No ts.xpt found for this study



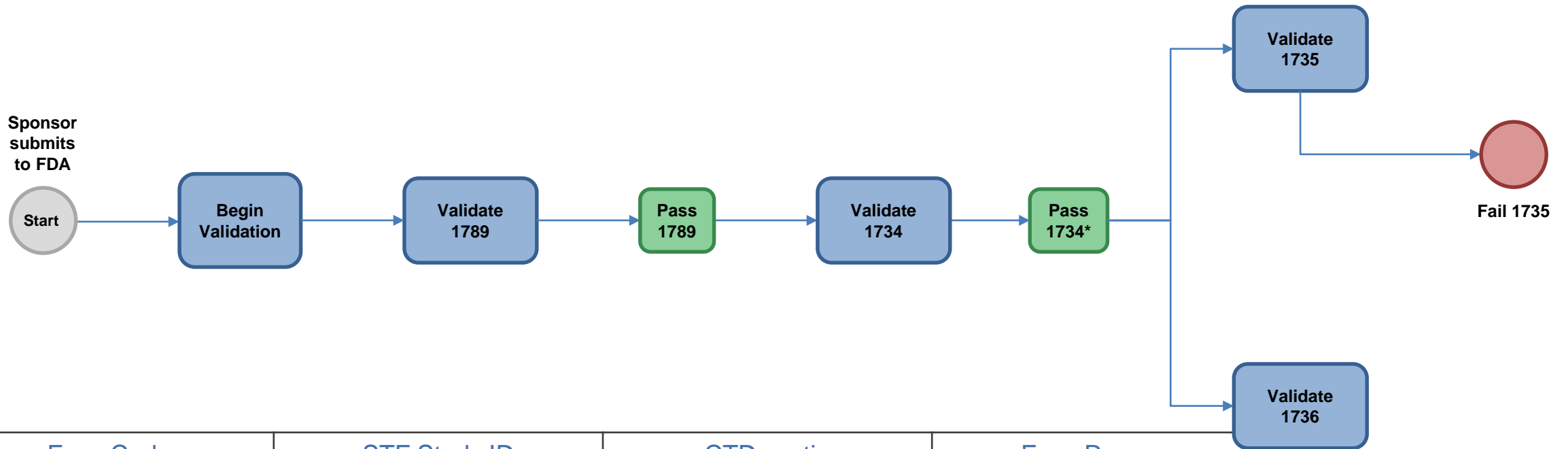
1734, 1735, and 1736 warnings include the Error, Study ID, eCTD Section, and Error Reason

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
1735	STUDY ID Example 1	m5-3-1-2-comparative-ba-and-bioequivalence-study-reports	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

Multiple errors are reported 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)*

