Regulatory Submissions, Information, and Document Management Forum

February 14-16
North Bethesda, MD

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U.S. FOOD & DRUG ADMINISTRATION

Technical Rejection Criteria for Study Data

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Agenda

- Benefits of Standardized Data
- Technical Rejection Criteria for Study Data (TRC)
  - Overview
  - Trends
  - Top Errors
- Impacts & Improvements from Standardized Study Data

Benefits of Standardized Data

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 consistency 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 COTS 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

Electronic Submission Guidance

"**Study Data Guidance**" - *Providing Regulatory Submissions in Electronic Format -- Standardized Study Data (last updated June 2021)*

- **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 uses eCTD validations (1734, 1735, 1736, 1789)** to confirm Sponsors are conforming to the FDA Data Standards Catalog. This subset of eCTD validations are described in detail in the Technical Rejection Criteria for Study Data (TRC).

For more information on how to submit and what will be validated, see the documents below:

- Technical Rejection Criteria for Study Data – Latest update August 2021
- Study Data Technical Conformance Guide – Latest update September 2021
- Study Data for Submission to CDER and CBER website
- SBIA Webinar, FDA Study Data Technical Rejection Criteria (TRC): What you need to know!

Technical Rejection Criteria for Study Data (TRC)

Technical Rejection Criteria for Study Data

- eCTD Validations 1734, 1735, 1736, 1737, and 1789 are now effective (as of Sept. 15th, 2021)
- If a submission contains study information and fails eCTD validations in listed in 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.

Overview of Technical Rejection Criteria for Study Data

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

Error	Description	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

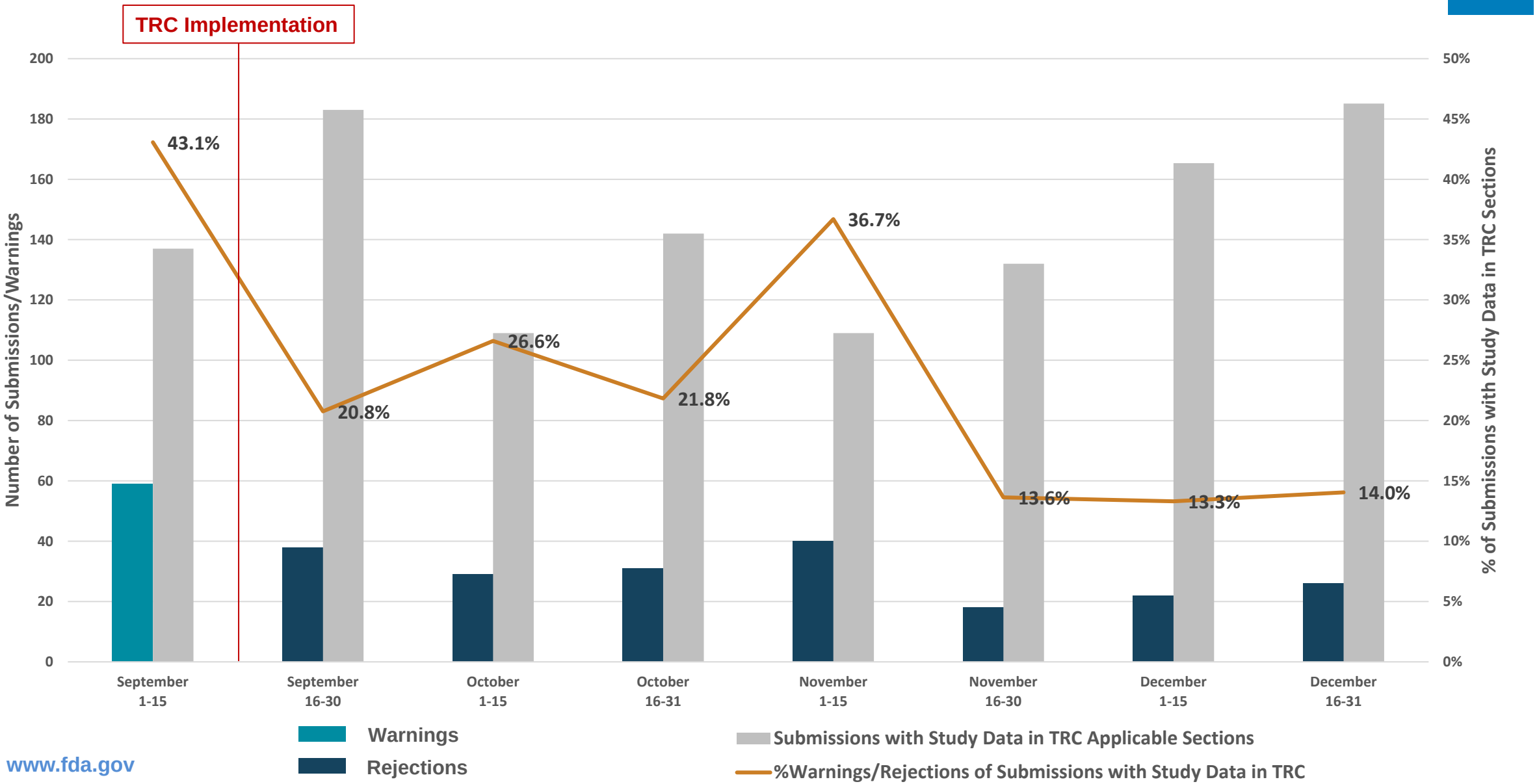
Overview of Technical Rejection Criteria for Study Data

