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PRESENTER

Heather Crandall

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

FDA Study Data Technical Rejection Update

PharmaSUG 2021

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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 – What’s New

- ❖ eCTD Validations 1734, 1735, 1736, 1737, and 1789 are now effective (starting Sept. 15th, 2021)
- ❖ If a submission contains study information and fails eCTD validations listed in the Technical Rejection Criteria for Study Data, CDER and CBER will reject the submission
- ❖ Sponsors will receive a rejection notice if a submission fails eCTD validations


**Validation Rule 1734 in the
[Specifications for eCTD Validation Criteria:](#)**

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
Problem:	You have not submitted a dataset named ts.xpt with information on study start date for each study in Module 4, section 4.2, or in Module 5, section 5.3
Corrective Action:	Resubmit, including a dataset named ts.xpt with information on study start date for each study in Module 4, section 4.2, and Module 5, section 5.3
Guidance Source:	Providing Regulatory Submissions in Electronic Format – Standardized Study Data; Study Data Technical Conformance Guide.


eCTD Rejection Notice



- ❖ Sponsors receive a rejection notice from FDA when an eCTD validation error is identified
- ❖ Rejection notices specify each error and provide: Error Code; Error Reason; STF Study ID; eCTD Section (if applicable)

 **From: CDER Electronic Document Room Staff**

Center for Drug Evaluation and Research
U.S. Food and Drug Administration



REJECTION NOTIFICATION

Problem with Electronic Submission sent to CDER

While processing your electronic submission, we encountered the issues stated below. Please review the issues and take the appropriate corrective action.

The electronic portion of your submission is technically deficient and is being rejected for the following reasons.

Gateway Core Id: ci0000000000.0000000@fdabc00000_te0
Application Number: IND000000
eCTD Sequence Number: 0004

Your submission failed with following error(s):

Error Code	STF Study ID	eCTD section	Error Reason
1734	abc-123	m4-2-3-1-single-dose-toxicity	No ts.xpt found for this study
1734	abc-123	m4-2-3-1-single-dose-toxicity	No ts.xpt found for this study
1734	abc-123	m4-2-3-2-repeat-dose-toxicity	No ts.xpt found for this study
1734	abc-123	m4-2-3-2-repeat-dose-toxicity	No ts.xpt found for this study
1734	abc-123	m4-2-3-2-repeat-dose-toxicity	No ts.xpt found for this study

For study data specific assistance (e.g. 1734, 1735, and 1736 errors), please contact: eData@fda.hhs.gov
If you have any questions regarding this communication, please contact : ESUB-REJECT@fda.hhs.gov

- For information on electronic submission requirements, please visit www.fda.gov/ectd for guidance, specifications, and other helpful information

For all PROMOTIONAL submission-related questions:

- Email Office of Prescription Drug Products at OPDPECTD@FDA.HHS.GOV or
- Call the OPDP RPM at 301-796-8522.



Overview of Technical Rejection Criteria



eCTD validation rule 1789 has different expectations than 1734, 1735, and 1736.

Error	Description (Reference to FDA Study Data Technical Rejection Criteria March 2021 version)	Severity Level	Effective Date
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	Sept. 15, 2021

- ❖ 1789 applies to all subsections of modules 4 and 5 except:
 - sections 4.3, 5.2, 5.4, and 5.3.6
- ❖ An STF must be provided for all applications and data types for both CDER and CBER regardless of study start date

Overview of Technical Rejection Criteria

The TRC are eCTD validation criteria to determine compliance with requirements for submitting standardized study data in required sections in Modules 4 and 5, including:

