U.S. FOOD & DRUG ADMINISTRATION

# Study Data Technical Rejection Criteria

SEND F2F Fall 2021

Public Meeting

November 3, 2021

# FDA Disclaimer

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# Agenda

- Technical Rejection Criteria for Study Data (TRC)
- FDA's Study Data Guidance and Requirements
- TRC Conformance Statistics and Trends
- Addressing the Most Common TRC Error
- 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 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. |

# FDA's Electronic Common Technical Document (eCTD) & Study Data Standards Web Pages

## Electronic Common Technical Document (eCTD)

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The eCTD is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

### Important Dates

Reminder: Per Providing Regulatory Submissions In Electronic Format — Standardized Study Data, Guidance for Industry, electronic submission of standardized study data is required for NDA, BLA, ANDA, and Commercial IND. FDA plans to implement eCTD validation checks when submissions contain content under modules 4 and 5 beginning **September 15, 2021**. Submissions which fail this validation will be subject to rejection. Please see the Technical Rejection Criteria for Study Data and the eCTD Validation Criteria (error code 1734, 1735, 1736, 1789) for details.

**Quick Links**

- NDA to BLA eCTD Transition Instruction to Industry (PDF - 90 KB)
- eCTD Guidance (Final, Rev 7) (PDF -11 KB)
- eCTD Submission Standards (v4.3) (PDF - 130 KB) **NEW**
- FDA Data Standards Catalog
- eCTD Technical Conformance Guide (PDF - 303 KB)
- Drug Master Files (DMFs)
- Technical Rejection Criteria for Study Data Information
- eCTD Submission Types and Sub-Types (PDF - 630 KB)

## Study Data Standards Resources

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Study data standards describe a standard way to exchange clinical and nonclinical study data. These standards provide a consistent general framework for organizing study data, including templates for datasets, standard names for variables, identify appropriate controlled terminology and standard ways of doing calculations with common variables. Data standards also help FDA receive, process, review, and archive submissions more efficiently and effectively.

**Quick Links**

- Data Standards Catalog v7.3 (September 14, 2021)
- Study Data Technical Conformance Guide v4.8 (September 2021)

This Study Data Resources page includes required items and helpful tools for submission of study data to FDA's Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH).

**1. FDA Data Standards Catalog**

FDA accepts electronic submissions that provide study data using the standards, formats, and terminologies described in the FDA Data Standards Catalog.

- FDA Data Standards Catalog v7.3 (XLS -73KB) (September 14, 2021)

# Updates to the Technical Rejection Criteria for Study Data

- Updated March 2021 to include the effective dates for implementation of the criteria
- Updated August 2021 to reference the Study Data Technical Conformance Guide for technical recommendations
- Published to the *Study Data for Submission to CDER and CBER* web page

**Technical Rejection Criteria for Study Data**

**Study data standards are required in clinical and nonclinical studies that start after December 17, 2016.[1] Technical rejection criteria have been added to the existing electronic common technical document (eCTD) validation criteria to determine compliance with the requirements for submitting standardized study data[2] and will be implemented on September 15, 2021.**

## Study Data for Submission to CDER and CBER

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Data standards enable FDA to modernize and streamline the review process. They also enable more consistent use of analysis tools to better view drug data and highlight areas of concern.

Study data standards describe a standard way to exchange clinical and nonclinical research data between computer systems. These standards provide a consistent general framework for organizing study data, including templates for datasets, standard names for variables, and standard ways of doing calculations with common variables.

FDA is instituting new requirements for data standards that will apply to most study data submitted to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

Beginning after the dates specified below, FDA may refuse to file for New Drug Applications (NDAs) and Biologics License Applications (BLAs) or refuse to receive for Abbreviated NDAs (ANDAs) any electronic submission whose study data do not conform to the required standards specified in the FDA Data Standards Catalog. See the Technical Rejection Criteria for Study Data (PDF) for more information. FDA conducted an analysis of study data conformance on submissions received during a

**Stay Connected**

If you have study data questions for CDER, please contact the CDER eDATA Team at cder-edata@fda.hhs.gov.

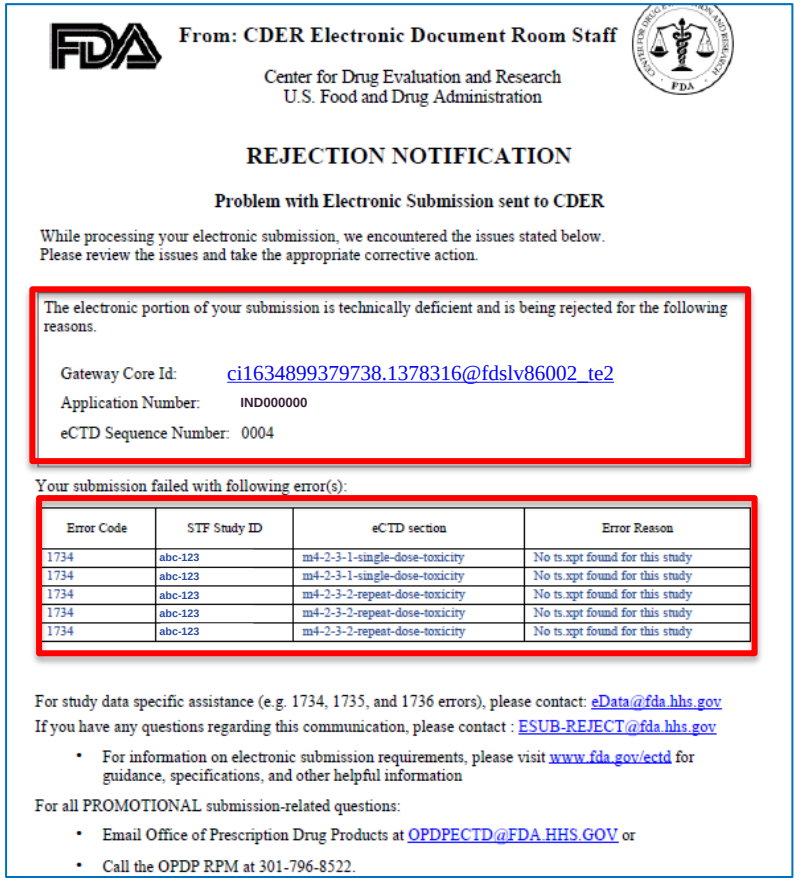
For electronic submissions, contact the CDER Electronic Submission (ESUB) Support Team at esub@fda.hhs.gov.

