U.S. FOOD & DRUG ADMINISTRATION

Study Data Technical Rejection Criteria

SEND F2F Spring 2023

Public Meeting

April 19th, 2023

FDA Disclaimer

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Agenda

- Technical Rejection Criteria for Study Data (TRC)
- TRC Conformance Statistics and Trends
- Addressing the Most Common TRC Error

Technical Rejection Criteria for Study Data (TRC)

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 15th, 2023
- **FDA uses eCTD validations (1734, 1735, 1736)** 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:

- Study Data Standards Resources
  - Study Data Technical Conformance Guide_v5.1_March 2023 (fda.gov)
  - Data Standards Catalog v9.0 (January 2023)
- Electronic Common Technical Document (eCTD) website
- Study Data for Submission to CDER and CBER website

TRC is located within the Study Data Technical Conformance Guide

eCTD Validation Updates (Effective on 3/16/2023)

TRC Updates

1. **CBER SEND Date Requirements**
   - CBER now requires SEND datasets for non-clinical studies with a Study Start Date after 3/15/2023
   - Date applies to all application types
2. **1734 – Remove Study ID Matching**
   - 1734 no longer validates for STUDYID mismatch between ts.xpt and STF file
   - New validation rule 1738 now validates STUDYID matching
3. **1735 – Allow define.xml Files to be Tagged as "data-listing-data-definition"**
   - A Define.xml file tagged as "data-listing-data-definition" no longer triggers a 1735 error