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:

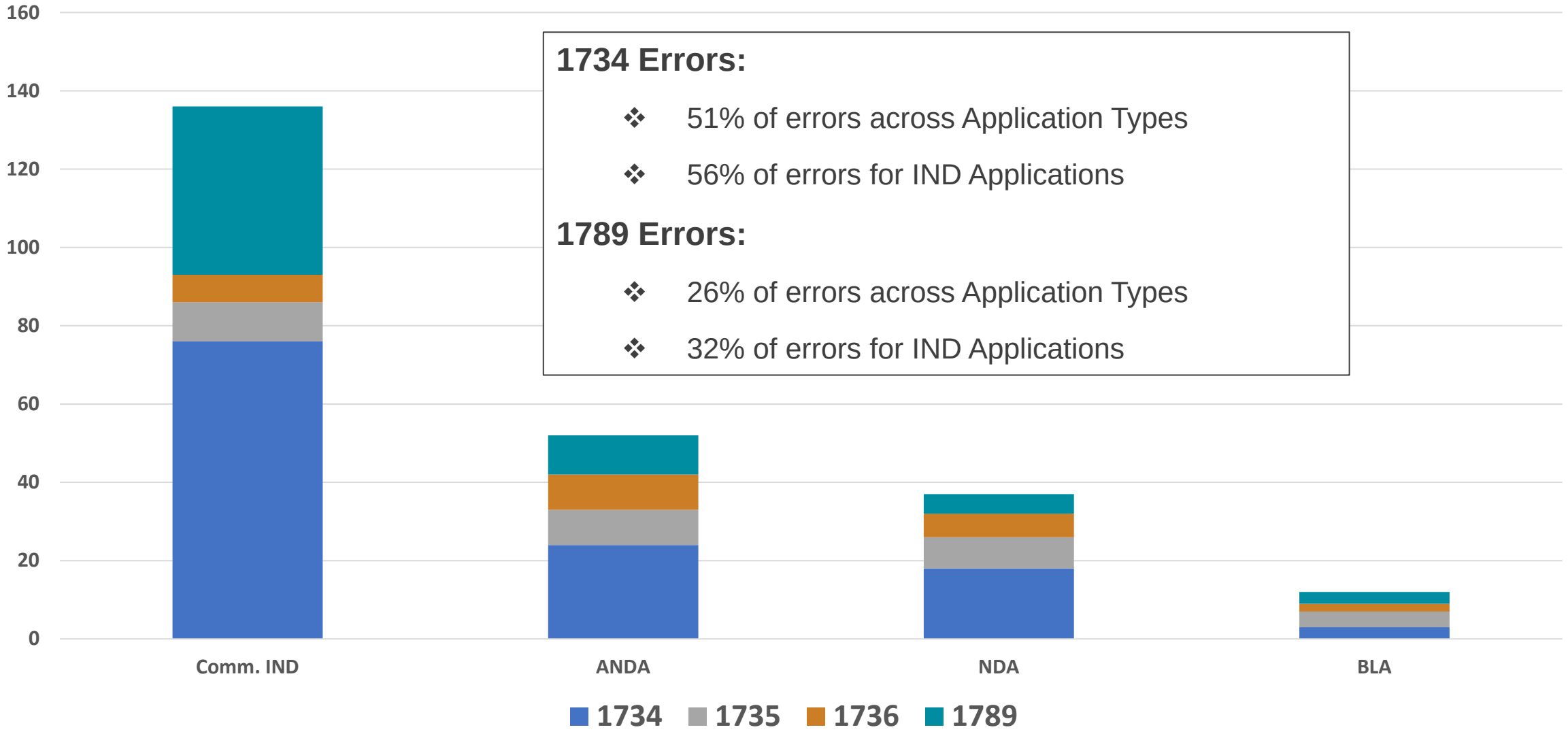
- 4.2.3.1, 4.2.3.2, 4.2.3.4
- 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2