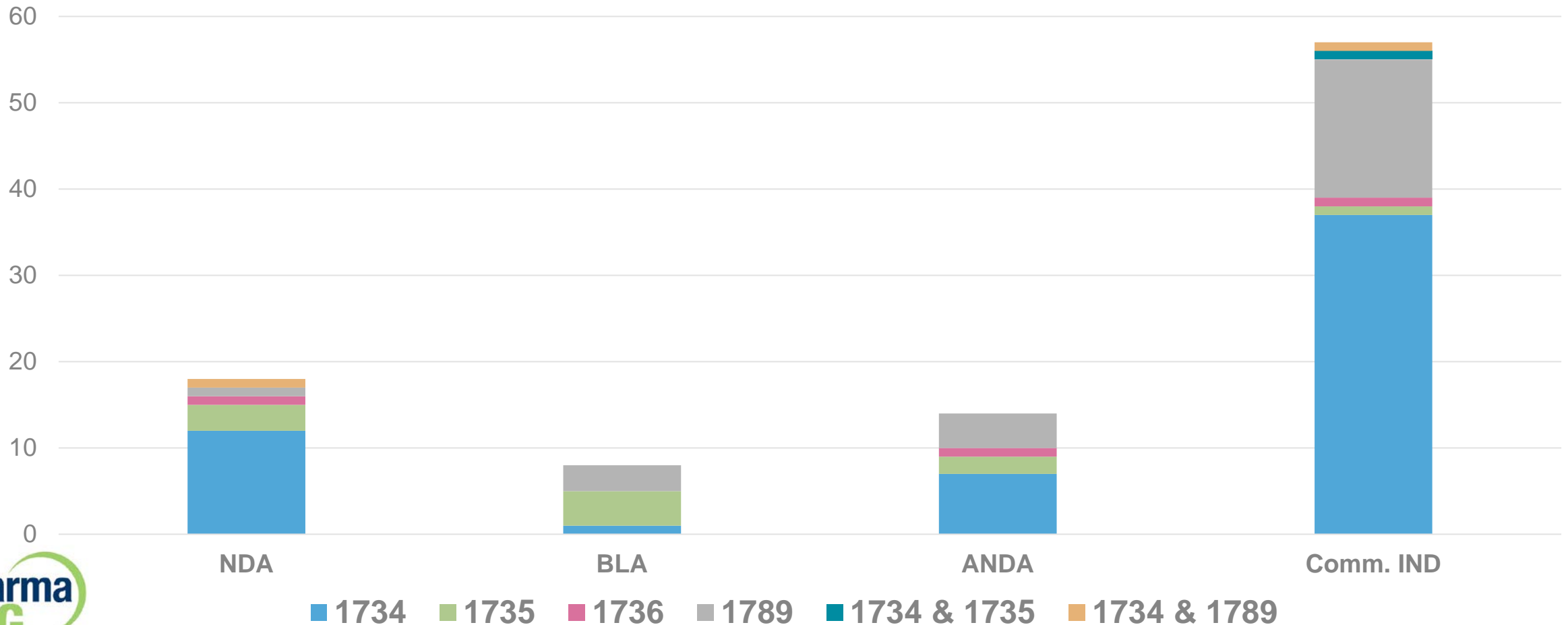
- ❖ 4.2.3.1, 4.2.3.2, 4.2.3.4
- ❖ 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2

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	



TRC Rejections (September 15th – October 31st, 2021)

- ❖ 1734 is the most common rejection reason, especially for Commercial IND submissions
- ❖ 1789 is the second largest rejection reason and is particularly high for Commercial IND submissions



Note: Rejection metrics generated by CDER between September 15th and October 31st, 2021



Tools to Help Industry Pass TRC Validation



The Self-Check Worksheet



- ❖ Designed to walk sponsors through each step of the 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](#)



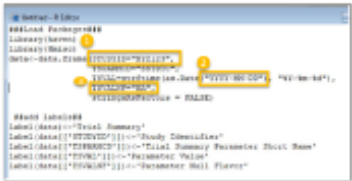
[Self-Check Worksheet Instructions](#)

		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* <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"/>	
Note: Repeat Sections 2 through 5 for each study included in the submission.				
Section 2: Study Information				
2a. Study ID* <input type="text"/>				
<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>				
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 <i>If you answered "No" in Field 2b, do not proceed. This self-check worksheet is designed for newly submitted study data.</i>				
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 <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>				
FORM FDA 4061 (11/19) Page 1 of 3 PSC Publishing Services (301) 443-6740				

The Simplified ts.xpt Creation Guide

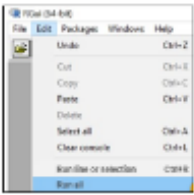
- ❖ Helps industry create simplified TS files using free and open-source software, R and Python
- ❖ Provides step by step instructions to install the necessary software
- ❖ Users can copy and paste code samples from the guide into R or Python
- ❖ Available on FDA's web page, [Study Data for Submission 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"

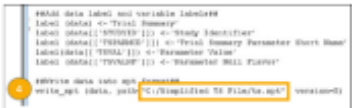


Please Note – While editing Study ID, TRTSEQ, and TRTSEQID, drop the question marks around the values you enter.

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.