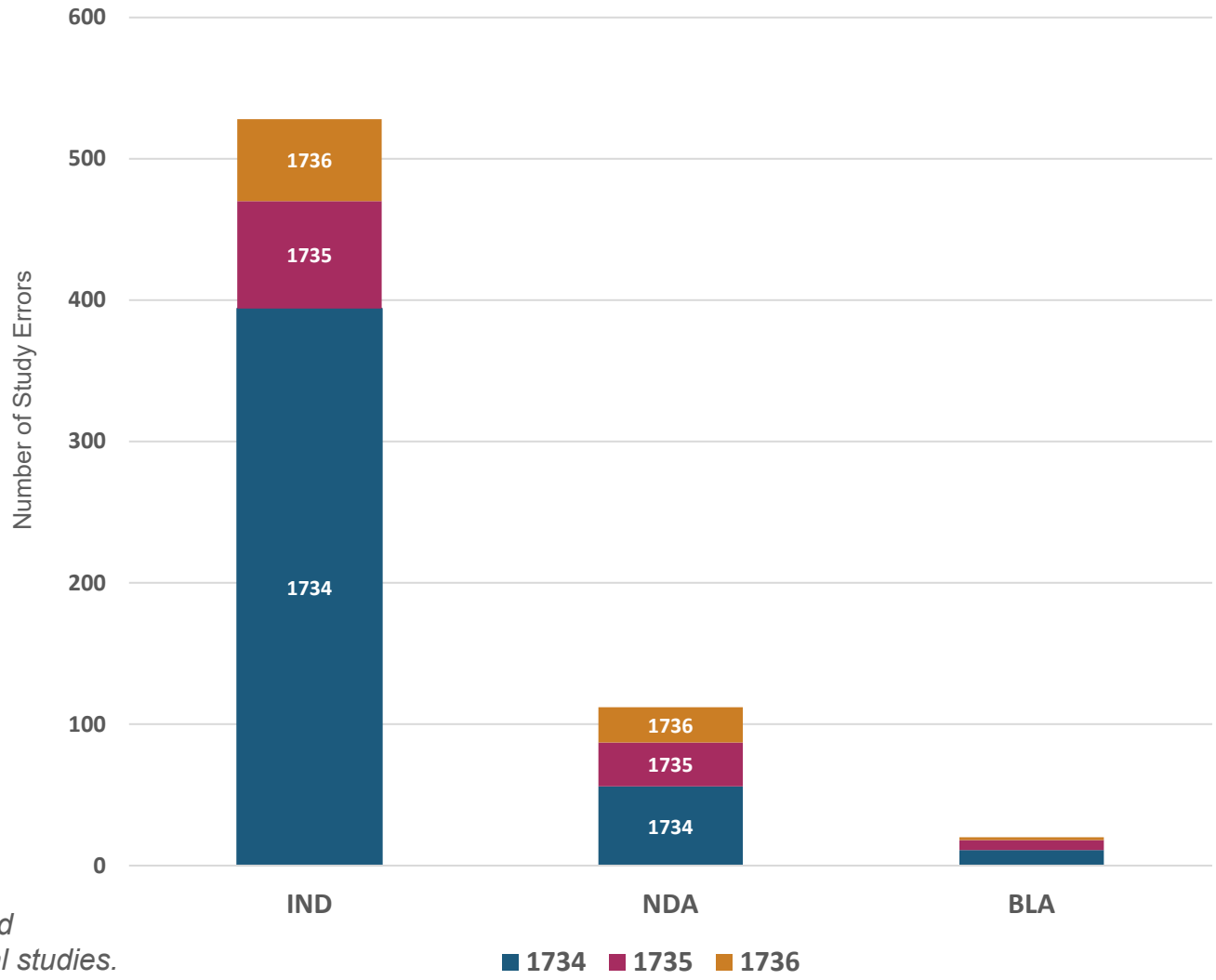
Other Study Data Validation Updates

1. **1737 – Apply Rule to All Sections Except 4.3, 5.2, 5.4, & 5.3.6**
   - 1737 now applies to same sections as validation rule 1789
   - Medium severity error
   - 1737 is not currently included in the Self-Check Worksheet
2. **1738 – New Study ID Matching Rule**
   - 1738 is not currently included in the Self-Check Worksheet
   - 1738 now validates for STUDYID mismatch between ts.xpt and STF file
   - Medium severity error
   - Applies to all sections except 4.3, 5.2, 5.4, & 5.3.6

TRC Conformance Statistics and Trends

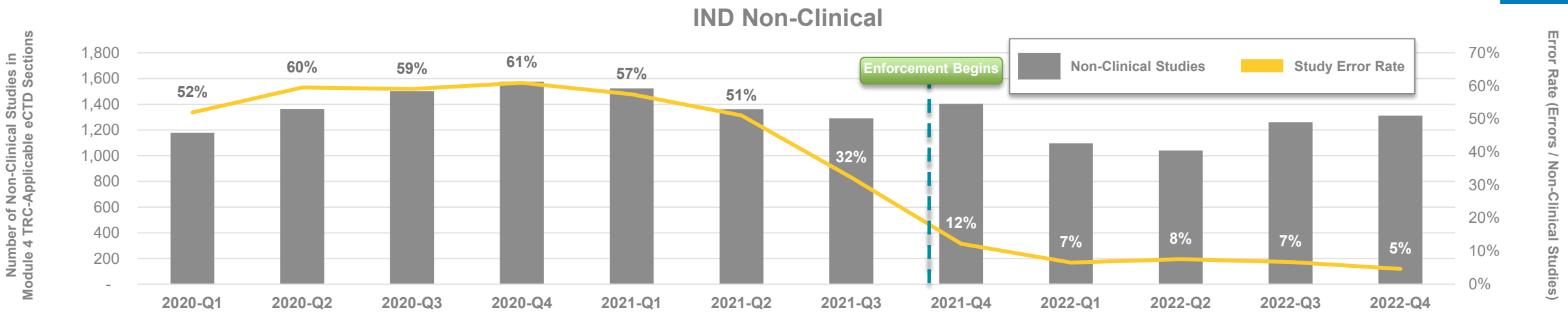
Rejected Submissions: February 15, 2022 – February 15, 2023