If you have study data questions for CBER, please contact CBER-edata@fda.hhs.gov.

For electronic submissions, contact CBER ESUB at esubprep@fda.hhs.gov.

# 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: ci1634899379738.1378316@fdslv86002_te2
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.

# FDA's Study Data Guidance and Requirements

# Purpose of eCTD and Study Data Requirements

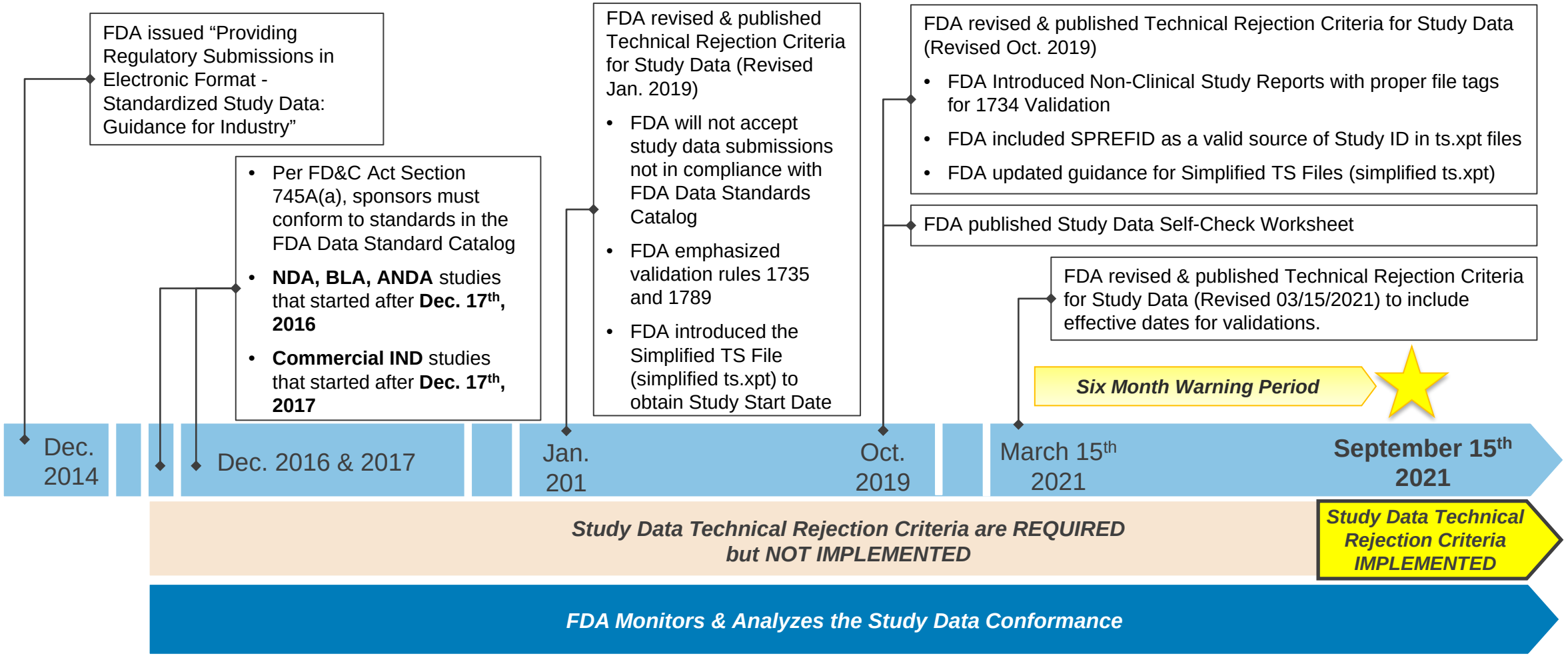
- Reviewing study data in a timely manner is critical for FDA's review process (e.g. Reviewers have 30 days to review an IND application)
- When sponsors submit data to the FDA in a reliable and accessible format, it improves efficiency and consistency of review decisions
- CDISC Standards enable FDA 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

# Technical Rejection Criteria Revisions Timeline

**September 15th 2021:** The eCTD validations listed in the Technical Rejection Criteria for Study Data became effective and FDA is rejecting submissions that fail these validations.



# Overview of Technical Rejection Criteria for Study Data

eCTD validation rule 1789 has a 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 for Study Data