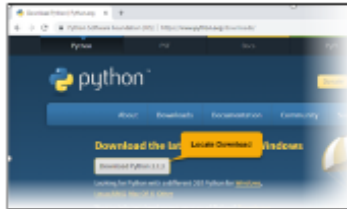


Please Note – When adding a new file path, be sure the slash marks are forward (/). Backward slashes will result in an error when running the code.

b) Option 2: Use Python

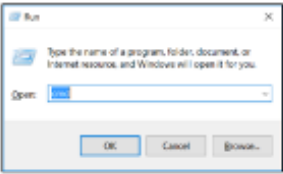
Pre-Requirement: Install Python and IDLE

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)

Addressing Common TRC Errors

Error 1734

Causes of 1734 Errors

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

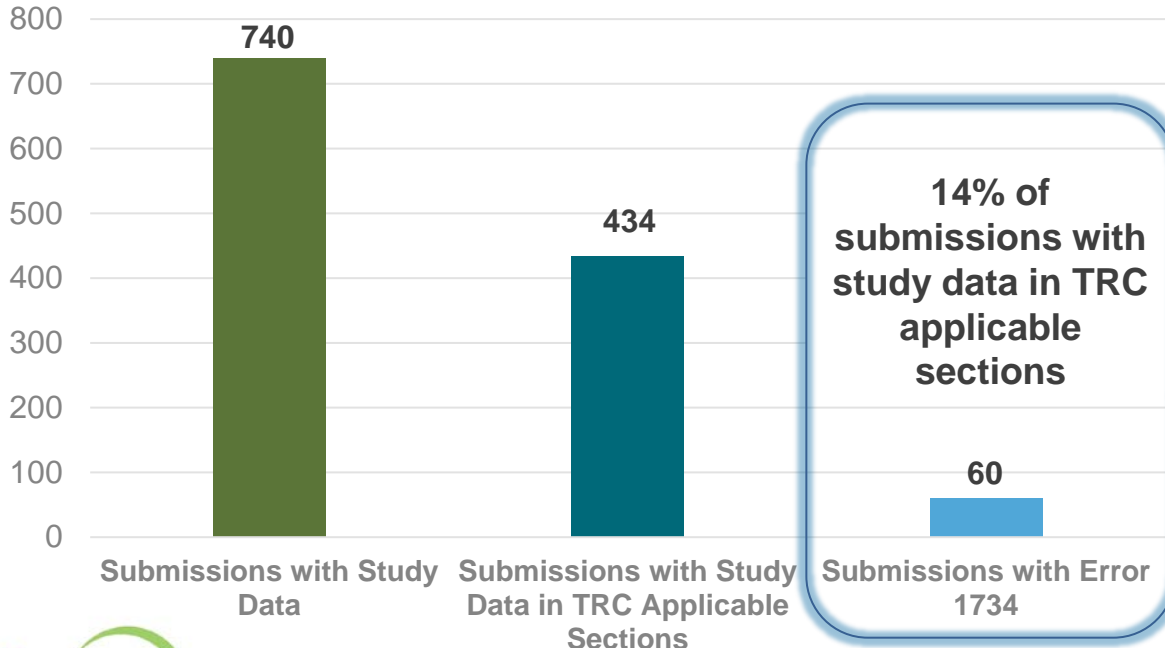
✓ Trial Summary Dataset (ts.xpt) is present

✓ Study ID (or SPREFID) matches STF Study ID

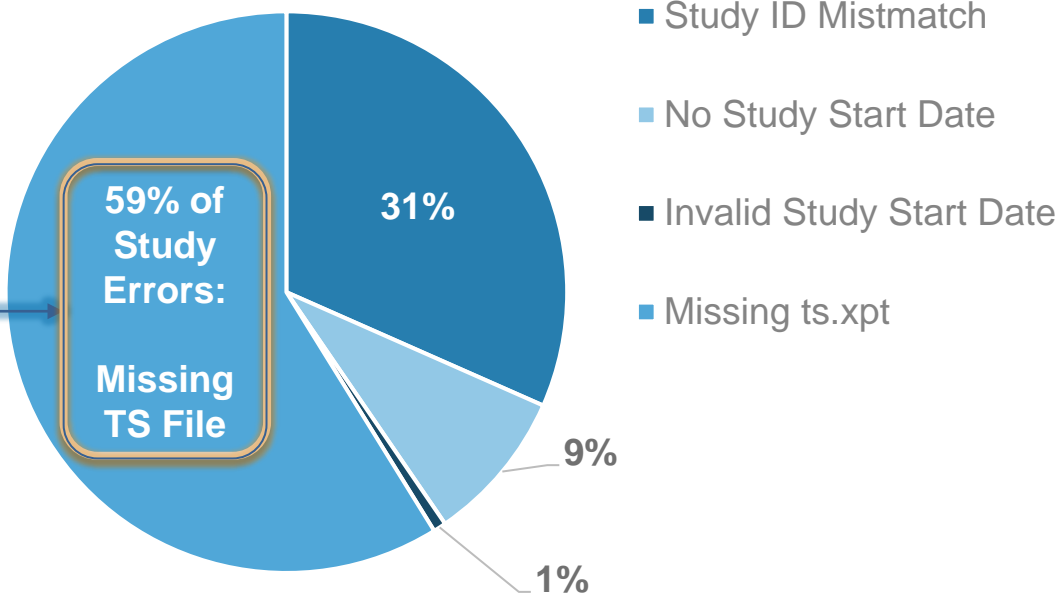
✓ Study start date is provided (or TSVLNF = NA)