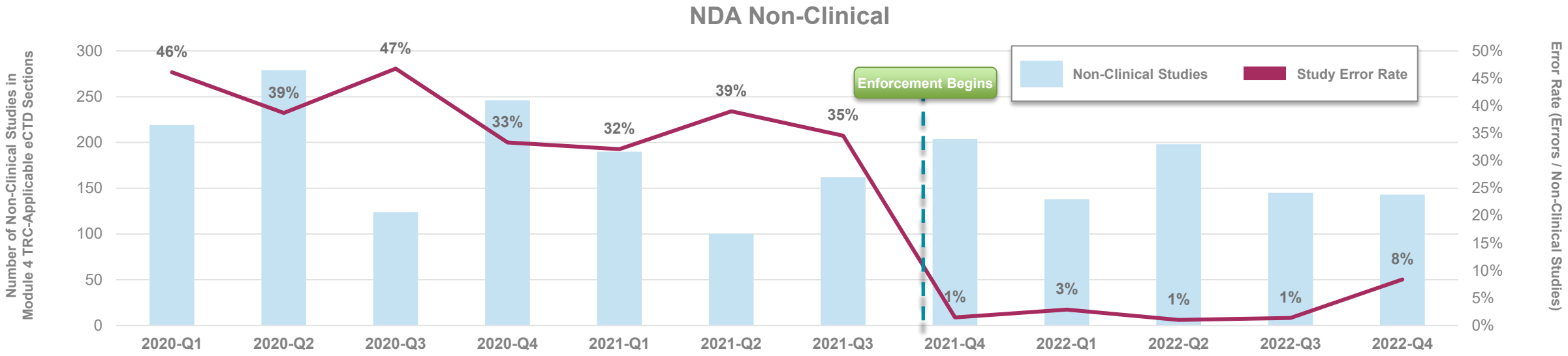
- 1734 is the most common error and rejection reason for a missing ts.xpt
- Commercial IND submissions have highest number of errors and rejections overall



Notes: *Metrics generated from data between February 15, 2022 and February 15, 2023 and includes both clinical and non-clinical studies.*

Trend of Non-Clinical Study Errors: 2020-2022





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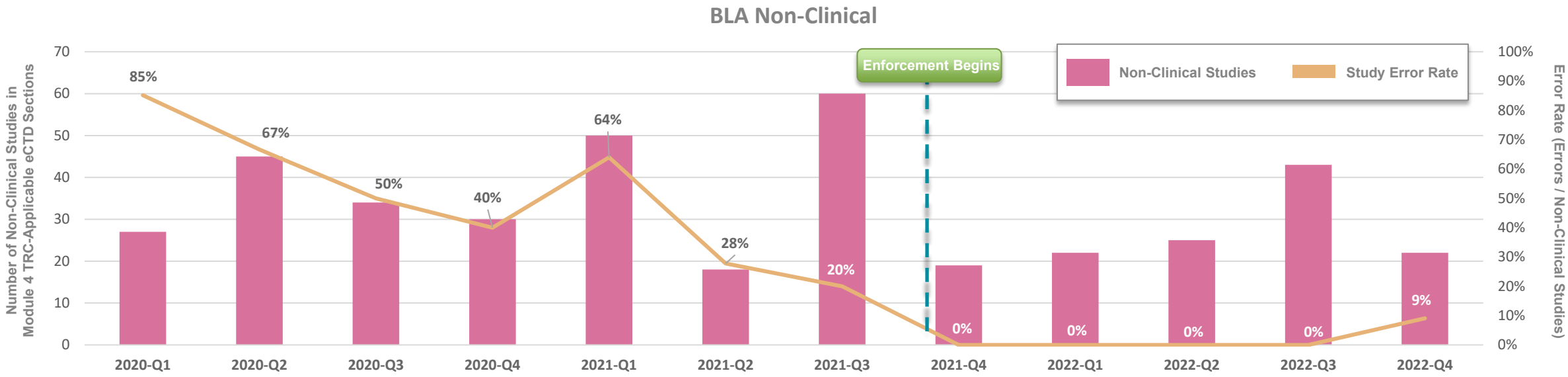
Timeframe: January 1, 2020 – December 31, 2022