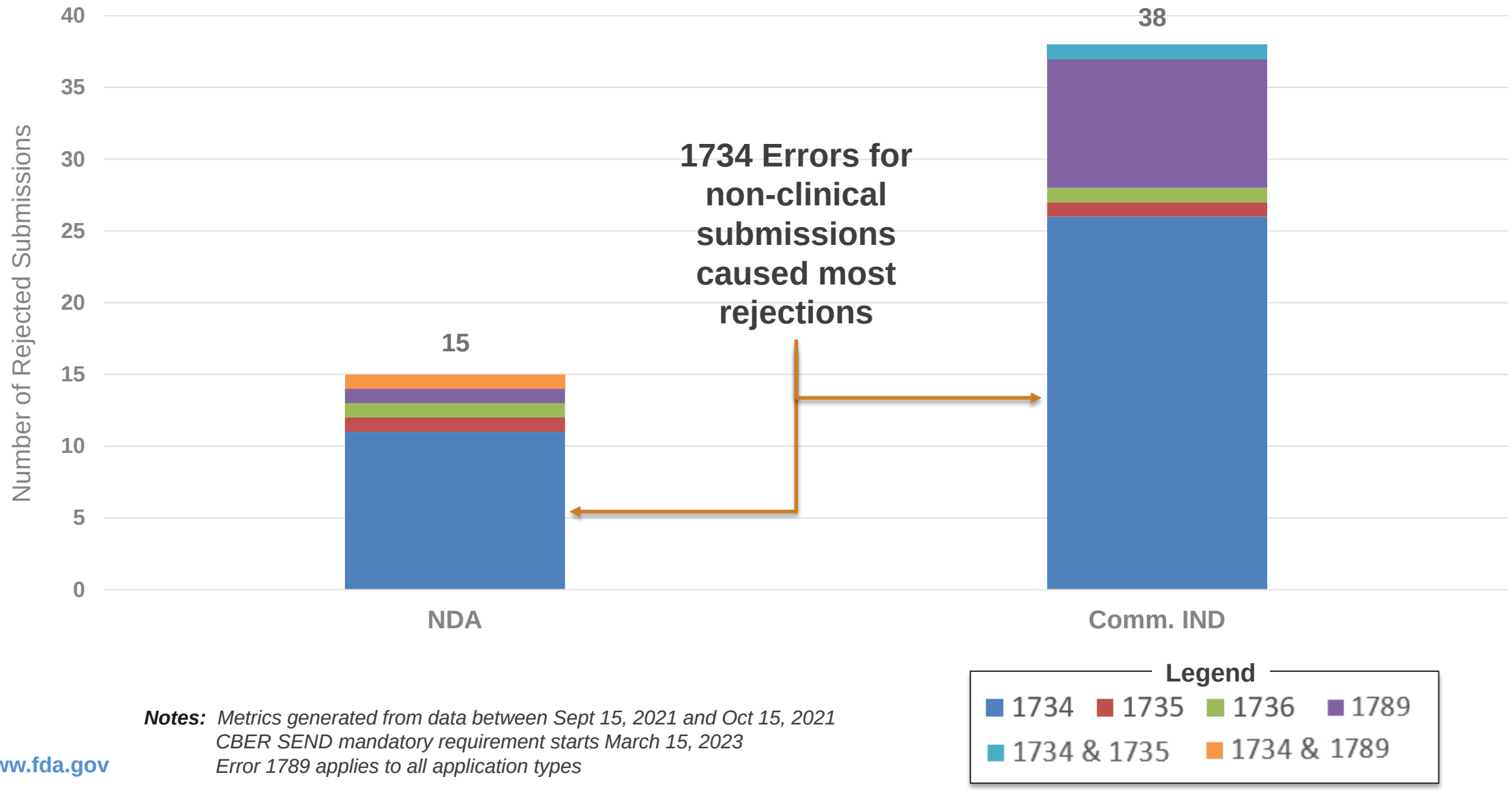
The TRC are eCTD validation criteria to determine compliance with requirements for submitting standardized study data in required sections in Modules 4 and 5, including:

- 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 (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<br>For Study Data Tabulation Model (SDTM) data, a DM dataset and define.xml must be submitted in Module 5 required sections<br>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 Conformance Statistics and Trends

# TRC Rejections between Sept. 15th – Oct. 15th, 2021



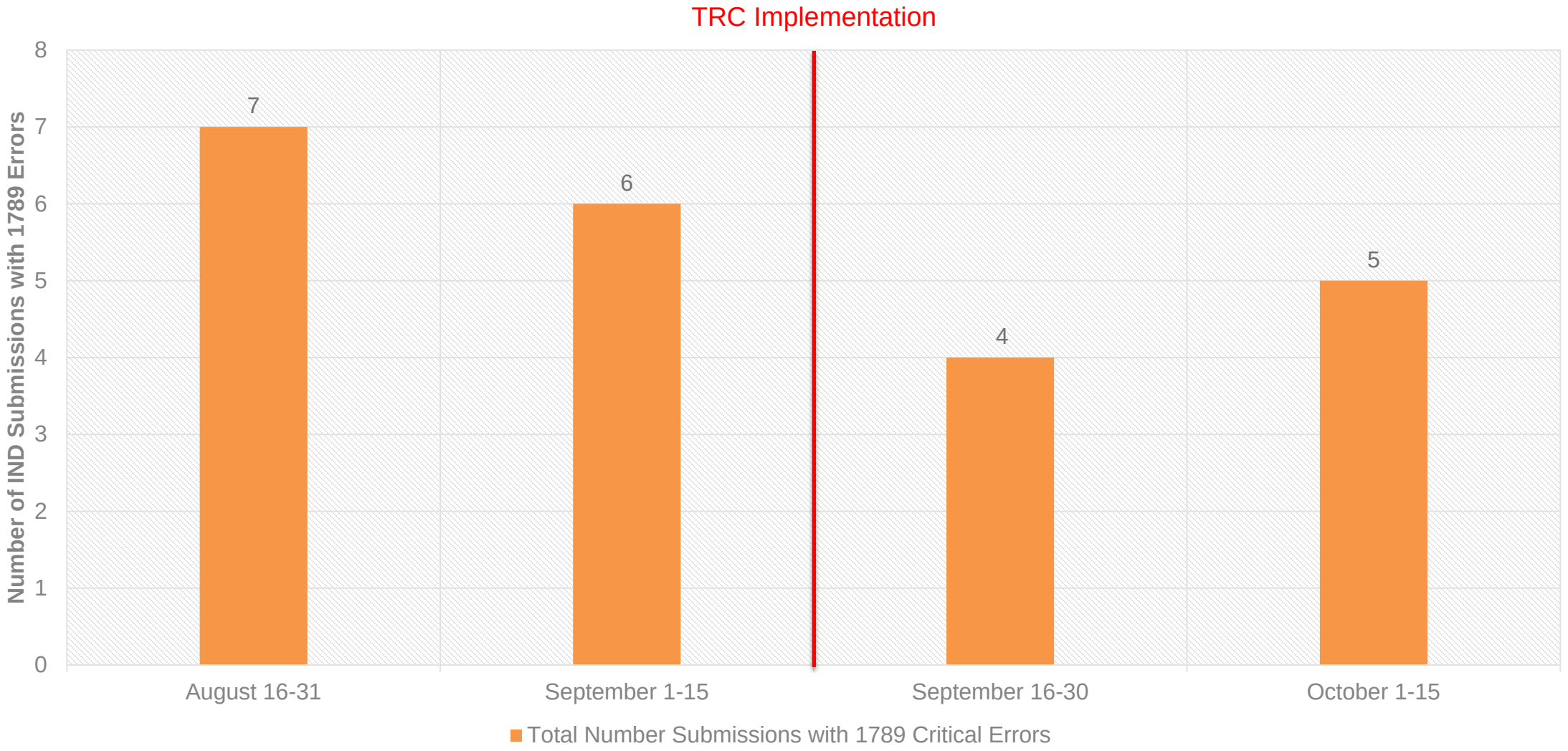

***Notes:*** *Metrics generated from data between Sept 15, 2021 and Oct 15, 2021*
*CBER SEND mandatory requirement starts March 15, 2023*
*Error 1789 applies to all application types*

