INVALUABLE INFORMATION AND INSIGHTS
ON GENERICS AND BIOSIMILARS

PROCESS + PROGRESS

aam Association for Accessible Medicines

Biosimilars Council
A Division of AAM

VIRTUAL CONFERENCE
GRx+Biosims™
GENERICS + BIOSIMILARS CONFERENCE

NOVEMBER 8-10, 2021

#GRxBIOSIMS | GRxBIOSIMS.ORG

eCTD Validations and Study Data

Jonathan Resnick
Office of Business Informatics
CDER | US FDA

2021 AAM GRx+Biosims Conference

Disclaimer

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

Agenda

1. Electronic Submissions To FDA
2. TRC & ANDA Study Data Conformance Analysis
3. Top Error Reasons For eCTD Validation 1734 and 1735
4. FDA Tools & Resources

Electronic Submissions to FDA

Purpose of eCTD and Study Data Requirements

- Reviewing study data in a timely manner is critical for FDA's review process (e.g., Reviewers have 30 days to review an IND application)
- When sponsors submit data to the FDA in a reliable and accessible format, it improves efficiency and timeliness of review decisions
- CDISC Standards enable FDA to streamline the review process:
  - Reduce time for reviewers to locate and identify study data
  - Reduce the burden on sponsors and reviewers from IRs (Information Requests)
  - Reduce review time by enabling the use of commercial off the shelf reviewer's tools (such as JReview, JMP Clinical, etc.) to automate review analyses
  - Support data driven decisions by applying data mining and data analytic techniques

"The agreement to assemble all the Quality, Safety and Efficacy information in a common format (called CTD - Common Technical Document) has revolutionized the regulatory review processes, led to harmonized electronic submission that, in turn, enabled implementation of good review practices. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities."

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

Purpose of eCTD and Study Data Requirements

- Per FD&C Act Section 745A(a), drug application sponsors must use the standards defined in the FDA Data Standards Catalog starting 24 months after final guidance for a specific submission type.

- FDA issued “Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry” in December 2014.

- Sponsors must conform to standards in the FDA Data Standards Catalog:
  - NDA, BLA, ANDA studies that started after December 17th, 2016
  - Commercial IND studies started after December 17th, 2017

- FDA published the “Technical Rejection Criteria for Study Data (TRC)” to provide detail on how eCTD validations are used to determine whether a submission complies with FDA’s standards for study data

- If an ANDA First Applicant submission is rejected, it will potentially impact the ability to be a First Applicant, if not resubmitted on the same business day, and therefore applicants may not be eligible for 180-day exclusivity

TRC & ANDA Study Data Conformance Analysis

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's Study Data Technical Rejection Criteria Sept 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	