Trend of Non-Clinical Study Errors: 2020-2022



Timeframe: January 1, 2020 – December 31, 2022

Addressing the Most Common TRC Error

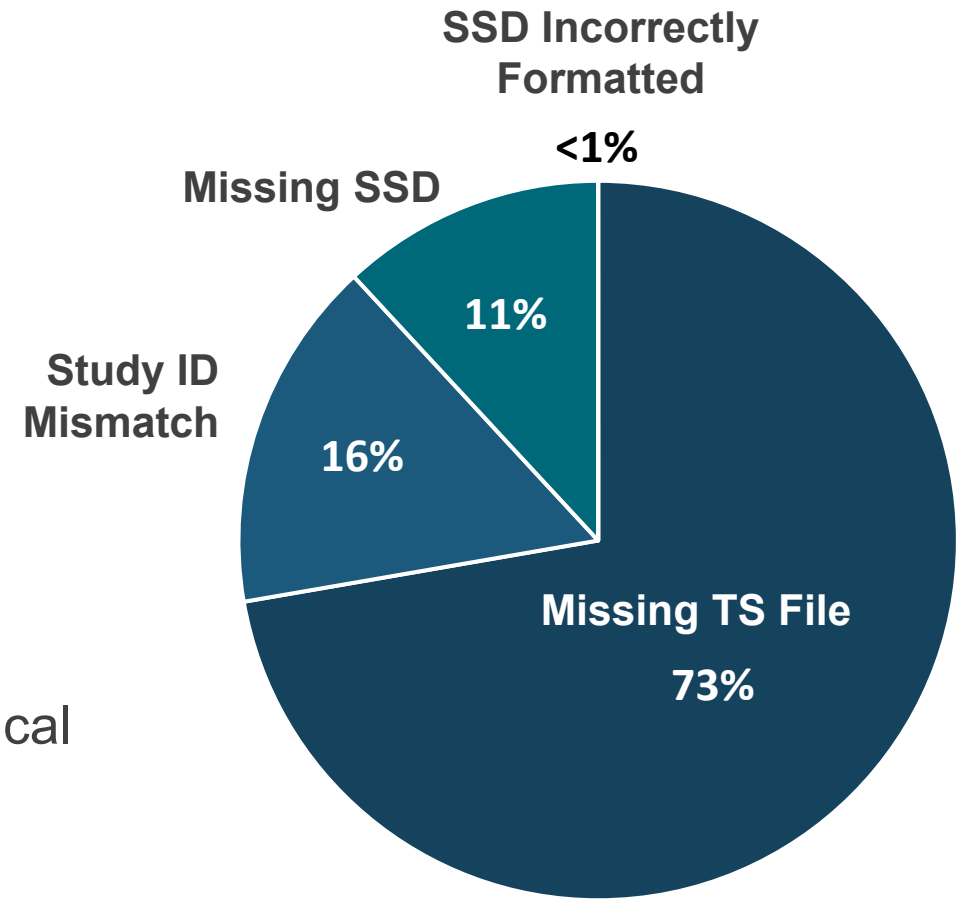
1734 Error Reasons: September 15, 2021 – February 15, 2023

- 453 IND, NDA & BLA non-clinical studies failed Rule 1734
- 73% (329 of 453) failed due to a missing ts.xpt
- 71% (322 of 453) were Repeat Dose Toxicology studies

Toxicology Sections	Count
Repeat dose toxicology (m4.2.3.2)	322
Single dose toxicology (m4.2.3.1)	100
Carcinogenicity (m4.2.3.4)	31
	453

- Submitting a simplified ts.xpt for many of these non-clinical studies will greatly reduce the 1734 error rate
- SEND datasets require a full ts.xpt

