

FDA Study Data Technical Rejection Update

PDUFA VI
Quarterly Meeting

April 12, 2022

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:**

- CDER & CBER Clinical Studies
 - NDA, BLA, ANDA studies that started after December 17th, 2016
- CDER Non-clinical Studies
 - NDA, BLA, ANDA studies that started after December 17th, 2016
 - Commercial IND studies that started after December 17th, 2017
- CBER Non-clinical studies
 - NDA, BLA, ANDA, and Commercial IND studies that started after March 15, 2023

❖ **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 Specification for eCTD Validation Criteria.

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

- ❖ [Study Data Technical Conformance Guide](#) – Latest update March 2022
- ❖ [Study Data for Submission to CDER and CBER website](#)

eCTD Validation Updates

- Study Data Validation Effective Date updated:
9/15/2021 (CBER module 4 sections, 03/16/2023)

Error	Description
1734	A dataset named ts.xpt with information on study start date must be present for each study in required sections*
1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*
1736	For SEND data, DM dataset and define.xml must be submitted in Module 4 required sections* For SDTM data, DM dataset and define.xml must be submitted in Module 5 required sections* For ADaM data, ADSL dataset and define.xml must be submitted in Module 5 required sections*
1737	For each study in required sections, no more than one dataset of the same name should be submitted as new*

* 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

Please review [eCTD Validation Specification](#) all details are not included in this presentation