# Trend of 1789 Submission Errors

| | NDA | | | | Commercial IND | | | |
|---|---|---|---|---|---|---|---|---|
| | August 16-31 | September 1-15 | September 16-30 | October 1-15 | August 16-31 | September 1-15 | September 16-30 | October 1-15 |
| | Warnings | | Rejections | | Warnings | | Rejections | |
| Total Number of **Submissions** with study data in TRC Applicable Sections (m4 & m5) | **286** | **228** | **367** | **227** | **3017** | **2572** | **2840** | **2910** |
| Total Number **Submissions** with 1789 Critical Errors | **1** | **0** | **2** | **0** | **7** | **6** | **4** | **5** |
| Error Rate (% among failed **Submissions** with study data in TRC Applicable Sections) | **0.35%** | **0.00%** | **0.54%** | **0.00%** | **0.23%** | **0.23%** | **0.14%** | **0.17%** |

**Notes:** *1) Analysis includes NDA and Commercial IND submissions with study data received by CDER between August 16, 2021 and October 15, 2021*
*2) Analysis is conducted according to the revised TRC (Revised August 2021)*

# Trend of 1789 Submission Errors: IND's

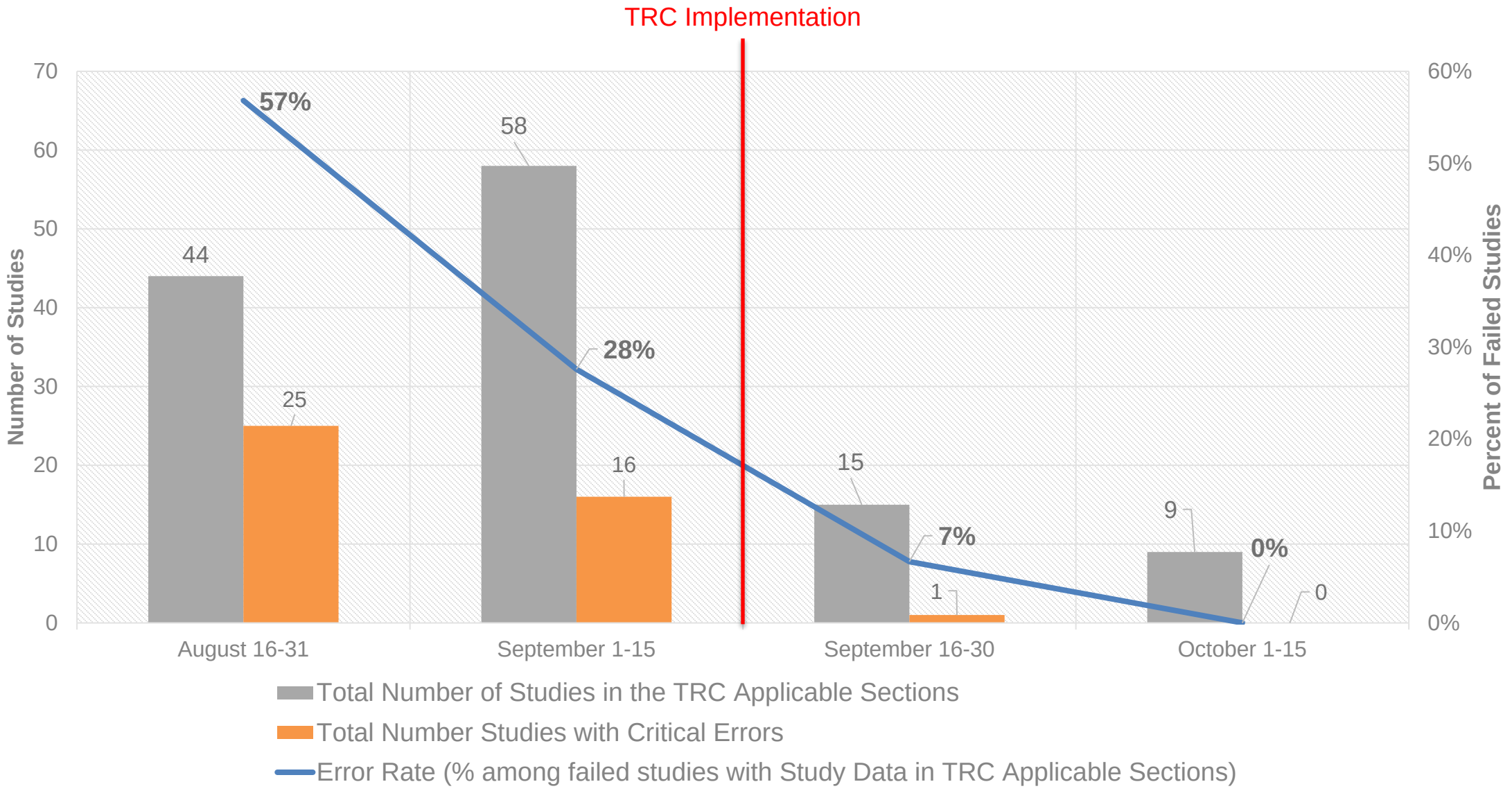


# Trend of Non-Clinical Study Errors

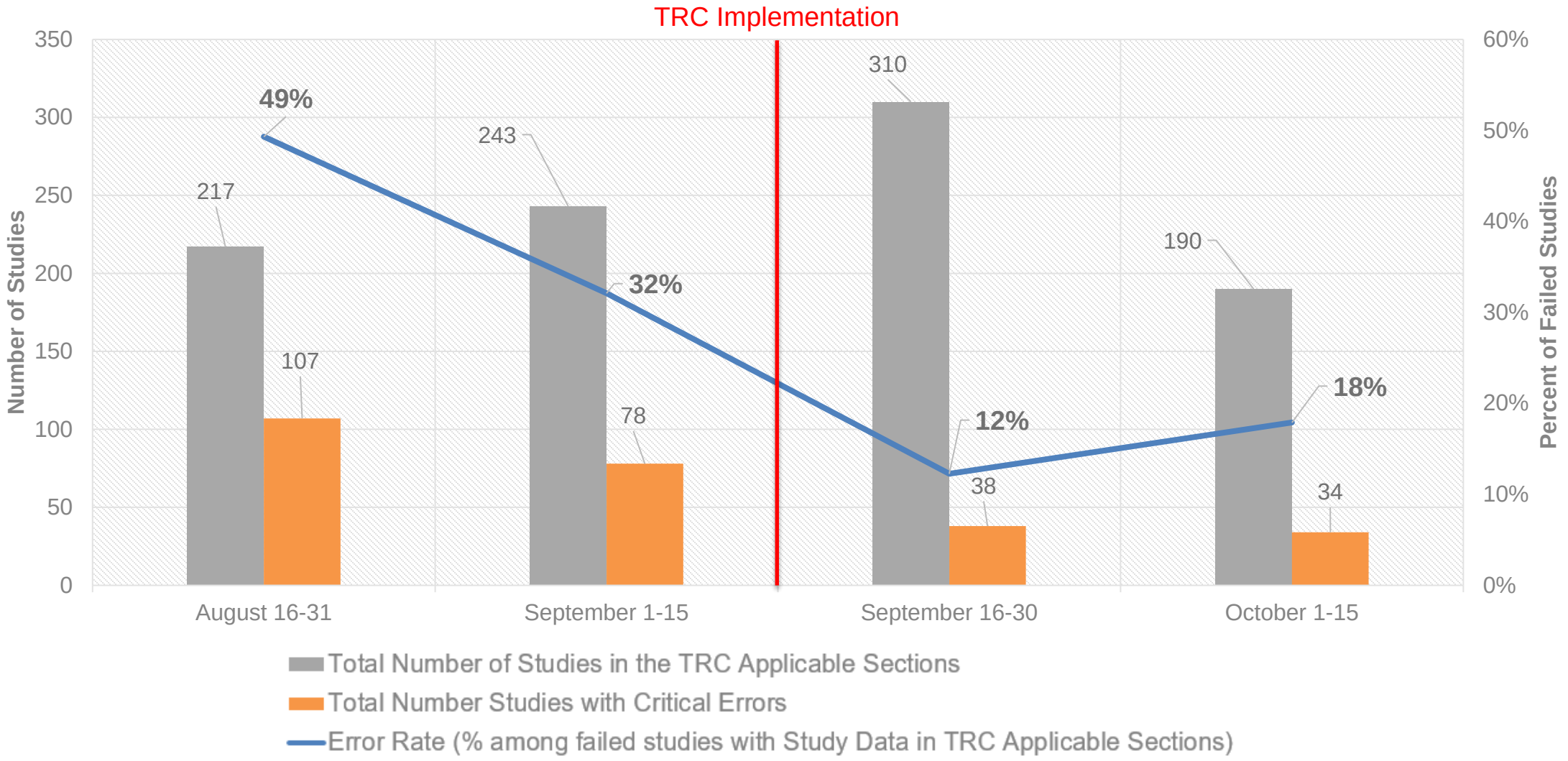