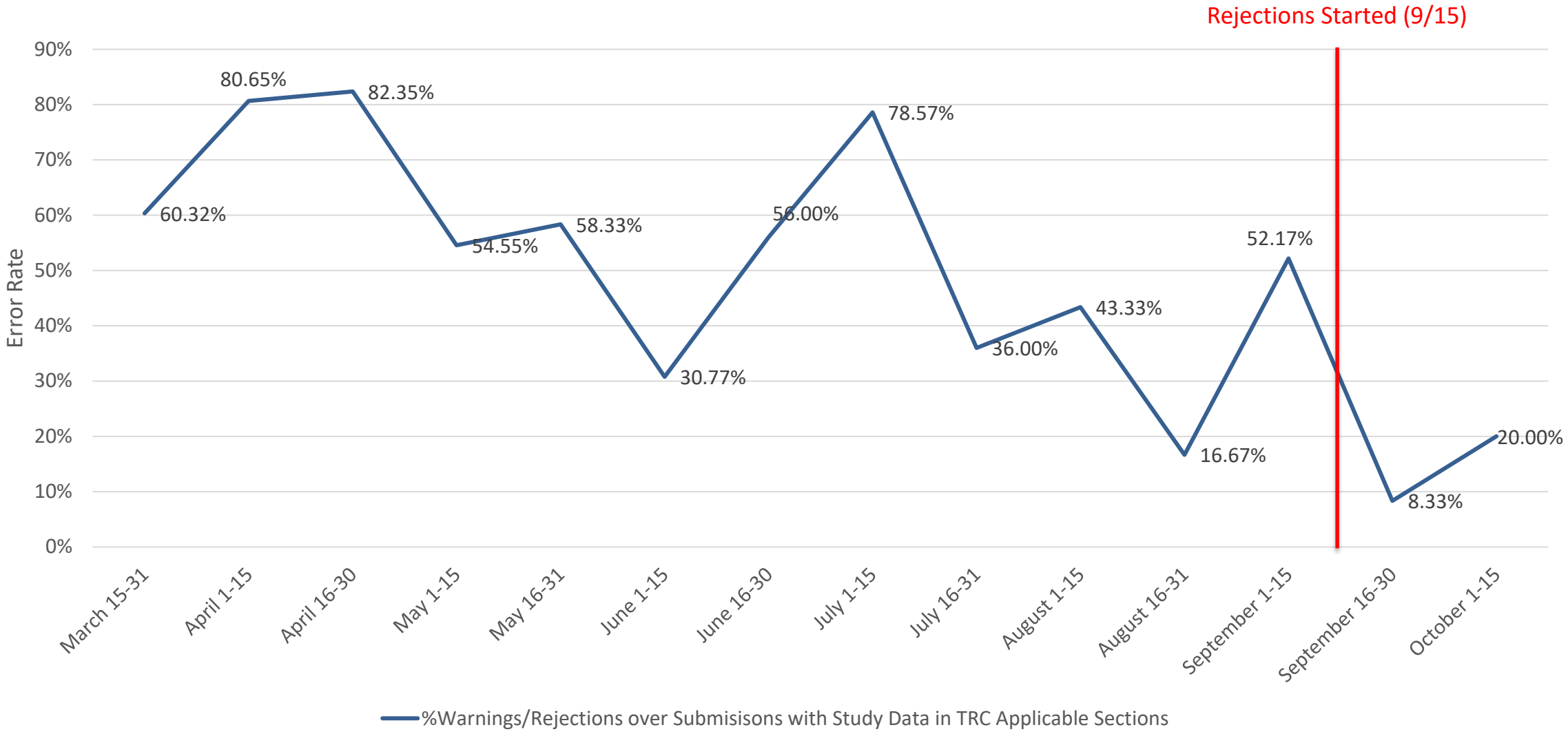
Overview of Technical Rejection Criteria

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

Error	Description (Reference to FDA Study Data Technical Rejection Criteria Sept 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

