DIA 2019
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FDA View: Technical Rejection Criteria for Study Data

Heather Crandall
Office of Business Informatics
Center for Drug Evaluation and Research

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FDA 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

- TRC Revisions
- CDER Conformance Analysis Trend
- CBER Conformance Analysis Trend
- Typical Error Examples
- Implementation Timeline
- Summary

Revised Technical Rejection Criteria

FDA Guidance and Data Standards Catalog

- 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**

Summary of Latest Revisions to the Technical Rejection Criteria for Study Data (Revised Jan. 2019)

Technical Rejection Criteria for Study Data (Revised 05/01/2018)
The FDA may refuse to file (RTF) for NDAs and BLAs, or refuse to receive (RTR) for ANDAs, an electronic submission that does not have study data in conformance to the required standards specified in the FDA Data Standards Catalog.

Technical Rejection Criteria for Study Data (Revised 01/22/2019)
FDA will not accept an electronic submission that does not have study data in compliance with the required standards specified in the FDA Data Standards Catalog

References:
FDA Study Data Technical Rejection Criteria (Revised May 2018)
FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

Summary of Latest Revisions to the Technical Rejection Criteria for Study Data (Revised Jan. 2019)

Error	Description - Technical Rejection Criteria for Study Data (Revised 05/01/2018)	Severity Level
1734	Trial Summary (TS) dataset must be present for each study in eCTD section 4.2 and 5.3	High
1736	Demographic dataset (DM) and the define.xml must be submitted in Module 4 for nonclinical data; DM dataset, the subject-level analysis dataset (ADSL) and define.xml must be submitted in Module 5 for clinical data	High

Error	Description - Technical Rejection Criteria for Study Data (Revised 01/22/2019)	Severity Level
1734	Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections*	**High**
1735	Correct STF file tags must be used for all standardized datasets and corresponding define.xml files in required sections*	**High**
1736	For SEND data, a DM dataset and define xml must be submitted in required sections* For SDTM data, a DM dataset and define.xml must be submitted in required sections* For ADaM data, an ADSL dataset and define.xml must be submitted in required sections*	**High**
1789**	Study files must be referenced in a Study Tagging File (STF)	**High**

** Refer to the latest Technical Rejection Criteria for Study Data*
*** From Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specification, Section J: Datasets must only be provided in modules 3, 4, or 5 and not in modules 1 or 2*