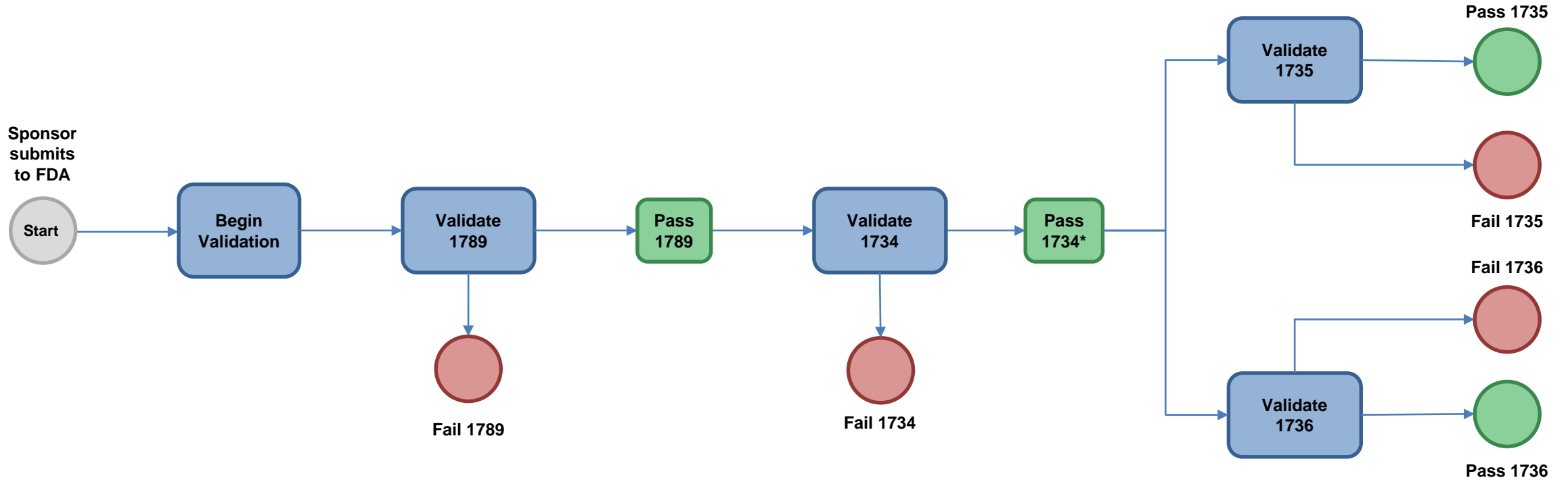


TRC Validation Rule Flow



Legend

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



* 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

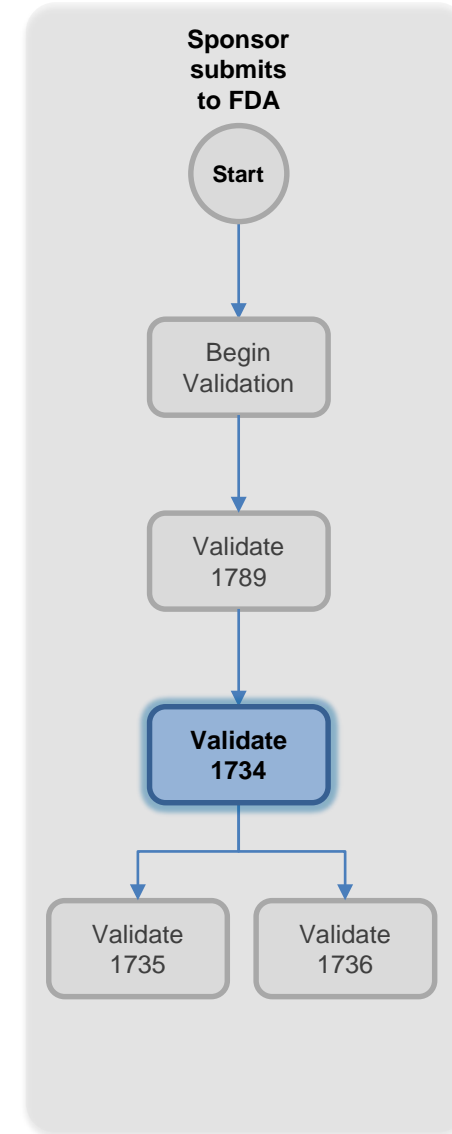
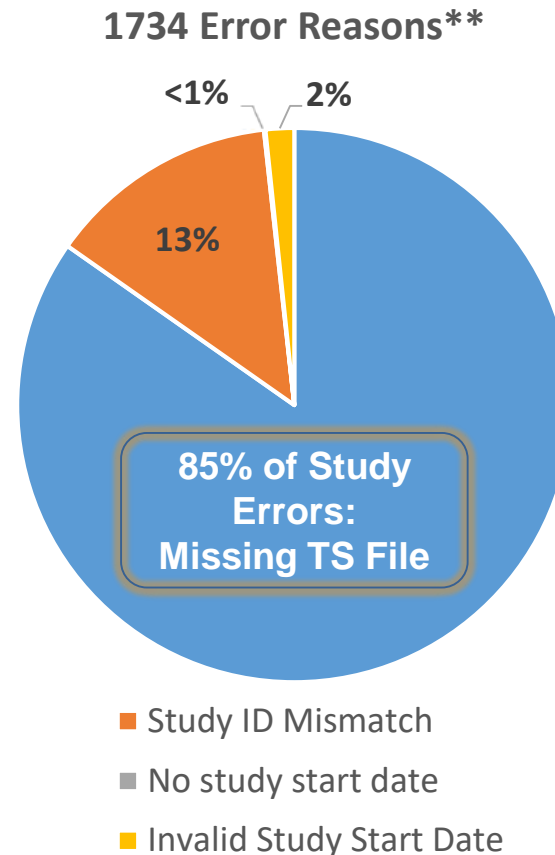
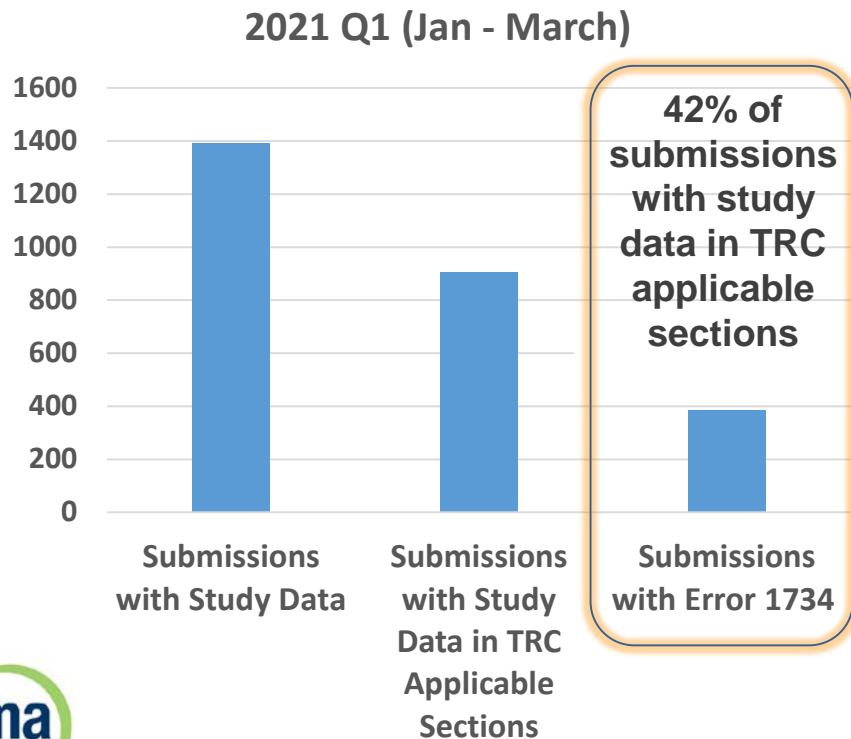
A dataset named ts.xpt with information on study start date must be present for each study in required sections*

✓ Trial Summary Dataset (ts.xpt) is present

✓ Study ID (or SPREFID) matches STF Study ID

✓ Study start date is provided (or TSVLNF = 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:

<p>3f. Are XPT Datasets (other than the ts.xpt File) Included?*</p> <p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>	<p>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"?"*</p> <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
--	--

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:

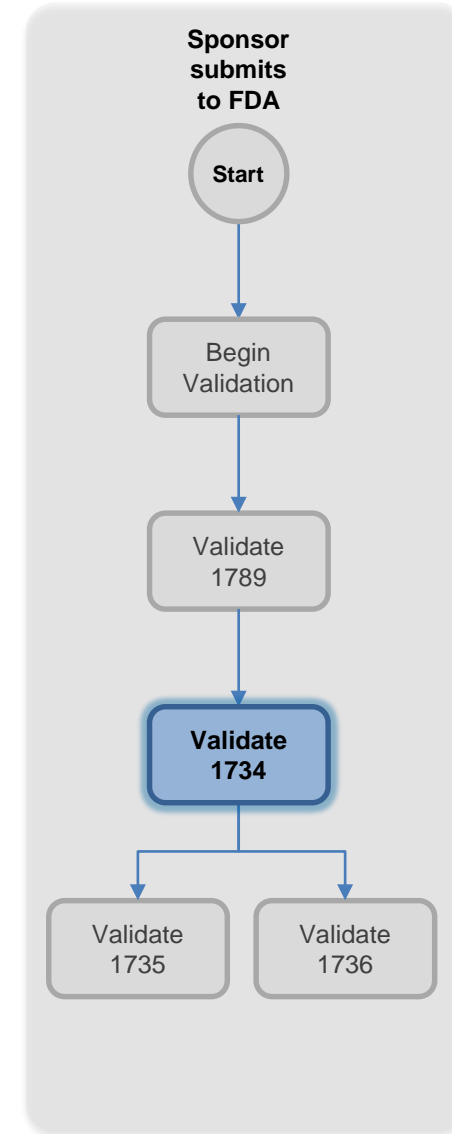
Prior to or on **17-Dec-2016** After **17-Dec-2016**

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	

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	<pre>##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")</pre>	<pre>##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")</pre>

Simplified TS File Creation Guide



```
RGui (64-bit)
File Edit Packages Windows Help

R Console
C:\Users\Ryan.Olivett\OneDrive - FDA\Documents\Sim...

R vers
Copyri
Platf
R is f
You ar
Type
Natu
R is a
Type
'citat
Type
'help.
Type
> |

##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/ts.xpt")
```

R Application

2. Edit the Study ID

3. Edit the Study Start Date and TSVAlNF Value

4. Edit where to save the file

Option 2: PHUSE Utility

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

The screenshot shows the 'Creating TS Domain' interface. It includes a 'Show/Hide sidebar' button, 'Create' and 'View' tabs, and four main input fields: 'Study ID (STUDYID) *', 'Study Type Parameter (TSPARMCD) *' (set to 'Nonclinical (STSTDTC)'), 'Study Start Date (TSVAL)', and 'Exception Code (TSVALNF)' (set to '__Blank__'). A 'Download' button is at the bottom. Four numbered callouts point to these fields: 1. Enter the Study ID, 2. Select the TSPARMCD Code, 3. Enter the Study Start Date or TSVALNF Value, and 4. Download the 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

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

[Referenced Validation Error Number 1734](#)

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

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

[Referenced Validation Error Number 1734](#)

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

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

[Referenced Validation Error Number 1734](#)