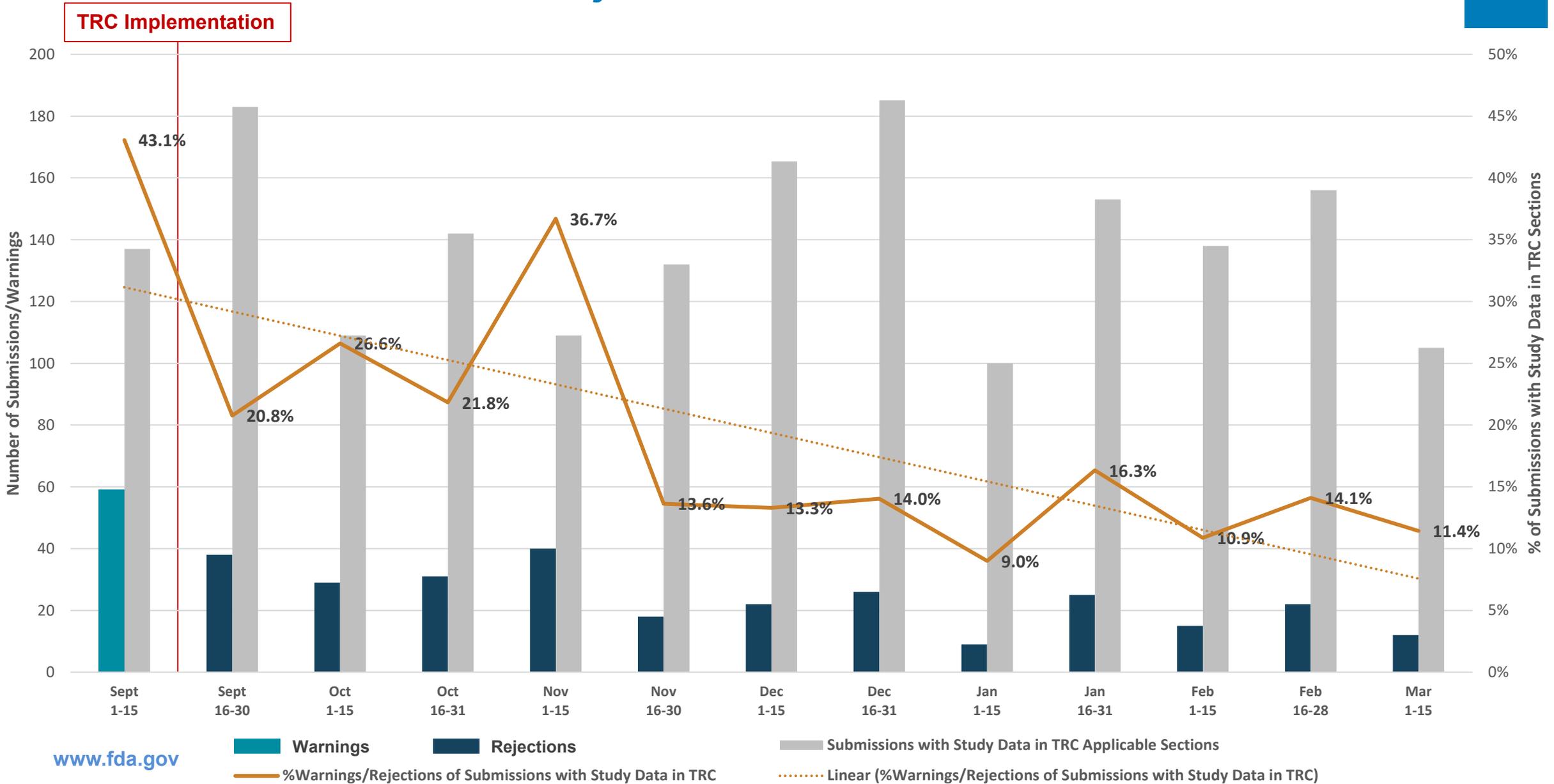
eCTD Validation Updates

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

Error	Description
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

- ❖ 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

CDER Trend of TRC Rejections



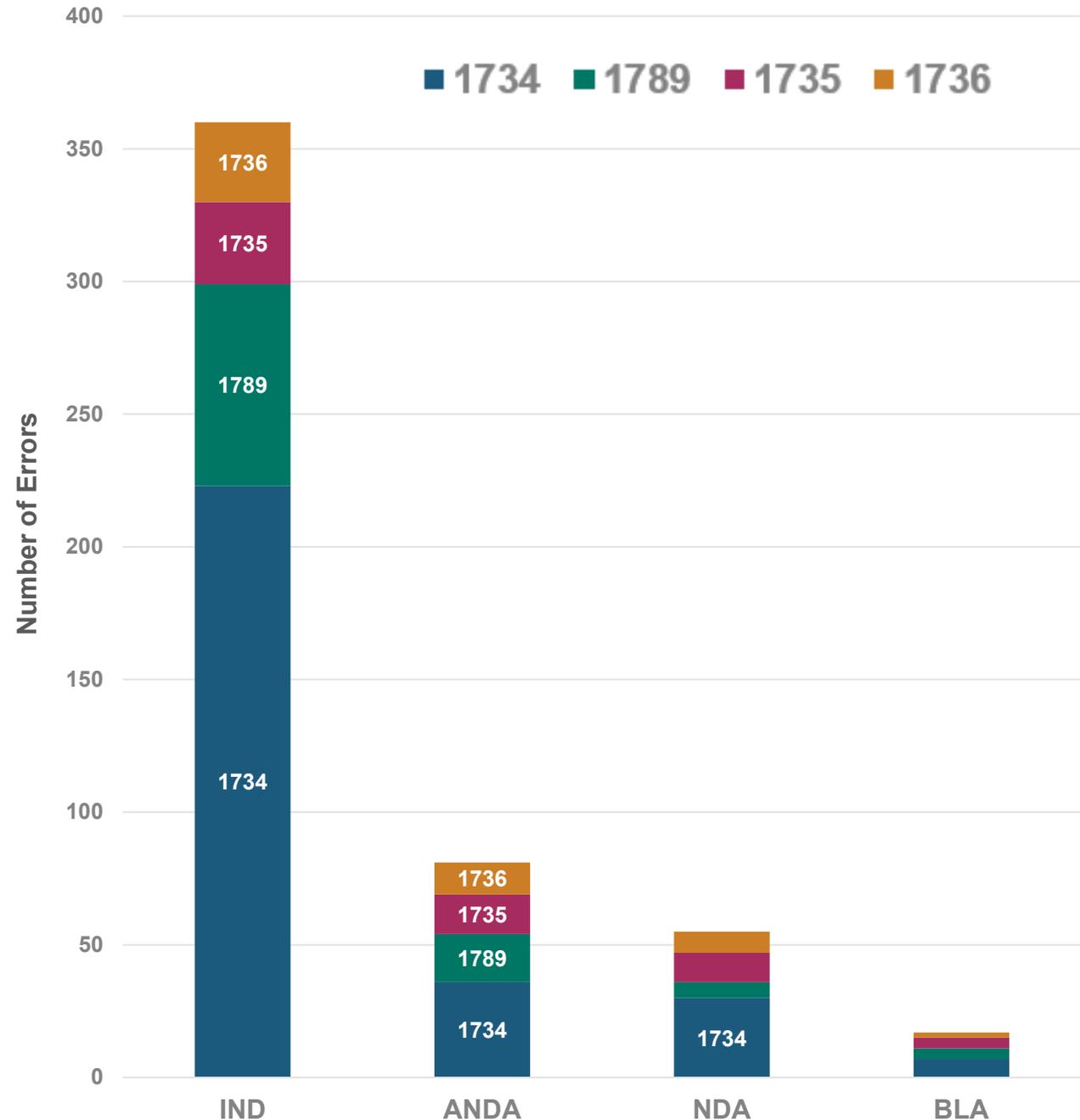
CDER TRC Rejections