453 Non-clinical Studies with Error 1734:



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SSD = Study Start Date

Timeframe: September 15, 2021 – February 15, 2023

Addressing 1734 Errors: Missing TS File

- From the **Study Data Guidance** - *Providing Regulatory Submissions in Electronic Format -- Standardized Study Data (last updated June 2021)*
  - "…to ensure that FDA can assess whether sponsors and applicants are subject to particular study data format requirements, FDA must rely on information provided by the submitter about study start date and the file type being submitted. Generally, the datasets necessary to assess conformance to the standard include the demographic dataset file (SDTM and SEND dm.xpt), the subject level analysis dataset file (ADaM adsl.xpt), and the define.xml file (SDTM, SEND, and ADaM). For further details, see the ***Technical Rejection Criteria for Study Data, the Conformance Guide, and the Data Standards Catalog***."

Addressing 1734 Errors: Missing TS File

CDER and CBER expectations for standardized data:

Data Type	Modules & Submodules	Center	Application Type	Study Start Date	Requirement
Non-clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	CDER	NDA, BLA, ANDA	On/Prior to December 17, 2016	Submit simplified ts.xpt*
				After December 17, 2016	Comply with CDISC standards
			Commercial IND	On/Prior to December 17, 2017	Submit simplified ts.xpt*
				After December 17, 2017	Comply with CDISC standards
		CBER	NDA, BLA, ANDA, Commercial IND	On/Prior to March 15, 2023	Submit simplified ts.xpt*
				After March 15, 2023	Comply with CDISC standards
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	CDER & CBER	NDA, BLA, ANDA	On/Prior to December 17, 2016	Submit simplified ts.xpt if study contains an xpt dataset (other than ts.xpt)
				After December 17, 2016	Comply with CDISC standards
		CDER & CBER	Commercial IND	Rejection criteria not applied	

**Rejection criteria will be applied if a study report with one of the three file tags, 'pre-clinical-study-report', 'legacy-clinical-study-report', or 'study-report-body' is included , and/or an xpt file (other than the ts.xpt) is submitted.*

Addressing 1734 Errors: Missing TS File

- From the Study Data Technical Conformance Guide:
  - "When SEND is not submitted for reasons outlined under Section 4.1.3.4.1 (Scope of SEND for SENDIGs v3.0 and v3.1), use of a simplified ts.xpt file may be needed where the value “NA” (Not Applicable) should be populated in the TSVALNF field..."
  - Sponsors must submit a dataset named ‘ts.xpt’ with at least the variables (STUDYID, TSPARMCD, TSVAL, and/or TSVALNF) and one row of information. Example datasets are shown below:

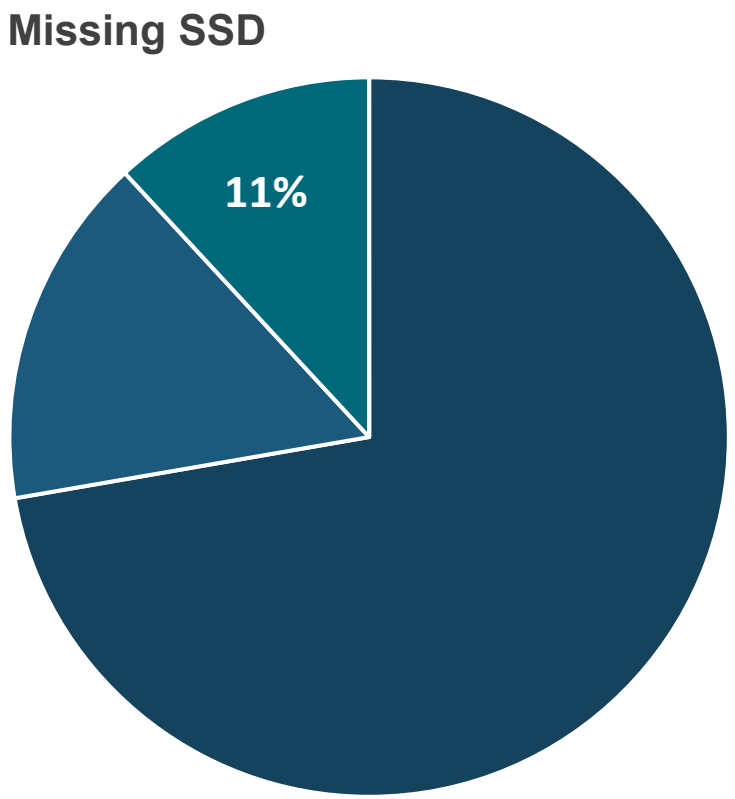
For a study with a valid SSD (example C):