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

Addressing Common TRC Errors

Error 1789

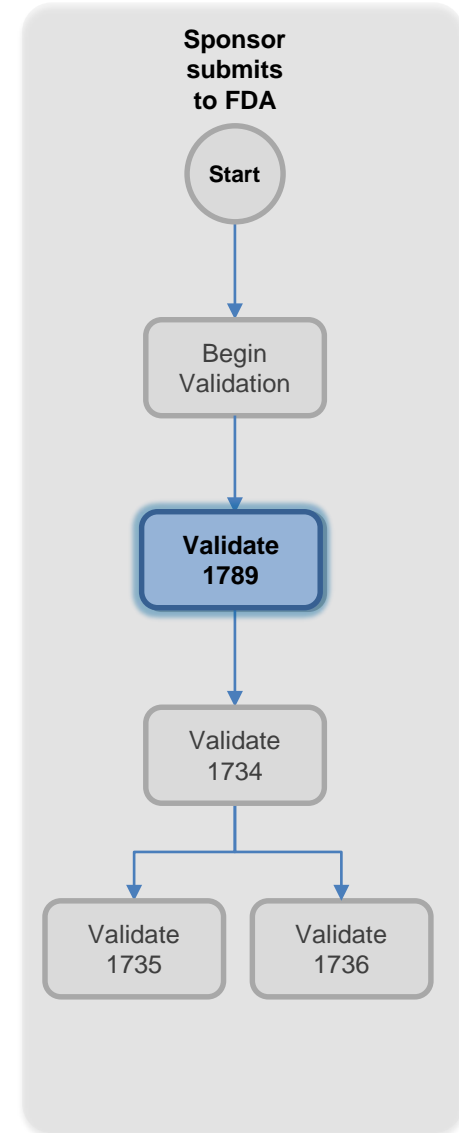
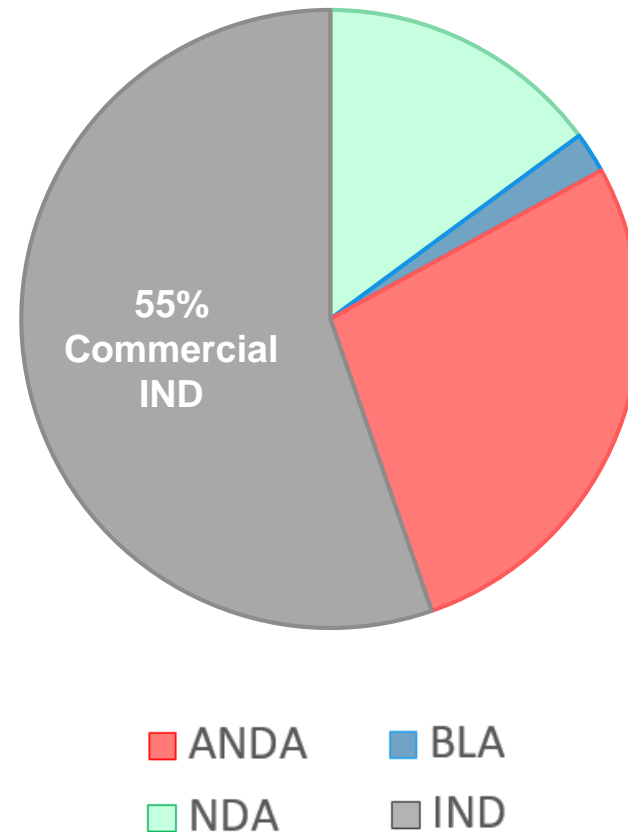
Validation Rule 1789

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*



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?*

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 (study-id) in STF File*

xyz-123

3e. Does the Study ID in the STF File Match Field 2a?

Yes No

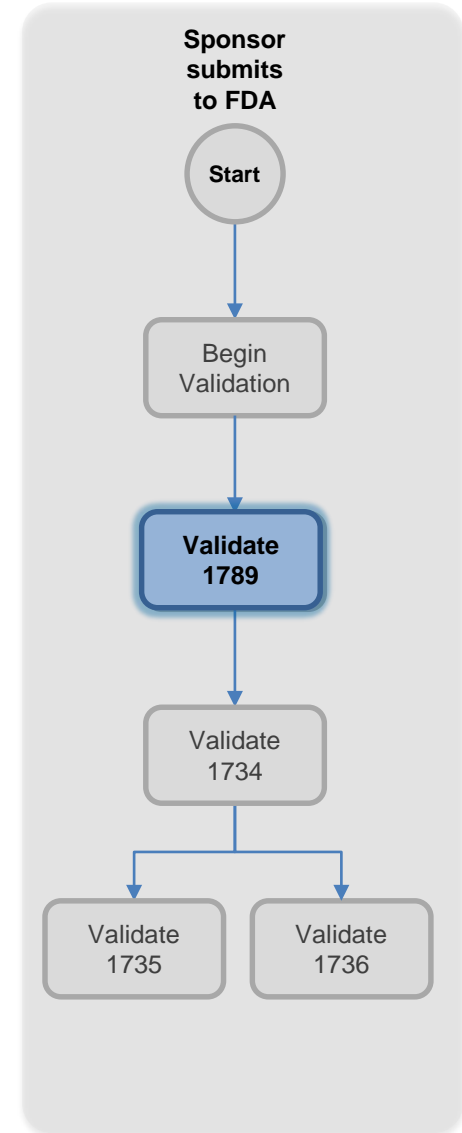
If you answered "No" in **Field 3e**, ensure the study ID is consistent across all the files being submitted for the same study.