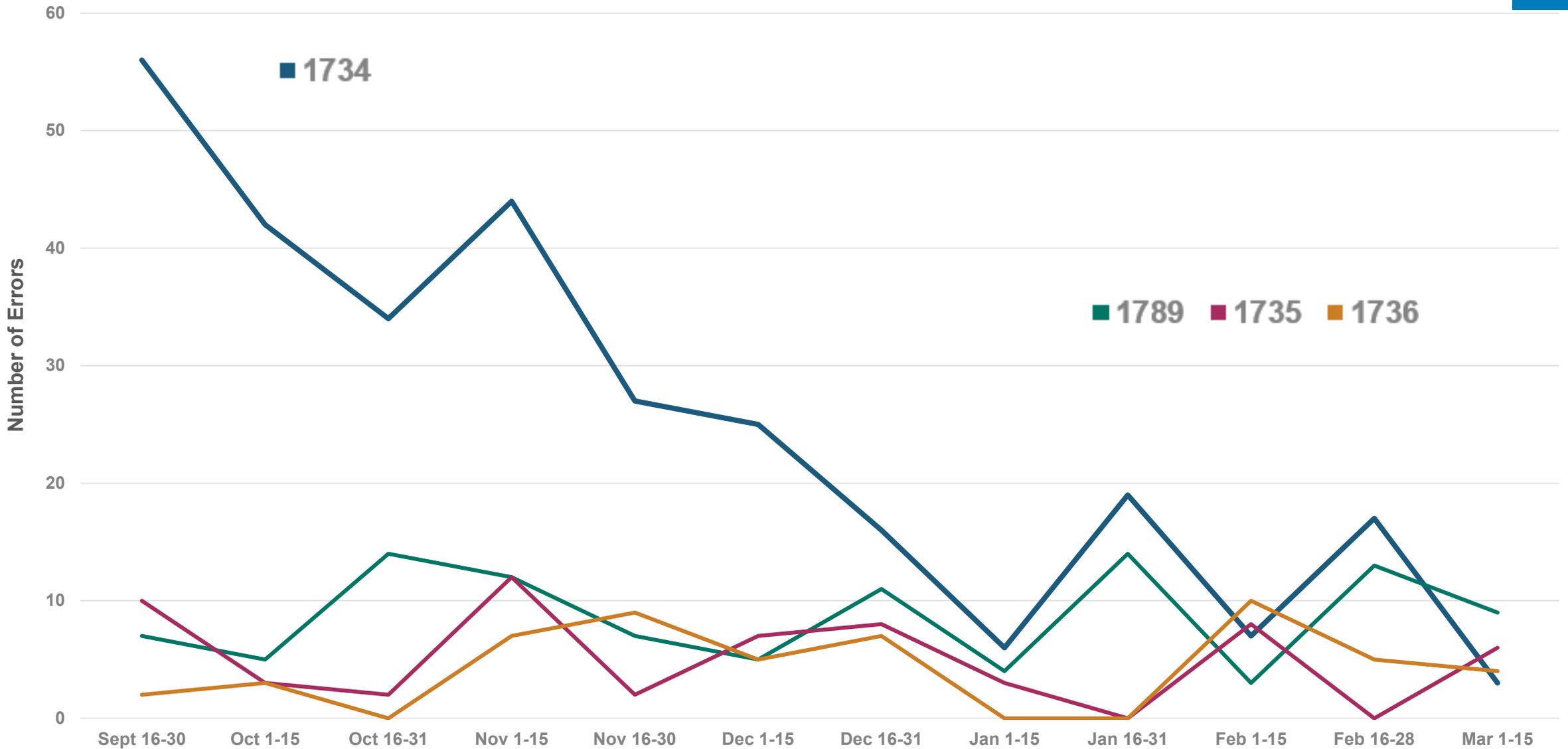
- ❖ 1734 is the most common error and failure reason for all application types for a missing ts.xpt
- ❖ 1789 is the second most common error and failure reason
- ❖ Commercial IND submissions have highest number of failures overall and have particularly high numbers of both 1734 and 1789 errors