Error	Description	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	

Trend of TRC Warnings & Rejections



Top TRC Rejection Errors



1734 Errors:

- 51% of errors across Application Types
- 56% of errors for IND Applications

1789 Errors:

- 26% of errors across Application Types
- 32% of errors for IND Applications

Timeframe: September 15 – December 31, 2021

Note: Submissions with multiple, different errors are counted more than once

Addressing Top Errors: 1734

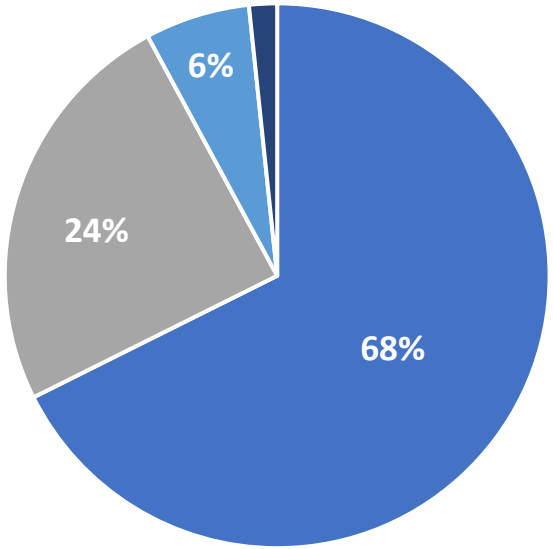
- **51% of errors across Application Types**
- **56% of errors for IND Applications**

1734 Validation

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

24% due to Study ID Mismatch



68% due to Missing ts.xpt

87% of Missing ts.xpt 1734 Errors are for Non-Clinical Studies in M4

- No ts.xpt found for this study
- Study ID in ts.xpt does not match study ID from STF
- No ts.xpt with value for SSD found (and no null flavor value)
- Study start date is incorrectly formatted and TSVALNF has no null flavor value

Note: 241 1734 Study Errors between Sept. 15 – Dec. 31, 2021

Verifying Study Data Expectations for Rules 1734, 1735, & 1736

Table 1: eCTD Technical Rejection Criteria for Study Data Expectations

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

Table 1 found in the Technical Rejection Criteria for Study Data document:
https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

Verifying Study Data Expectations for Rules 1734, 1735, & 1736

Table 1: eCTD Technical Rejection Criteria for Study Data Expectations

Study Start Date	Application Type	Data Type	Study Sections	Expectation by Center	
				CDER	CBER
After 17-Dec-2016	NDA, BLA,ANDA	Non-clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; submit a full TS	Rejection criteria will not be applied
		Clinical	5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	Rejection criteria will be applied; submit a full TS	
After 17-Dec-2017	Commercial INDs	Non-clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; submit a full TS	Rejection criteria will not be applied
		Clinical	5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	Rejection criteria will not be applied	

Table 1 found in the Technical Rejection Criteria for Study Data document:
https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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.*

✓ Self-Check Worksheet and tools for creating a simplified ts.xpt can be found: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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 Top Errors: 1789