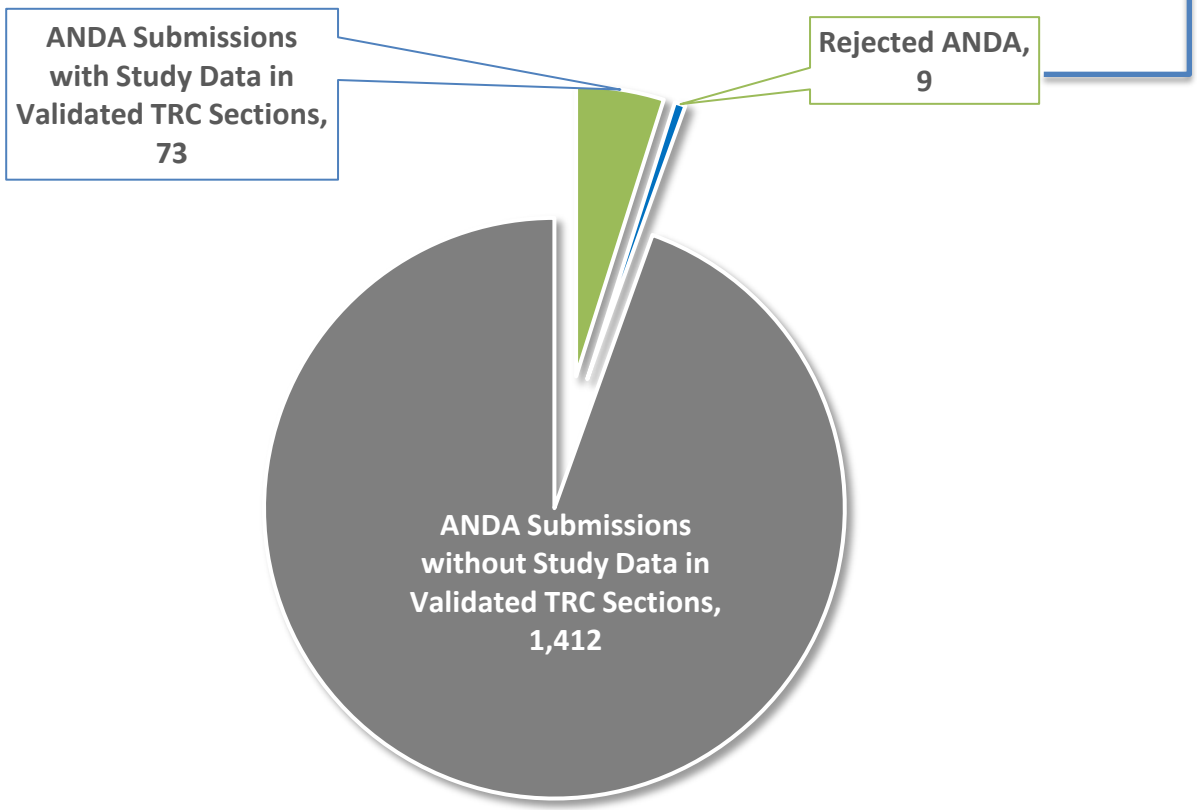
ANDA TRC Warning and Rejection Trend (March 15th – Oct 15th)