Notes: Metrics generated from data between September 15, 2021 and March 15, 2022

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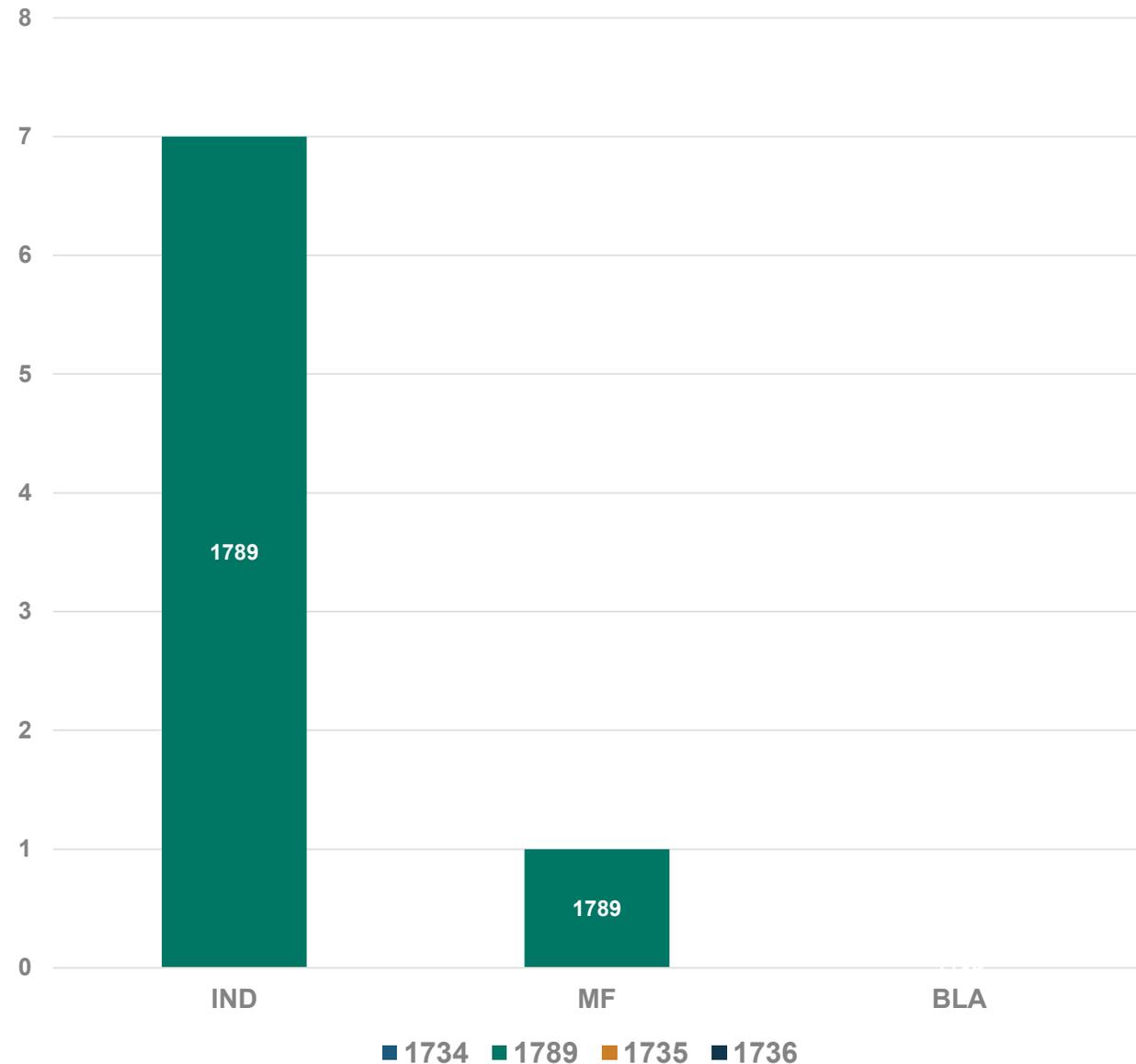