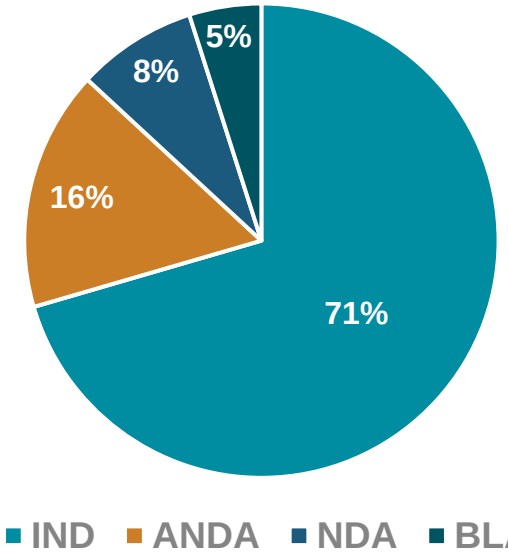
- **26% of errors across Application Types**
- **32% of errors for IND Applications**

1789 Validation:

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)

16% of all 1789 Errors for ANDA Applications

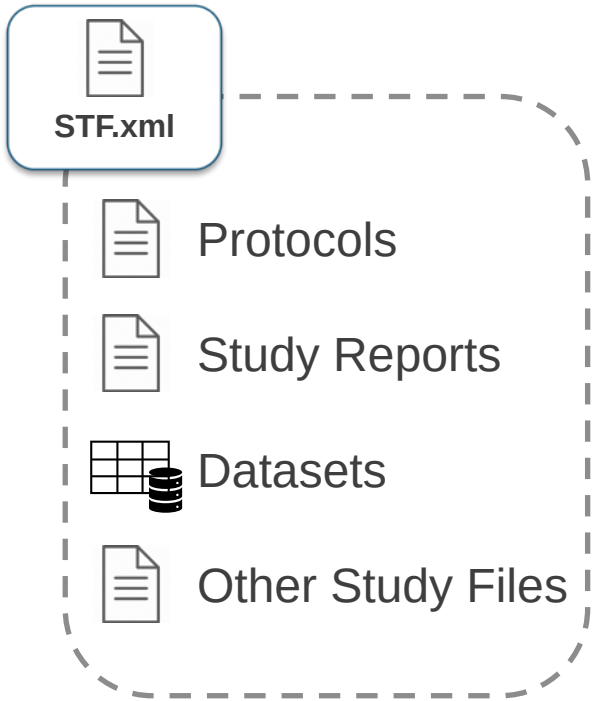


71% of all 1789 Errors for IND Applications

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.

Note: 61 1789 Submission Errors between Sept. 15 – Dec. 31, 2021

1789 & STF Files



Study Tagging Files:

- Identify and link together all files associated with a study
- index.xml and us-regional.xml do not contain enough information on the subject matter of several documents (e.g., study report documents) to support certain regulatory uses
- An STF must be provided with the submission of any file or group of files belonging to a study in Modules 4 and 5.
- The STF provides for additional heading elements, *file-tags*, and heading attributes not currently provided by the eCTD DTD

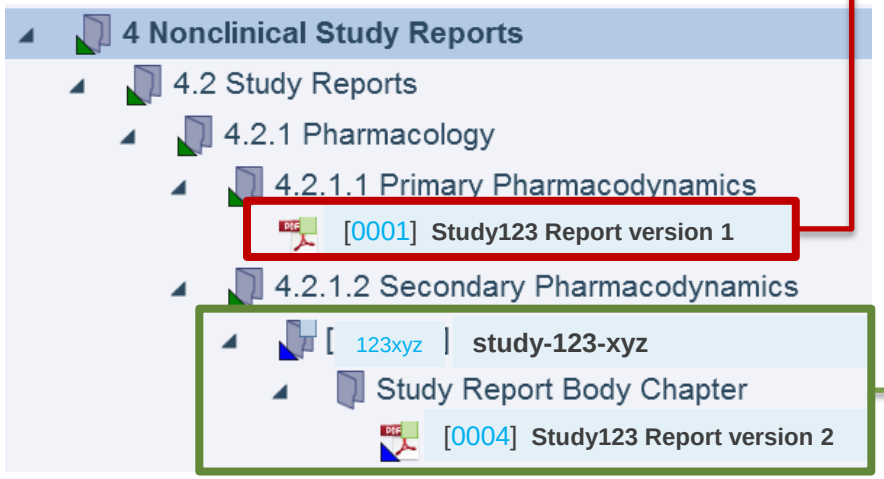
ICH Study Tagging File Specification

Impacts & Improvements from Standardized Study Data

Why is 1789 important?