3f. Are XPT Datasets (other than the ts.xpt File) Included?*

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



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>

```

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.

The file, bw.xpt, is included in the Index.xml but not 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

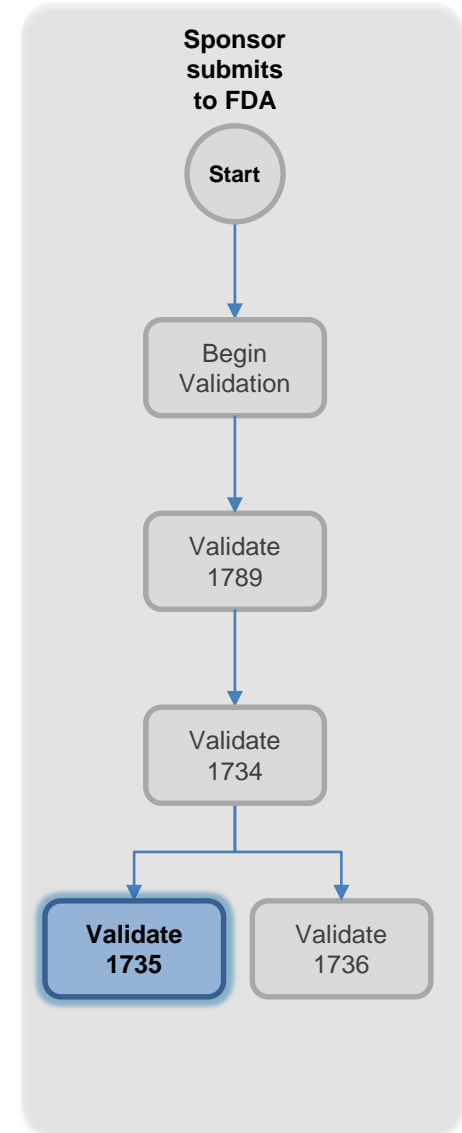
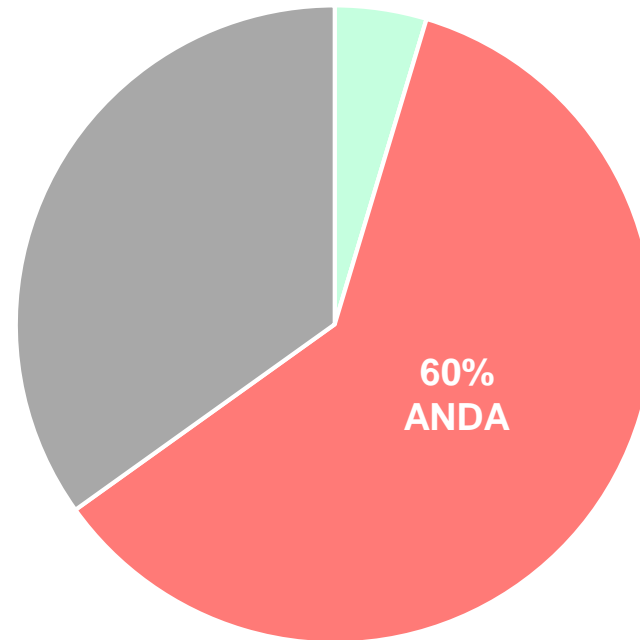
Validation Rule 1735

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*

Submission Types for 1735 Errors*



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?*

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.

5h. Are the STF File-Tags for the SDTM Datasets "data-tabulation-dataset-stdm"?

Yes No

[Referenced Validation Error Number 1735](#)

5i. Is the STF File-Tag for the Define File "data-tabulation-data-definition"?

Yes No

If you answered "No" in **Fields 5h or 5i**, Validation Rule 1735 FAILS.

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.

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

Yes No