✓ Study start date is in a valid format

CDER Submissions: September 15th – October 31st 2021



1734 Error Reasons**



* 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

**136 Studies in 60 Submissions with Error 1734 (September 15th – October 31st, 2021)

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"??*
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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?
<input type="checkbox"/> Full TS <input checked="" type="checkbox"/> 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.

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	

When SEND datasets are required, submit a Full TS.

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.

Addressing Common TRC Errors

Error 1789

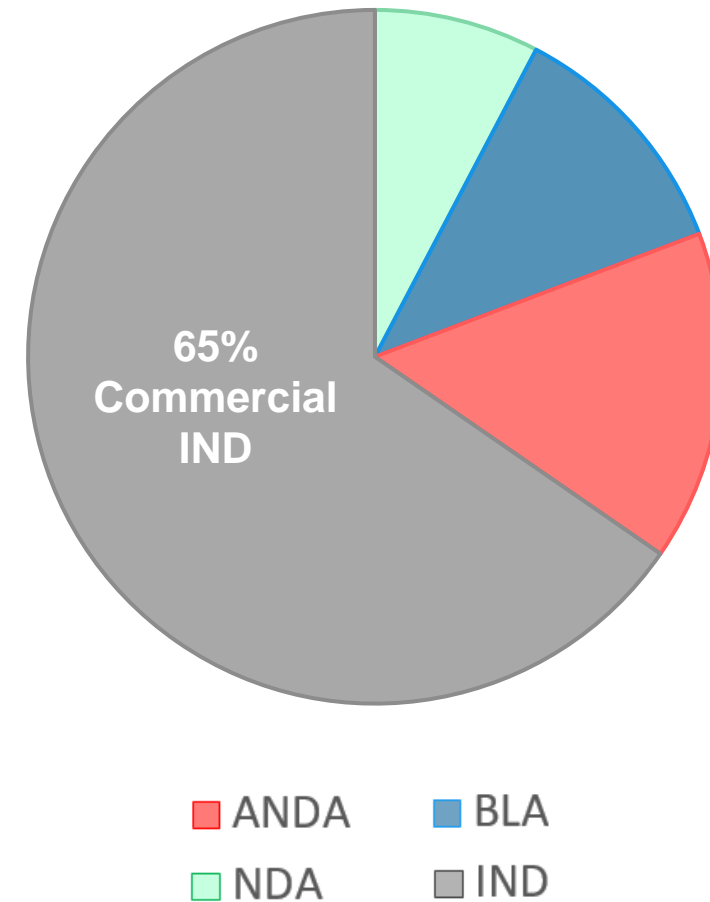
Validation Rule 1789

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*



*26 1789 failures out of 100 total rejections September 15 – October 31, 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? <i>(Not Applicable to Sections 4.3, 5.2, 5.3.6, and 5.4)*</i>	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
<i>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.</i>	
3b. Is STF File Included?*	3c. Does STF File Reference all Associated Study Files?*
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<i>If you answered "No" in Fields 3b or 3c, Validation Rule 1789 FAILS. Do not proceed.</i>	
3d. Study ID (study-id) in STF File*	3e. Does the Study ID in the STF File Match Field 2a?
xyz-123	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<i>If you answered "No" in Field 3e, ensure the study ID is consistent across all the files being submitted for the same study.</i>	
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"??*
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

[Referenced Validation Error Number 1789](#)