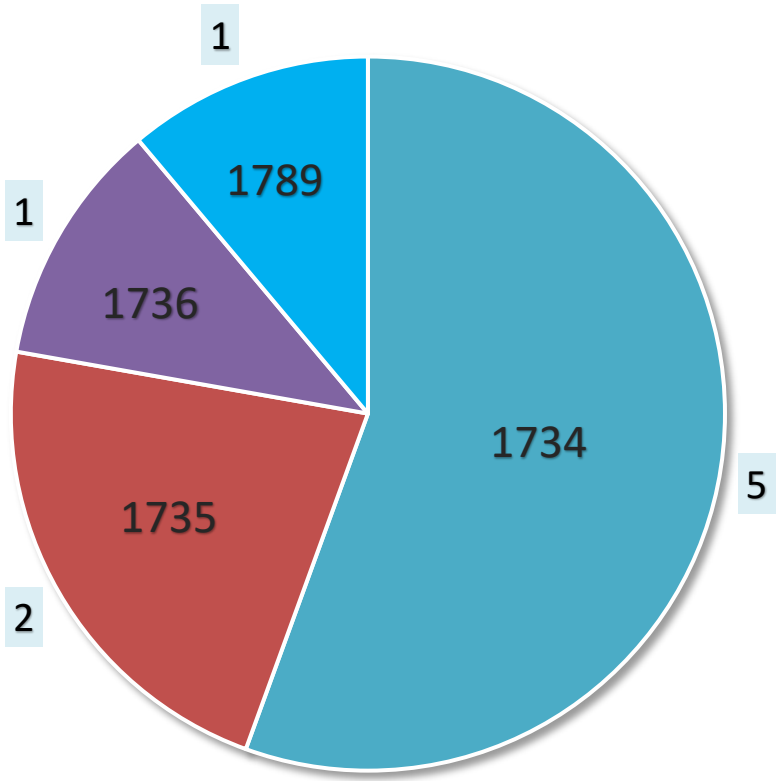


Validation Metrics since FDA began rejecting on September 15, 2021

1,485 ANDA Submissions

9 Submissions Rejected (Error Reason)





Timeframe: September 15, 2021 – October 15, 2021

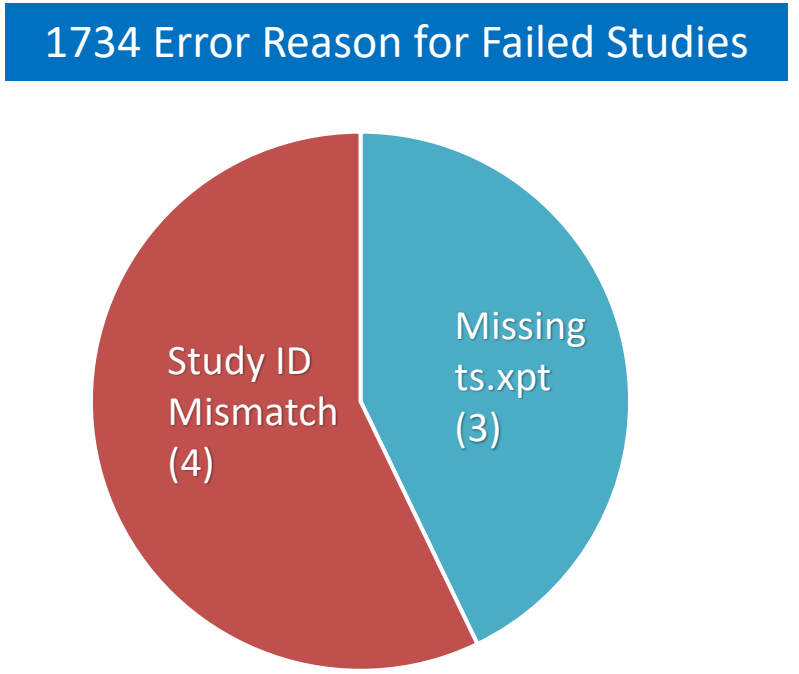
TOP ERROR REASONS FOR ECTD VALIDATION 1734

Top Error Reasons for Validation 1734

eCTD Validation 1734 → A dataset named ts.xpt with information on Study Start Date (SSD) must be present for each study

- Out of 9 Rejected ANDA Submissions
  - 5 Submissions failed validation 1734
    - Within those 5 submissions, 7 studies had 1734 error

- Error Reason 1
  - 57% failed due to Study ID mismatch
- Error Reason 2
  - 43% failed due to a missing ts.xpt



Error Reason 1 – Study ID Mismatch

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: ci1634915491954.22872778@fdslv86002_te1
Application Number: ANDA00000
eCTD Sequence Number: 0004

Your submission failed with following error(s):

Error Code	STF Study ID	eCTD section	Error Reason
1734	Abc-123	m5-3-1-2 Comparative BA and bioequivalence (BE) Study reports and related information	Study ID in ts.xpt does not match study ID from STF

STF

XML

```
<study-identifier>
    <title>Study Title </title>
    <study-id>Abc-123</study-id>
</study-identifier>
```

ts

XPT

STUDYID	DOMAIN	TSSEQ	TSGRPID	TSPARMCD	TSPARM	TSVAL
Xyz-234	TS	1		ACTSUB	Actual Number o...	
Xyz-234	TS	1		ADAPT	Adaptive Design	N
Xyz-234	TS	1		ADDON	Added on to Exis...	N

Error Reason 2 – Missing ts.xpt

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

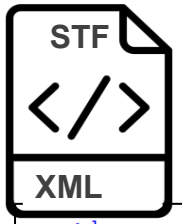
While processing your electronic submission, we encountered the issues stated below.
Please review the issues and take the appropriate corrective action.