Each study has its own stf.xml file with a unique study id and study title. When files are not referenced in a study tagging file they will not be connected to a specific study and may lead to reviewers not being able to find or review the data.

eCTD Viewer:

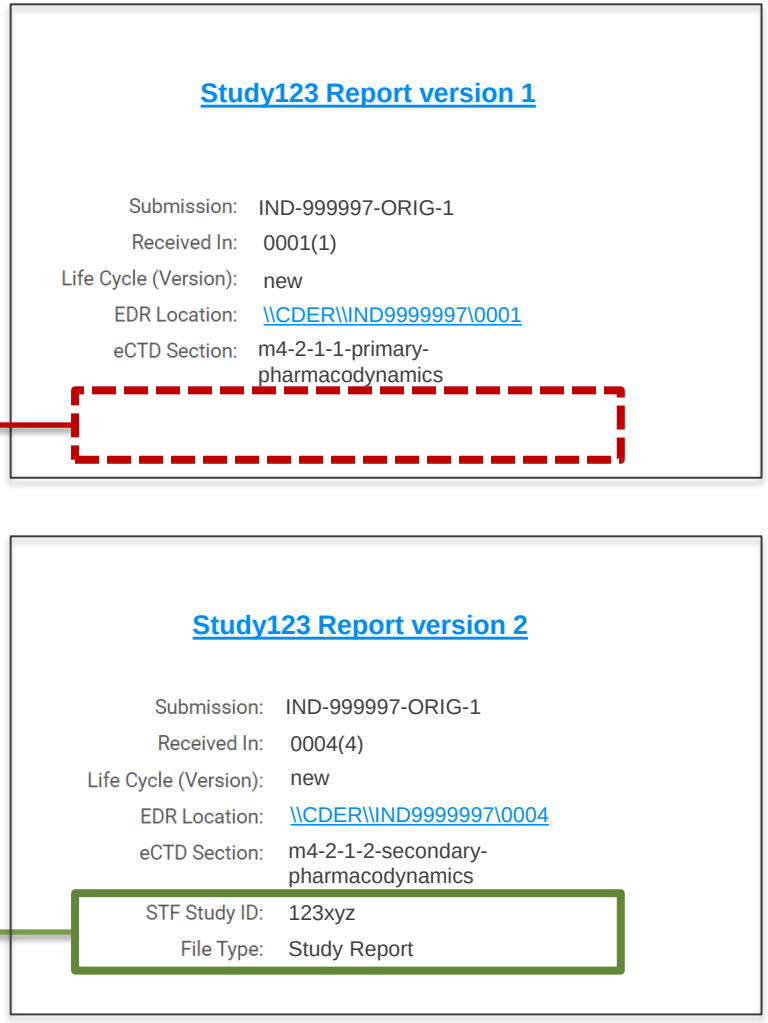


Unorganized and not connected to a study

Organized by Study Title and ID

File Tags indicate file types

Search:

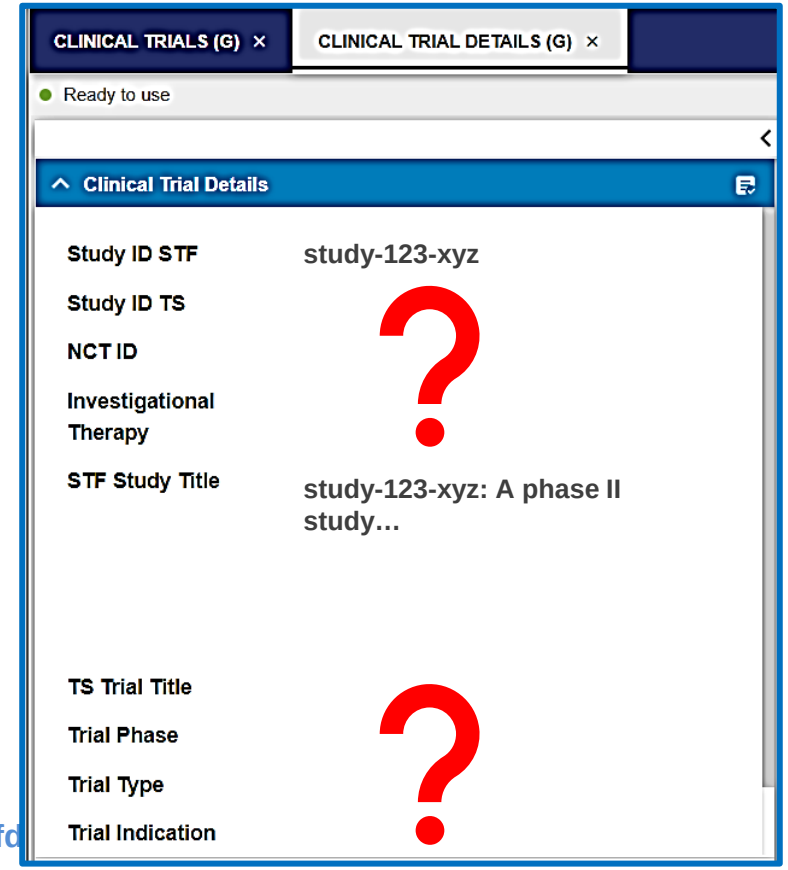


Why is 1734 important?

Missing ts.xpt:

X Can't determine the study start date, if TRC applies and whether standardized datasets are required

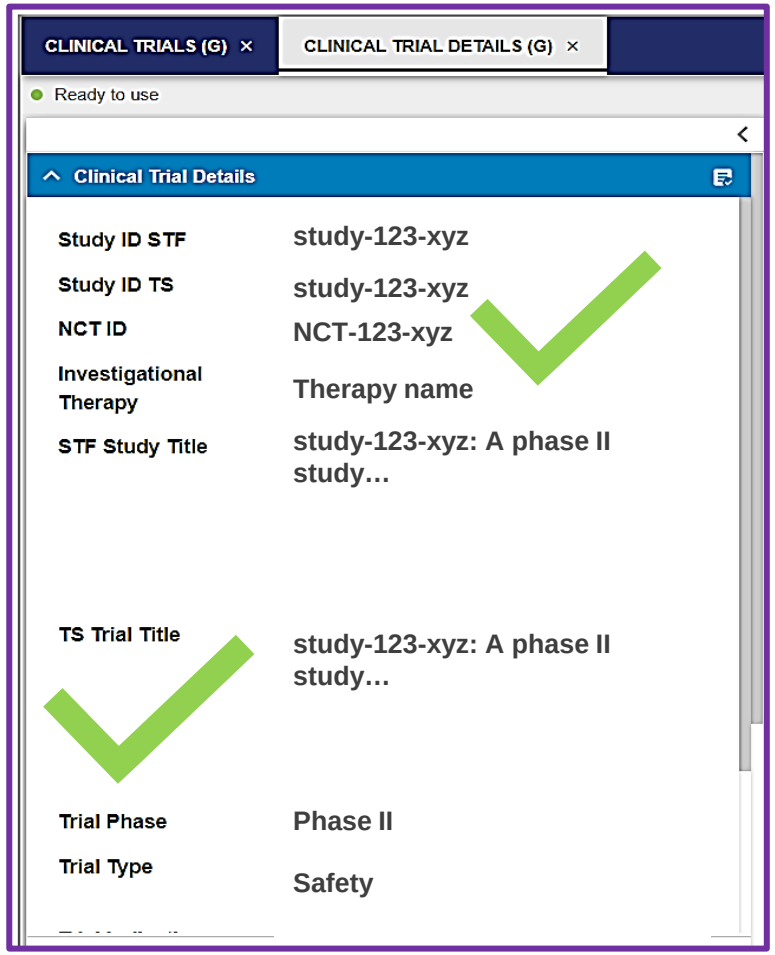
X Cannot connect to other clinical trial data and limits details available to reviewers



When a ts.xpt is included:

✓ Enables detailed searches

✓ Enables connections between data sources, such as ClinicalTrials.gov using NCT number