CDER Trend by Error Reason



CBER Study Rejections (Total)

- ❖ 1789 has been the only study data validation rejected upon for CBER



Notes: Metrics generated from data between September 15, 2021 and March 15, 2022

Addressing Top Errors: 1734

❖ 58% of errors across Application Types

❖ 62% of errors for IND Applications

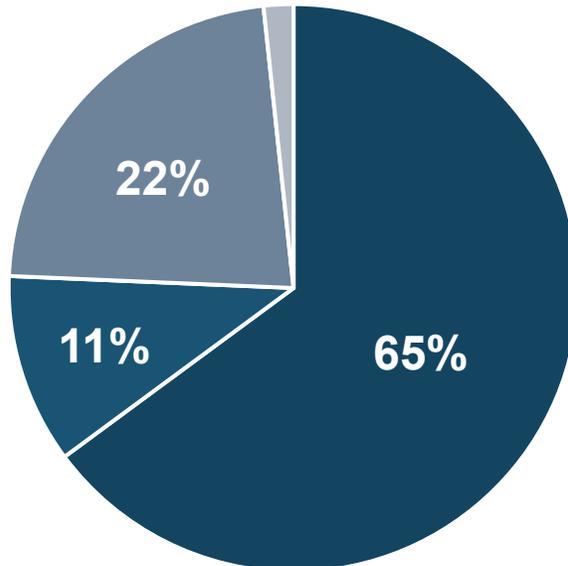
1734 Validation

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 TSVLNF = NA)
- ✓ Study start date is in a valid format

22% due to Study ID Mismatch



65% due to Missing ts.xpt



86% 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 TSVLNF has no null flavor value

VERIFYING STUDY DATA EXPECTATIONS FOR RULES 1734, 1735, & 1736



Application Type	Data Type	Modules & Sub-Modules	Expectation by CDER	Expectation by CBER
NDA, BLA, ANDA	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	<i>Study Start Date: On or prior to 2016-12-17</i> 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)	<i>Study Start Date: On or prior to 2023-03-15</i> 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)
NDA, BLA, ANDA	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	<i>Study Start Date: On or prior to 2016-12-17</i> Rejection criteria will be applied; submit a simplified TS if the study contains an xpt dataset (other than the ts.xpt)	
Comm. INDs	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	<i>Study Start Date: On or prior to 2017-12-17</i> 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)	<i>Study Start Date: On or prior to 2023-03-15</i> 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)
Comm. INDs	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	<i>Study Start Date: On or prior to 2017-12-17</i> Rejection criteria will not be applied	
NDA, BLA, ANDA	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	<i>Study Start Date: After 2016-12-17</i> Rejection criteria will be applied; submit a full TS	<i>Study Start Date: After 2023-03-15</i> Rejection criteria will be applied; submit a full TS
NDA, BLA, ANDA	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	<i>Study Start Date: After 2016-12-17</i> Rejection criteria will be applied; submit a full TS with standardized data	
Comm. INDs	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	<i>Study Start Date: After 2017-12-17</i> Rejection criteria will be applied; submit a full TS	<i>Study Start Date: After 2023-03-15</i> Rejection criteria will be applied; submit a full TS
Comm. INDs	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	<i>Study Start Date: After 2017-12-17</i> Rejection criteria will not be applied	