| | NDA | | | | Commercial IND | | | |
|---|---|---|---|---|---|---|---|---|
| | August 16-31 | September 1-15 | September 16-30 | October 1-15 | August 16-31 | September 1-15 | September 16-30 | October 1-15 |
| | Warnings | | Rejections | | Warnings | | Rejections | |
| | m4 | m4 | m4 | m4 | m4 | m4 | m4 | m4 |
| Total Number of **Studies** in TRC Applicable Sections | 44 | 58 | 15 | 9 | 217 | 243 | 310 | 190 |
| Total Number **Studies** with Critical Errors | 25 | 16 | 1 | 0 | 107 | 78 | 38 | 34 |
| Error 1734 | 25 | 16 | 1 | 0 | 94 | 68 | 37 | 34 |
| Error 1735 | 0 | 0 | 0 | 0 | 3 | 6 | 0 | 0 |
| Error 1736 | 0 | 0 | 0 | 0 | 10 | 4 | 1 | 0 |
| Error Rate (% among failed **Studies** in TRC Applicable Sections) | 56.82% | 27.59% | 6.67% | 0.00% | 49.31% | 32.10% | 12.26% | 17.89% |

**Notes:**
1) *Analysis includes NDA and Commercial IND submissions with study data received by CDER between August 16, 2021 and October 15, 2021*
2) *Validation of Error 1735 & 1736 is not performed if a study has Error 1734*
3) *Analysis is conducted according to the revised TRC (Revised August 2021)*