[Referenced Validation Error Number 1735](#)

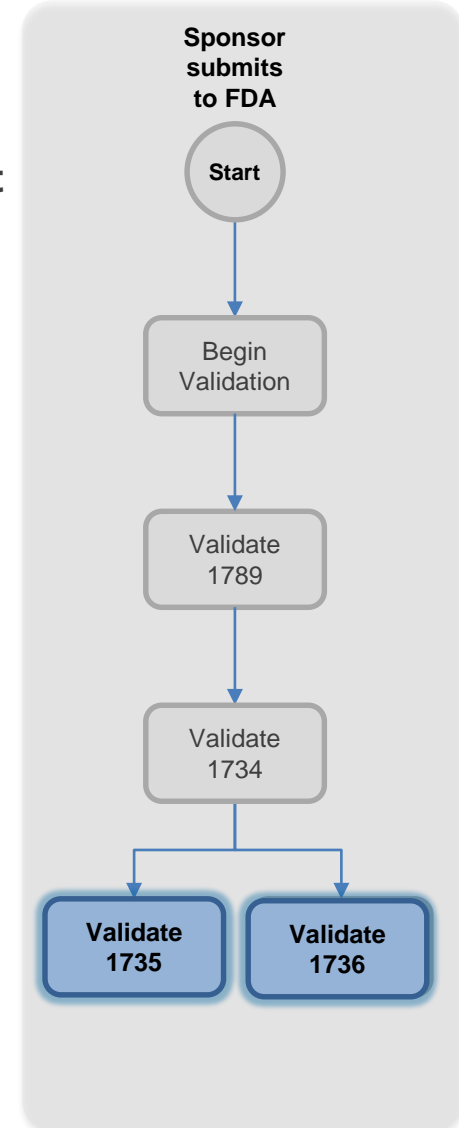
5m. Is the STF File-tag for the Define File "analysis-data-definition"?

Yes No

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

✓ **Correct File Tags**

✓ **Required Files/Datasets**



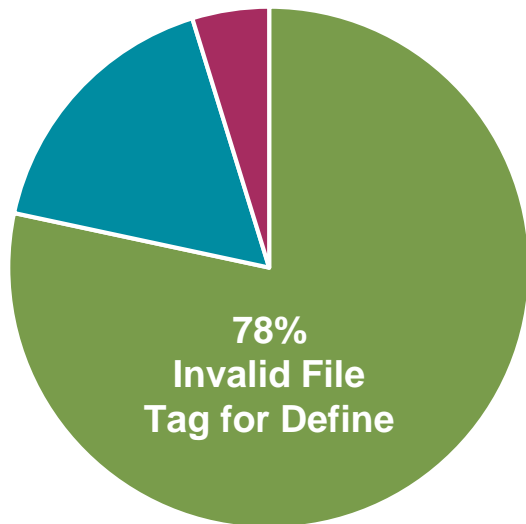
Addressing the Most Common 1735 Error

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

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

1735 Error Reasons*



- Invalid file tag for dm.xpt
- Invalid file tag for adsl.xpt

```

Standardized dataset domains (e.g. dm.xpt)
{
  <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>
Define.xml
{
  <doc-content
  xlink:href="../../../0001/index.xml#a57bb2ed13e2d2feb7606e65d59586355" xlink:type="simple">
  <file-tag info-type="us" name="data-tabulation-dataset-sdtm"/>
  </doc-content>
  
```

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

Correct File Tags

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 <i>Simplified ts.xpt Creation Guide</i> 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