Addressing Top Errors: 1789

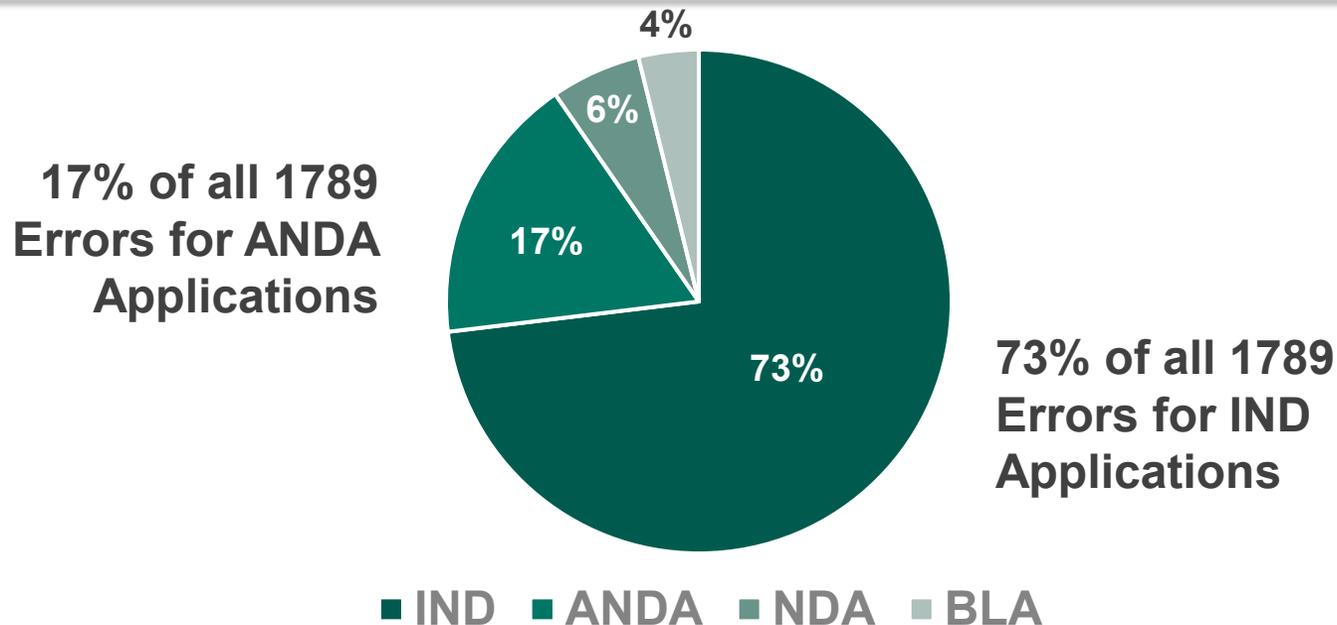
- ❖ 20% of errors across Application Types
- ❖ 21% of errors for IND Applications

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)



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.



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.