# Trend of Non-Clinical Study Errors: NDA's



# Trend of Non-Clinical Study Errors: IND's

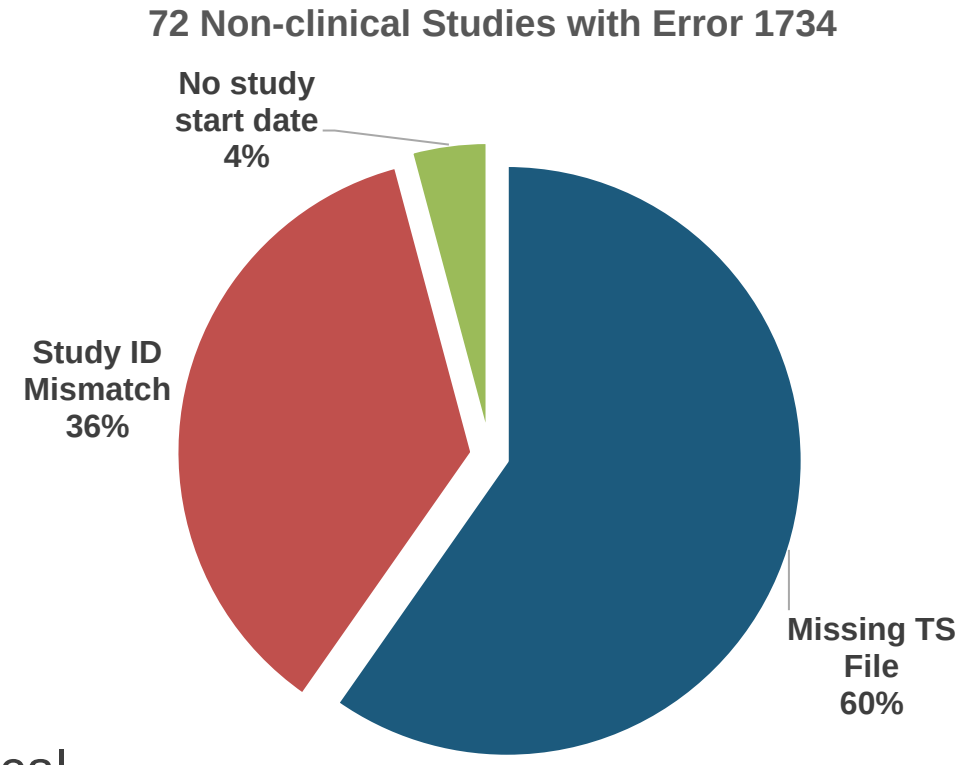


# Addressing the Most Common TRC Error

# 1734 Error Reasons between Sept. 15th – Oct. 15th, 2021

- 72 IND & NDA non-clinical studies failed Rule 1734
- 60% (43 of 72) failed due to a missing ts.xpt
- 78% (56 of 72) were Repeat Dose Toxicology studies

| Toxicology Sections | Count |
|---|---|
| Repeat dose toxicology (m4.2.3.2) | 56 |
| Single dose toxicology (m4.2.3.1) | 14 |
| Carcinogenicity (m4.2.3.4) | 2 |

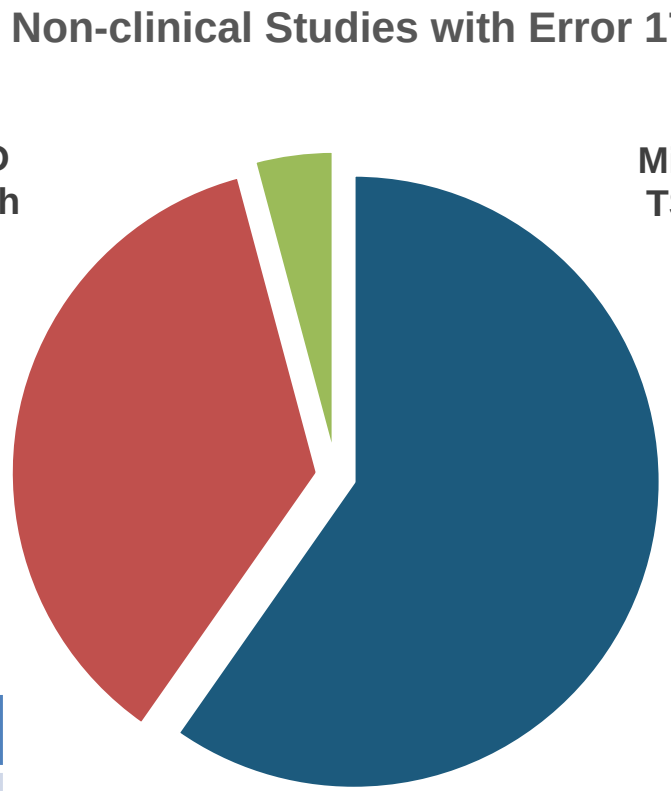



- Submitting a simplified ts.xpt for many of these non-clinical studies will greatly reduce the 1734 error rate
- SEND datasets require a full ts.xpt files



*Timeframe: September 15, 2021 – October 15, 2021*

# How Sponsors Have Addressed 1734 Errors




| Top 3 actions when resubmitting | Percentage |
|---|---|
| Removed the Study | 48% |
| Updated the STF Study ID | 39% |
| Updated the TS Study ID | 13% |

| Top 3 actions when resubmitting | Percentage |
|---|---|
| Submitted a Full or Simplified TS | 48% |
| Moved the Study to a Non-TRC Section | 28% |
| Removed the Study | 22% |

*Timeframe: September 15, 2021 – October 15, 2021*

# Error Reason: Study ID Mismatch

**Rejection Notice Error Details:**

| Error Code | STF Study ID | eCTD section | Error Reason |
|---|---|---|---|
| 1734 | STUDY ID | M4-2-3-1-single-dose-toxicity | Study ID in ts.xpt does not match study ID from STF |