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

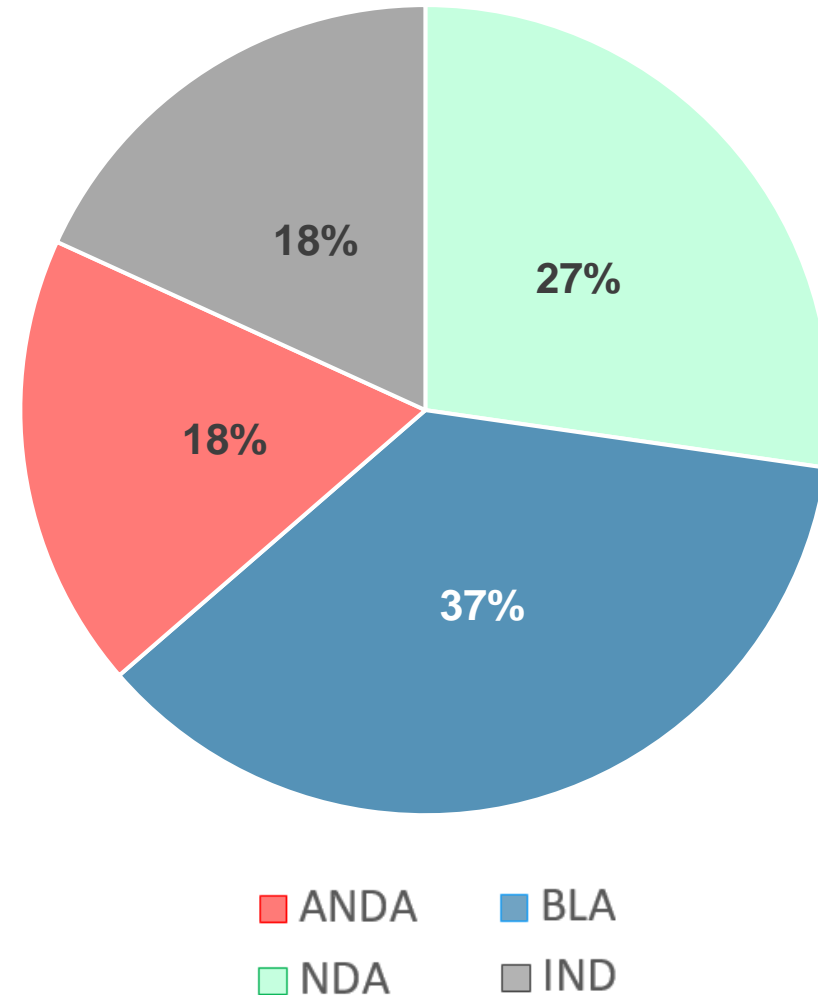
Error 1735

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

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-sdtm"?*

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

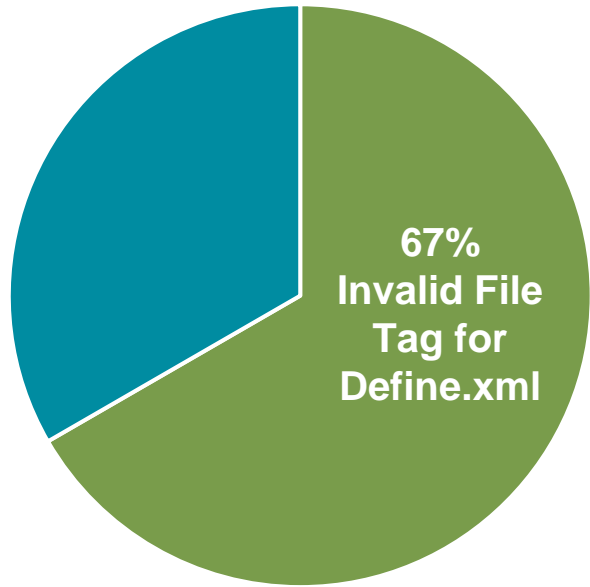
✓ Required Files/Datasets



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

1735 Error Reasons*



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



*15 studies with Error 1735 between September 15 – October 31, 2021

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)
{
  <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

References

❖ Study Data Standards Resources

- Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [June 2021]
- Study Data Technical Conformance Guide [Oct 2021]
- FDA Data Standards Catalog [Sept 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 [Aug 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>

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

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

References



❖ eCTD Standards Resources

- Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications Guidance for Industry [[Feb 2020](#)]
- eCTD Technical Conformance Guide [[Oct 2021](#)]
- eCTD Submission Standards [[Oct 2021](#)]
- Link: <https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd>

❖ 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 eSub Mailbox: esub@fda.hhs.gov

CDER eSub Mailbox: esubprep@fda.hhs.gov