Search:

SUBMISSIONS

[Study123 Report version 1](#)

Submission: IND-999997-ORIG-1
Received In: 0001(1)
Life Cycle (Version): new
EDR Location: [\CDER\IND9999997\0001](#)
eCTD Section: m4-2-1-1-primary-pharmacodynamics

SUBMISSIONS

[Study123 Report version 2](#)

Submission: IND-999997-ORIG-1
Received In: 0004(4)
Life Cycle (Version): new
EDR Location: [\CDER\IND9999997\0004](#)
eCTD Section: m4-2-1-2-secondary-pharmacodynamics

STF Study ID: 123xyz
File Type: Study Report

eCTD Viewer:

- 4 Nonclinical Study Reports
 - 4.2 Study Reports
 - 4.2.1 Pharmacology
 - 4.2.1.1 Primary Pharmacodynamics
 - [0001] Study123 Report version 1
 - 4.2.1.2 Secondary Pharmacodynamics
 - [123xyz | study-123-xyz
 - Study Report Body Chapter
 - [0004] Study123 Report version 2

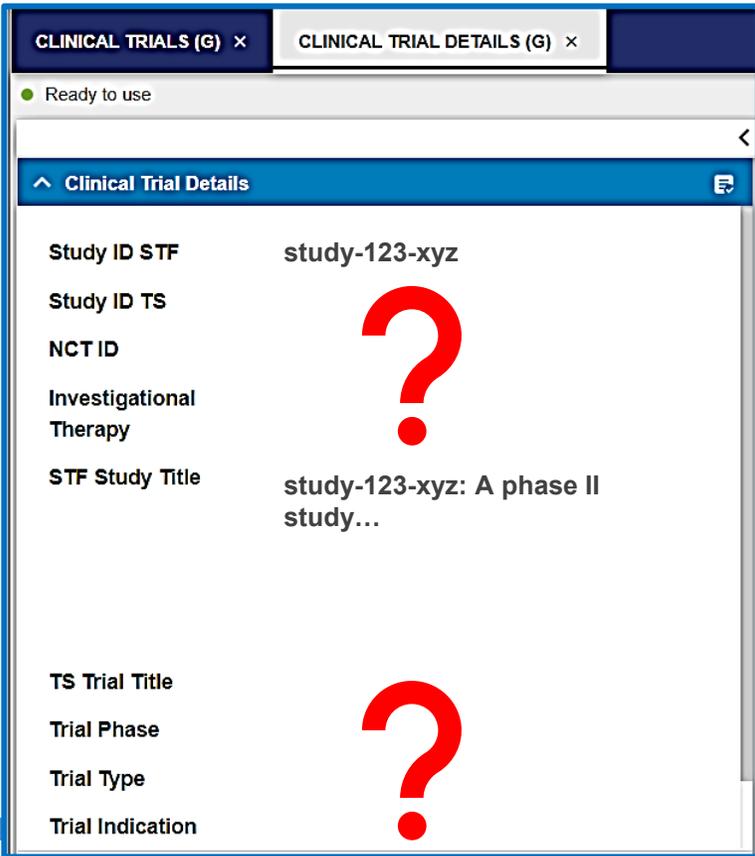
Unorganized and not connected to a study

Organized by Study Title and ID
File Tags indicate file types

Why is 1734 important?

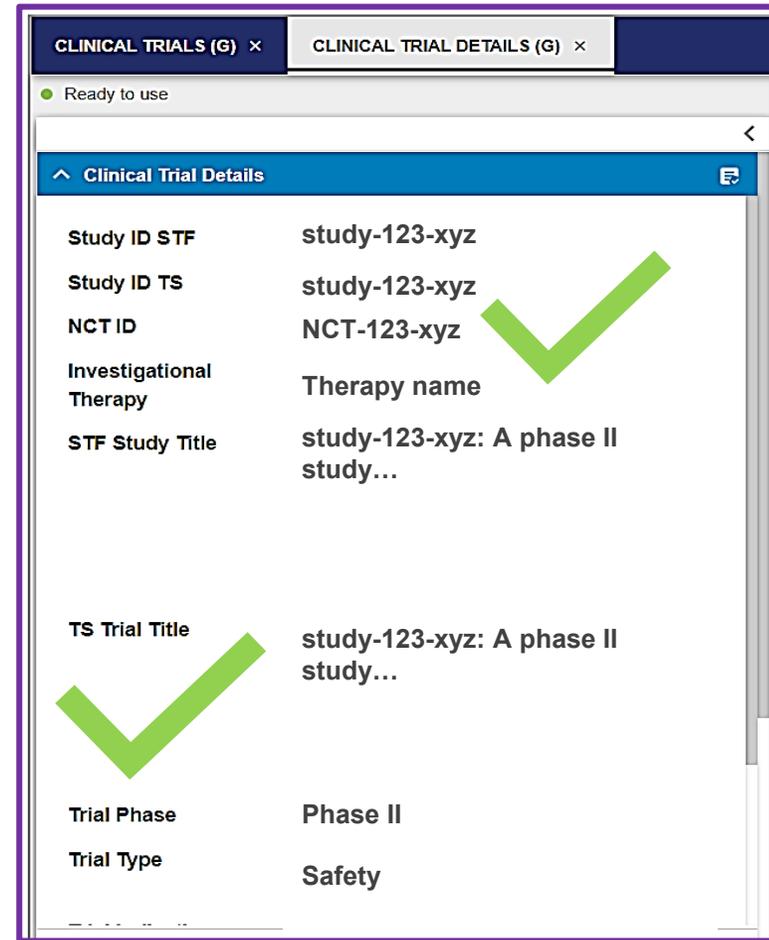
Missing ts.xpt:

- 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:

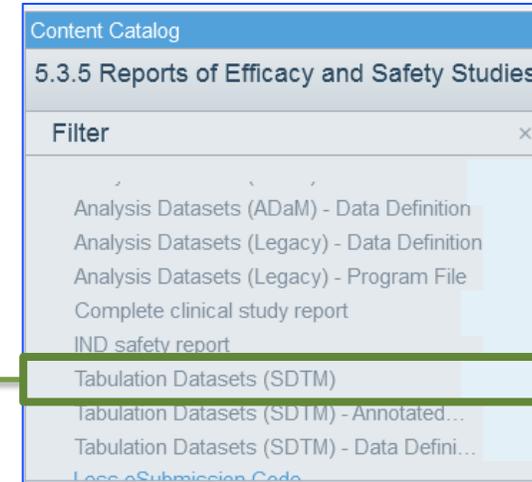
- ✓ Enables detailed searches by file type
- ✓ Enables filtering by file type
- ✓ Enables locating essential study files, including dm.xpt, adsl.xpt, and define.xml
- ✓ Enables automated loading into analysis applications

Reports & Filtering:

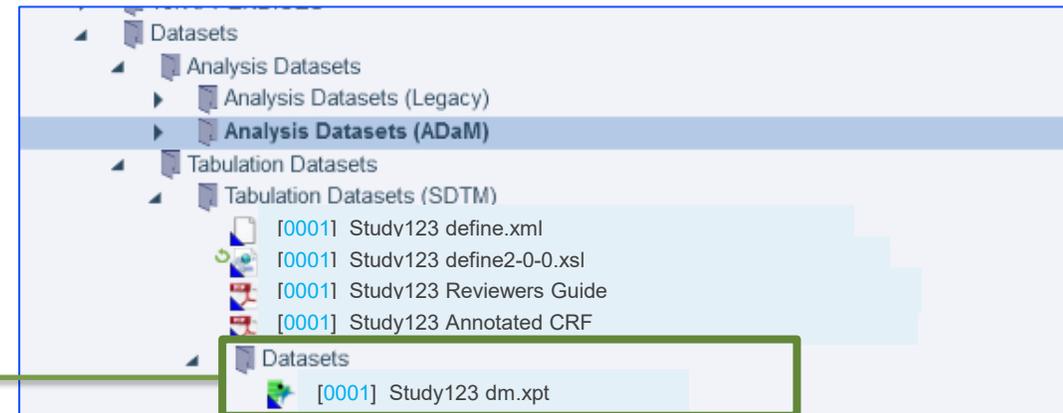
Count of Files by File Type and Submission Type	
Analysis datasets	42
Annotated CRF	1
Case report forms	1
Data tabulation	
Protocol or amend...	1111
Study reports and ...	1 17 1111 2 2 11 23 3 11
Synopsis	1

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 [March 2022]
- 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 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 [March 2022]
- Specifications for eCTD Validation Criteria [March 2022]
- 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>