3 Ways to address study ID mismatches between ts.xpt and stf.xml file:

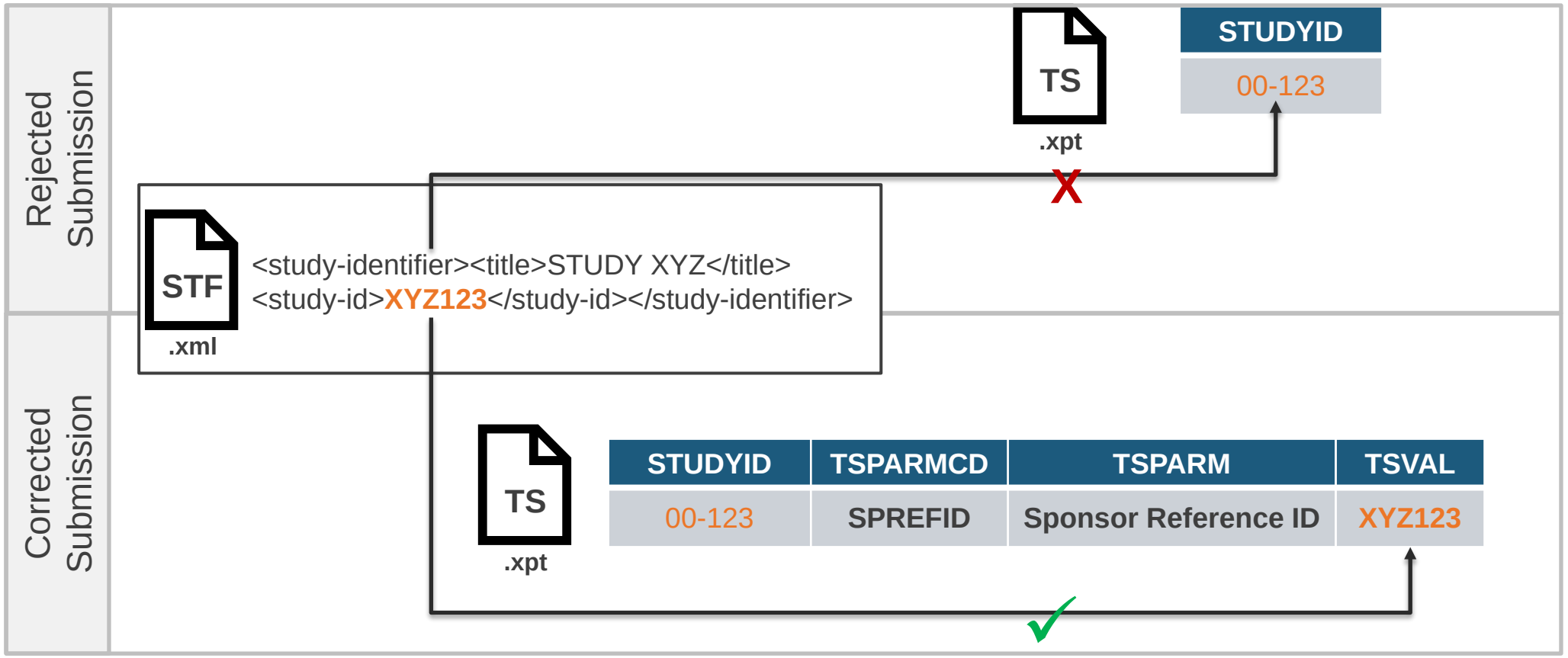
- Option 1: Update ts.xpt SPREFID
- Option 2: Update ts.xpt STUDYID
- Option 3: Update Study ID in stf.xml

| Sponsor actions when resubmitting | Percentage |
|---|---|
| Removed the Study | 48% |
| Updated the STF Study ID | 39% |
| Updated the TS Study ID | 13% |

*Timeframe: September 15, 2021 – October 15, 2021*

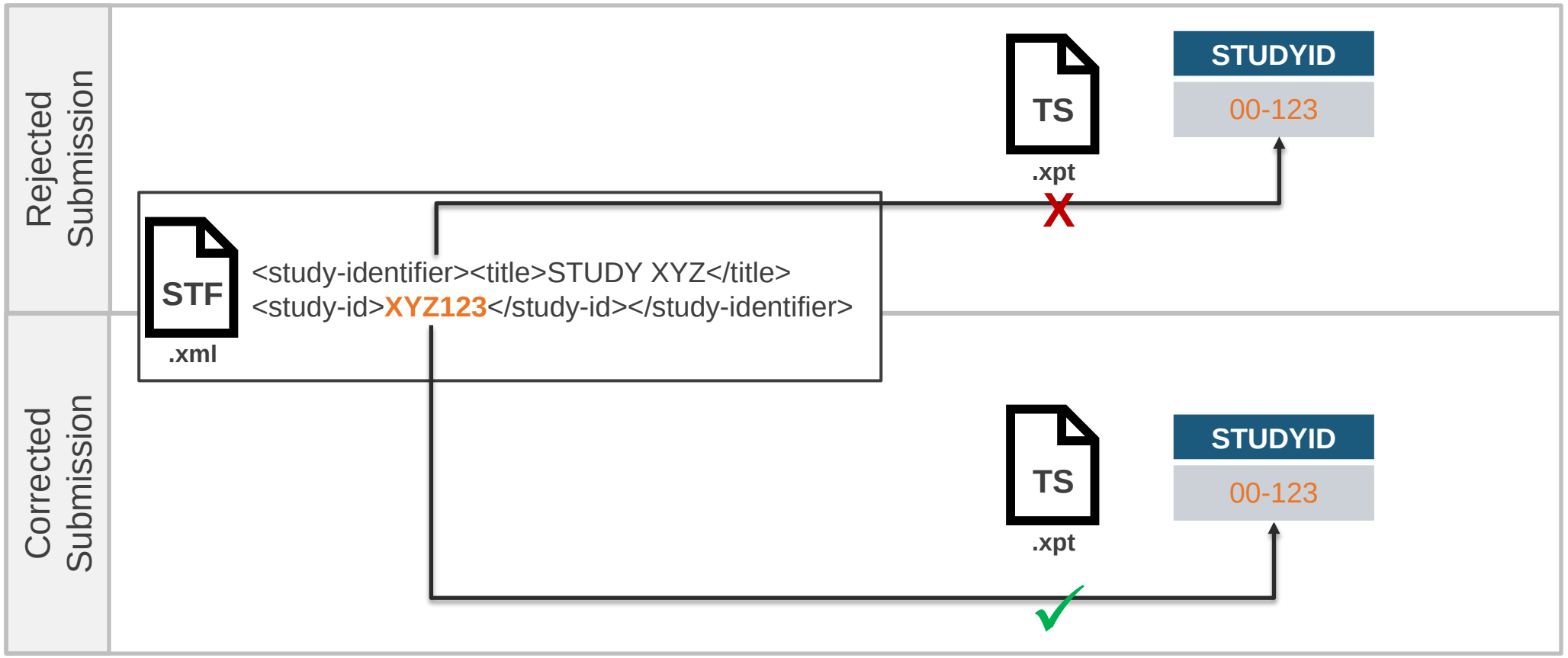
# Option 1: Update ts.xpt SPREFID

- Recommended when submitting a Full ts.xpt
- Avoids changing STUDYID in ts.xpt and other standardized datasets, e.g., dm.xpt, etc.