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

Gateway Core Id: ci1634915491954.22872778@fdslv86002_te1
Application Number: ANDA00000
eCTD Sequence Number: 0004

Your submission failed with following error(s):

Error Code	STF Study ID	eCTD section	Error Reason
1734	Abc-123	m5-3-1-2 Comparative BA and bioequivalence (BE) Study reports and related information	No ts.xpt found for this study



STF reference for dm.xpt

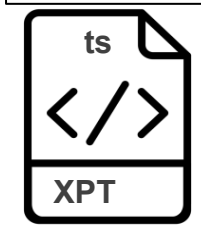
STF reference for ex.xpt

STF reference for ae.xpt

```
<doc-content xlink:h
"../../../../../../0014/index.xml#Nf7e8cf27227c4026b56c04
54d6ae7f3d">
  <file-tag name="data-tabulation-dataset-sdtm"
  info-type="us" />
</doc-content>

<doc-content xlink:href=
"../../../../../../0014/index.xml#N32e0995a170d40a4aaf7d
30b3fb5fd58">
  <file-tag name="data-tabulation-dataset-sdtm"
  info-type="us" />
</doc-content>

<doc-content xlink:href=
"../../../../../../0014/i                    9b413ebedd7
be8be2383ba">
  <file-tag name="data-tabulation-dataset-sdtm"
  info-type="us" />
</doc-content>
```



No reference for ts.xpt file submitted in the lifecycle of the study

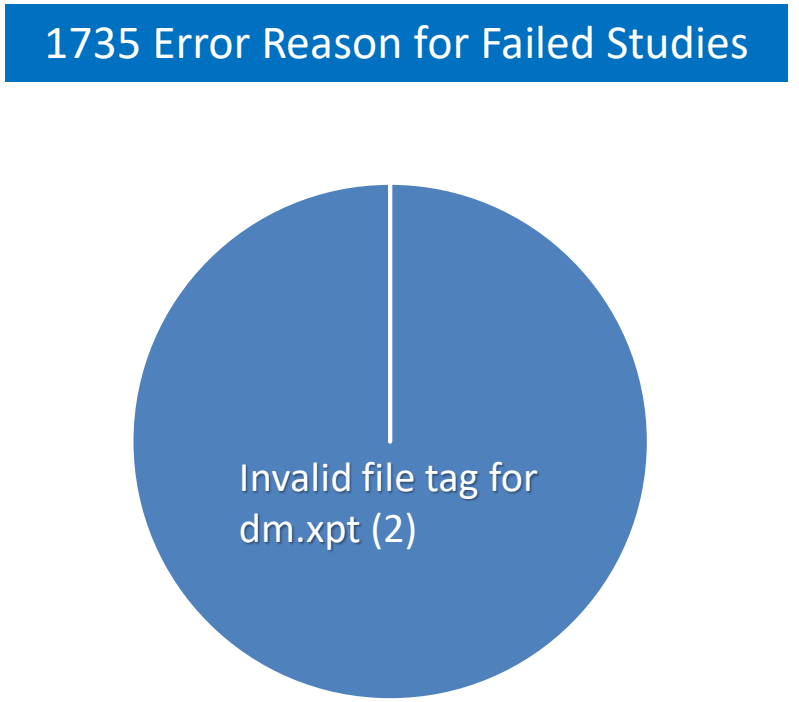
TOP ERROR REASONS FOR ECTD VALIDATION 1735

Top Error Reasons for Validation 1735

eCTD Validation 1735 → The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections

- Out of 9 Rejected ANDA Submissions
  - 2 Submissions failed validation 1735
    - ➢ Within those 2 submissions, 2 studies had 1735 error

- Error Reason
  - ➢ Invalid file tag for dm.xpt



Error Reason – Invalid File tag for dm.xpt

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

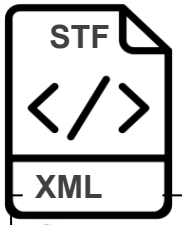
While processing your electronic submission, we encountered the issues stated below.
Please review the issues and take the appropriate corrective action.