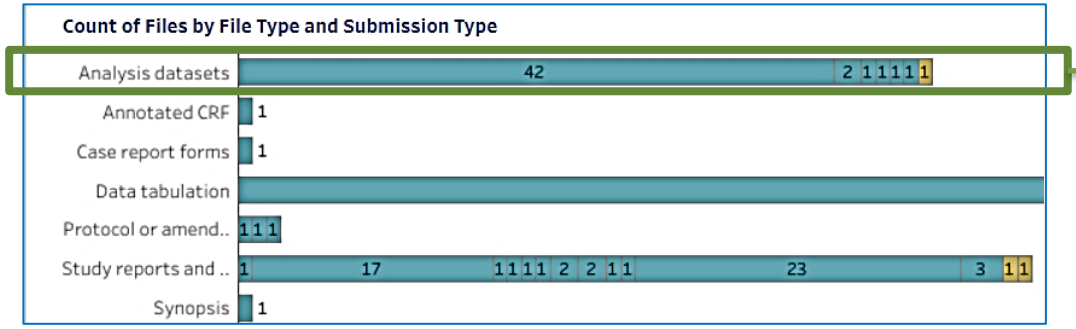
Why are 1735 & 1736 important?

File tags act as standardized sub-headings within a study to help distinguish and group files based on content.

When datasets are provided and tagged correctly:

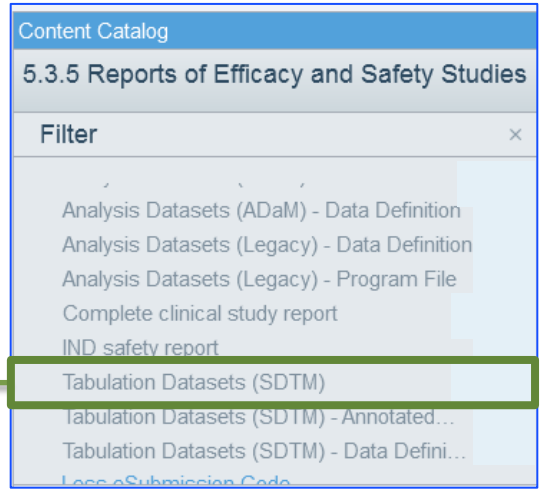
- ✓ Enables detailed searches by file type
- ✓ Enables filtering by file type
- ✓ Enables locating essential study files, including dm.xpt, adsl.xpt, and define.xml
- ✓ Enables automated loading into analysis applications

Reports & Filtering:

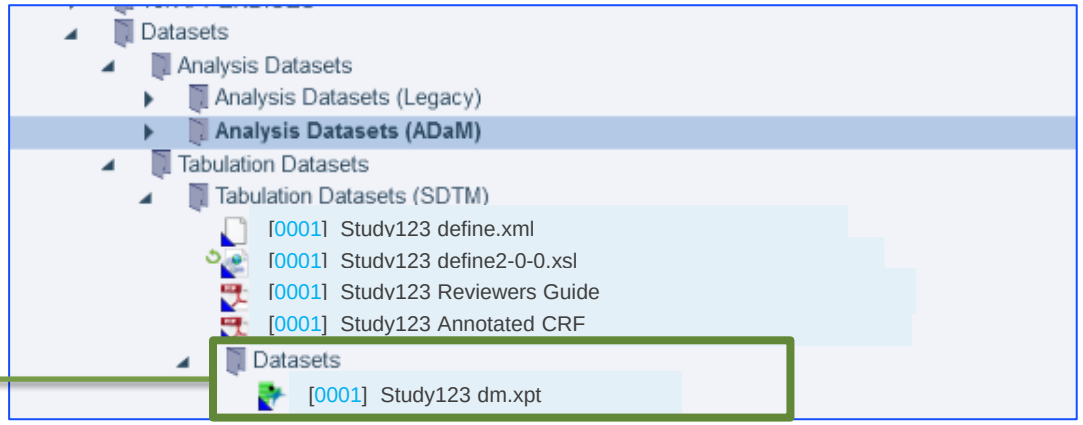


ADaM Datasets Grouped

eCTD Viewer:



SDTM Datasets Grouped



References

- **Study Data Standards Resources**
  - Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [June 2021]
  - Study Data Technical Conformance Guide [September 2021]
  - FDA Data Standards Catalog [September 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 [August 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

- **Electronic Common Technical Document (eCTD)**
  - Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications: Guidance for Industry [February 2020]
  - eCTD Submission Standards [October 2021]
  - Specifications for eCTD Validation Criteria [August 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

Thank You

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Questions?
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