STUDYID	TSPARMCD	TSVAL	TSVALNF
study ID in STF	STSTDTC	yyyy-mm-dd	

For a study without a valid SSD (example D):

STUDYID	TSPARMCD	TSVAL	TSVALNF
study ID in STF	STSTDTC		Use the value ‘NA’

Addressing 1734 Errors: Missing Study Start Date



Simplified ts.xpt when Study Start Date is available:

ts XPT

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	90-day-oral-tox-s...	STSTDTC	2018-06-14	

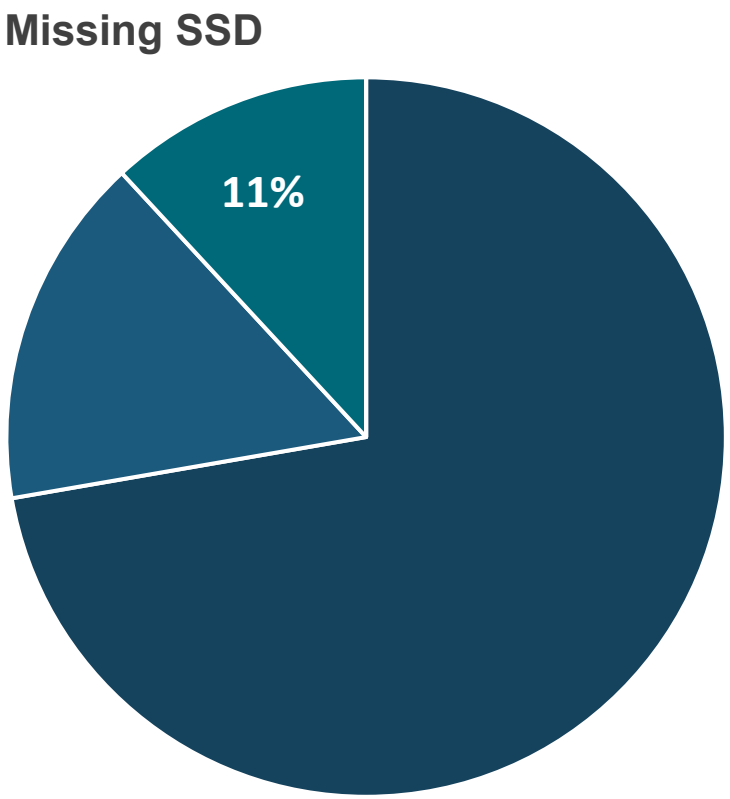
Causes of 1734 Missing Study Start Date:

- Missing value for SSD

ts XPT

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	90-day-oral-tox-s...	STSTDTC		

Addressing 1734 Errors: Missing Study Start Date



Simplified ts.xpt for when no Study Start Date is available:

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	90-day-oral-tox-s...	STSTDTC		NA

Causes of 1734 Missing Study Start Date:

- **Missing Parameter Code**

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	90-day-oral-tox-s...			NA

- **Incorrect Parameter Code**

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	90-day-oral-tox-s...	SSTDTC		NA

References

- **Study Data Standards Resources**
  - Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [April 2022]
  - Study Data Technical Conformance Guide [March 2023]
  - FDA Data Standards Catalog [August 2022]
  - 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 [December 2022]
  - Specifications for eCTD Validation Criteria [May 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

Questions

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  - eCTD: esubprep@fda.hhs.gov

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