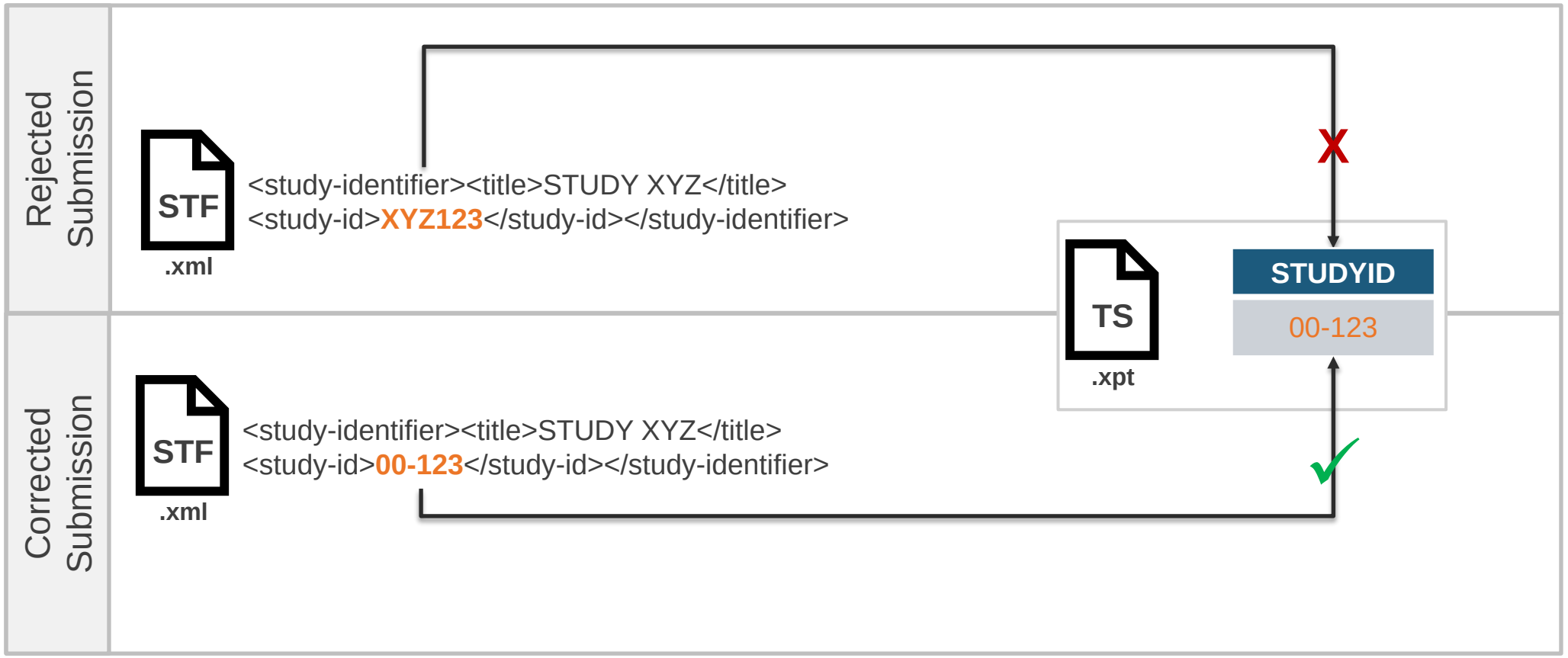
# Option 2: Update ts.xpt STUDYID

- Recommended when submitting a Simplified ts.xpt



# Option 3: Update Study ID in stf.xml

- Not recommended when submitting study files for a previously submitted study, i.e., a study that has already been submitted and identified by another Study ID



# Tools to Help Prepare Study Data for Submission

FDA has provided tools to help sponsors meet study data standard requirements and provide more transparency on the validation process.

**www.fda.gov**

**Sponsor reviews Study Data Standards & Resources:**

1. **Study Data Technical Rejection Criteria**
2. **Simplified TS File Generator Utility (PHUSE) & Simplified TS File Creation Guide**
3. **Study Data Self-Check Worksheet**

**Prepare Submission**

4. **Sponsor submits an eCTD and/or Standardized Data Sample to the FDA to receive feedback, highlighting errors found during processing of the sample**

**Gateway**

**Sponsor submits an application with study data**

1. **Technical Rejection Criteria for Study Data (Revised August 2021)**
   - Clarifies the requirements for eCTD Validation of submissions with study data
   - Provides a validation table and examples in Appendix 1 and Appendix 2 to illustrate the requirements
2. **Simplified TS File Generator Utility (PHUSE) & Simplified TS File Creation Guide**
   - Helps sponsors easily generate a Simplified TS file to provide a Study Start Date for a study

**3. Study Data Self-Check Worksheet**

- Helps sponsors understand criteria for submissions with study data to pass TRC validations
- Dynamically guides sponsors to prepare study data files according to TRC requirements

**4. eCTD and/or Standardized Data Sample Validation**

- Allows sponsors to validate sample submissions and receive feedback prior to submission

# References

## ❖ Study Data Standards Resources

- Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [June 2021]
- Study Data Technical Conformance Guide [Sep. 2021]
- FDA Data Standards Catalog [Sep. 14th 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

## ❖ Providing Regulatory Submissions In Electronic Format - Submissions Under Section 745a(a) Of The FD&C Act: Guidance For Industry

- Link: Providing Regulatory Submissions in Electronic Format

# Questions

For Questions Please Contact:

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

- eCTD Questions:
  esub@fda.hhs.gov

# Acknowledgements

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