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

Gateway Core Id: ci1634915491954.22872778@fdslv86002_te1
Application Number: ANDA00000
eCTD Sequence Number: 0004

Your submission failed with following error(s):

Error Code	STF Study ID	eCTD section	Error Reason
1735	Abc-123	m5-3-1-2 Comparative BA and bioequivalence (BE) Study reports and related information	Invalid File tag for dm.xpt




```
<doc-content xlink:href=
"../../../../../../0014/index.xml#Nf7e8...6ae7f3d">
  <file-tag name="data-tabulation-dataset-sdtm" info-type="us" />
</doc-content>

<doc-content xlink:href=
"../../../../../../0014/index.xml#N32e0995a17...8">
  <file-tag name="data-tabulation-dataset-sdtm" info-type="us" />
</doc-content>

<doc-content xlink:href=
"../../../../../../0014/index.xml#Nf5a5e9...3ba">
  <file-tag name="data-tabulation" info-type="us" />
</doc-content>
```

Valid File tag for dataset

Valid File tag for dataset

Invalid file tag for dataset (dm.xpt)

Technical Rejection Criteria and Use of a Simplified ts.xpt for Clinical Studies (From Study Data Technical Conformance Guide)

- There may also be cases where SDTM and ADaM are not required even though the study started after December 17, 2016.

- Other bioequivalence studies required to be submitted per 21 CFR 320.21(b)(1) and 314.94(a)(7)-examples (not an exhaustive list):
  - Pilot bioequivalence studies conducted on the same drug product formulation submitted to an ANDA application
  - Failed bioequivalence studies conducted on the same drug product formulation submitted to an ANDA application

- When SDTM and ADaM are not applicable in a study started after December 17, 2016, the following format of a simplified ts.xpt file should be used, where the TSVALNF field is to be populated with the null value “NA” (Not Applicable)

STUDYID	TSPARMCD	TSPARM	TSVALNF
Use Study ID in STF	SSTDTC	*(Leave blank)*	NA

Example of clinical simplified ts.xpt

Not sure if your study requires ts.xpt file?

- Please refer the Study Data Technical Conformance Guide (SDTCG)
- Please refer the Technical Rejection Criteria (TRC)
- You can utilize the “TRC Self Check Worksheet and Instructions” to confirm if the ts.xpt file is required for your study

FDA TOOLS & RESOURCES

Tools and Resources

	Resource	Description
1	Technical Rejection Criteria	This document focuses on the Study data criteria used for the automated validation process to determine compliance with the requirement to submit electronic standardized study data
2	Study Data Technical Conformance Guide	This Study Data Technical Conformance Guide (Guide) provides specifications, recommendations, and general considerations on how to submit standardized study data
3	Self Check Worksheet and Instructions	A checklist is for industry to validate the technical conformance of clinical and nonclinical study datasets included in a submission with study data.
4	Simplified TS creation Guide (Free Tool Using R and Python)	A Step-By-Step Guide to create a simplified ts.xpt using free and opensource software R and Python
5	Simplified TS creation (PHUSE Utility)	A free Utility Developed by PHUSE to create a simplified ts.xpt file
6	FDA Data Standards Catalog	The FDA Data Standards Catalog (Catalog) lists the data standards and terminologies that FDA supports for use in regulatory submission
7	Study Data Guidance	This guidance describe the requirements for an electronic submission of standardized clinical and nonclinical study data
8	Comprehensive Table of Headings and Hierarchy	This document describes the placement of files in the eCTD sections and sub sections

Questions

For Additional Questions Please Contact:

- Study Data Questions:
  edata@fda.hhs.gov

- eCTD Questions:
  esub@fda.hhs.gov

Acknowledgements

The author would like to thank Ethan Chen, Jonathan Resnick, Heather Crandall, Nitin Guptan, Anthony Fata, Ryan Olivett, Jiang Xu, Lina Cong, and other FDA staff for their time and effort in helping collect and analyze data and information as presented here.