Study Data Technical Rejection Criteria Conformance Trend

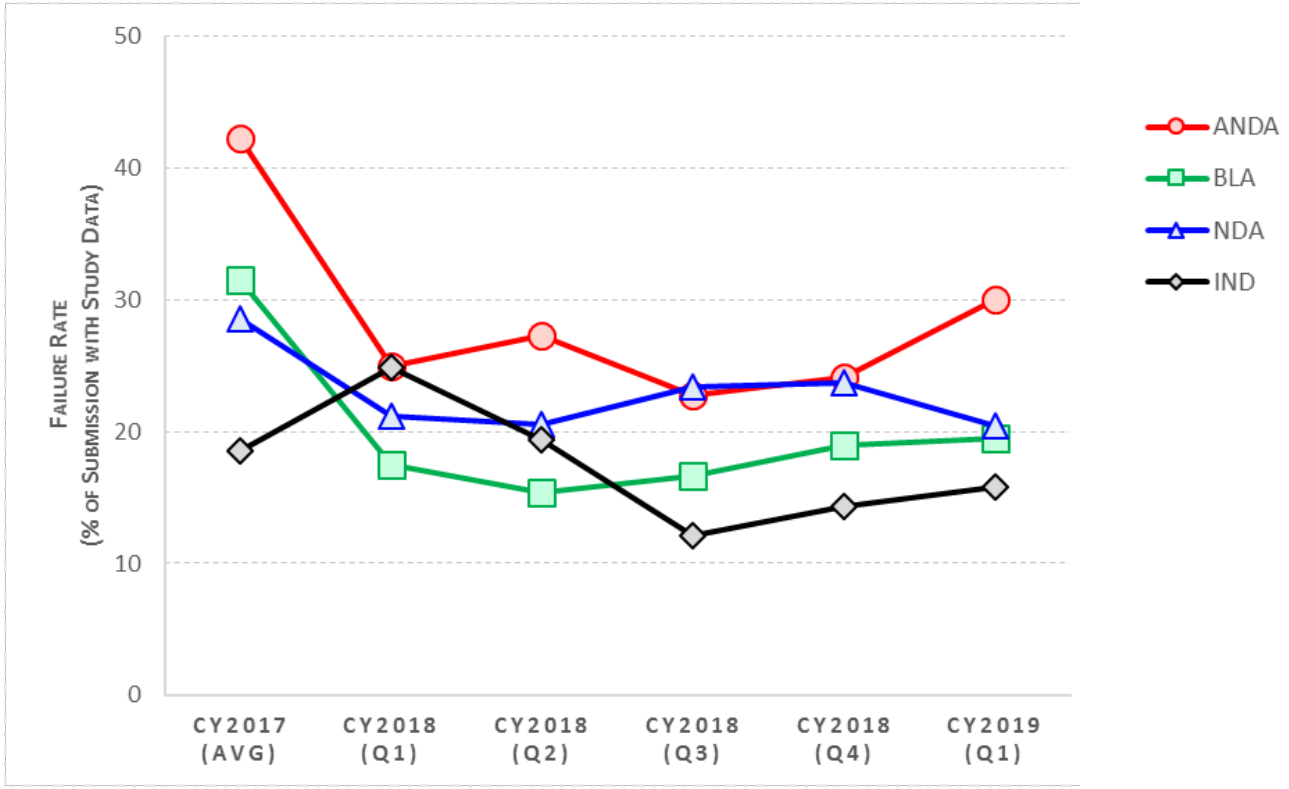
Study Data Conformance Trend Analysis

- Study Data was assessed for:
  - NDA, BLA, and ANDA Submissions received from 12/18/2016 to 3/31/2019
  - Commercial IND Submissions received from 12/18/2017 to 3/31/2019
  - No duplicates

- Conformance was checked against the two high-level validation rules as described in the Technical Rejection Criteria for Study Data:
  - 1734: TS Dataset and Correct Study Start Date must be present
  - 1736: DM Dataset, ADSL Dataset and define.xml must be present

Overall Conformance Trend for Validation Errors 1734 & 1736 for CDER

- Submissions with study data shows overall decreases in Validation Error 1734 and 1736 in all application types
- NDAs and INDs are showing the greatest improvements in conformance



Notes:

1) CY2017 analysis average excludes any submissions received in 2018 & 2019 and was conducted according to TRC (Revised May 2018)
2) CY2018 & CY2019 (Q1) analysis are conducted according to the TRC (Revised Jan. 2019)

CDER Conformance Analysis: Validation Error 1789

- ANDA, NDA, BLA, and Commercial IND Submissions were assessed for conformance to high-level error, 1789, as defined in the Technical Rejection Criteria for Study Data (Revised Jan. 2019)

	NDA		ANDA		BLA		Comm. IND		All	
	CY2018	CY2019 (Q1)	CY2018	CY2019 (Q1)	CY2018	CY2019 (Q1)	CY2018	CY2019 (Q1)	CY2018	CY2019 (Q1)
Total Number of Submissions	41,077	11,011	62,695	14,776	11,042	2997	79,473	22,226	194,287	51,010
Error 1789	43	11	225	53	1	0	193	62	462	126
Failure Rate (% among submissions with Study Data)	0.10%	0.10%	0.36%	0.36%	<0.01%	0.00%	0.24%	0.28%	0.24%	0.20%

Notes:

1) One drug application could contain multiple submissions throughout its review life-cycle, such as original, supplements, and amendments
2) Each submission may contain more than one study
3) Analysis includes NDA, BLA, ANDA and Commercial IND submissions received by CDER between 1/1/2018 to 3/31/2019
4) Analysis is conducted according to the revised TRC

Reference: FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

CDER Conformance Analysis: Validation Errors 1734, 1735 & 1736

- ANDA, NDA, BLA, and Commercial IND Submissions were assessed for conformance to three high-level error, 1734, 1735, & 1736, as defined in the Technical Rejection Criteria for Study Data (Revised Jan. 2019)
- Failure Rate for all applications increased **2.3%** (average) between 2018 and 2019

	NDA		ANDA		BLA		Comm. IND		All	
	CY2018	CY2019 (Q1)	CY2018	CY2019 (Q1)	CY2018	CY2019 (Q1)	CY2018	CY2019 (Q1)	CY2018	CY2019 (Q1)
Total Number of Submissions with Study Data	877	270	1078	243	291	77	649	183	2895	773
Total Number of Submissions with Study Data in TRC Applicable Sections		204		226		57		172		659
Total Number Submissions with Critical Errors	215	71	689	181	54	15	134	42	1092	309
Error 1734	185	52	186	53	48	15	96	24	515	144
Error 1735	34	23	497	130	5	0	26	15	562	168
Error 1736	16	3	88	21	2	0	18	5	124	29
Failure Rate (% among submissions with Study Data)	24.50%	26.30%	63.90%	73.70%	18.60%	19.50%	20.60%	23.00%	37.70%	40.00%
Failure Rate (% among submissions with Study Data in TRC Applicable Sections)		**34.80%**		**80.10%**		**26.30%**		**24.40%**		**46.90%**

Notes:

1) One drug application could contain multiple submissions throughout its review life-cycle, such as original, supplements, and amendments
2) Analysis includes NDA, BLA, ANDA and Commercial IND submissions received by CDER between 1/1/2018 to 3/31/2019
3) Submission with multiple studies can report both Errors 1734, 1735 and 1736
4) Validation of errors 1735 and 1736 are not performed if a study has Error 1734
5) Analysis is conducted according to the revised TRC

CBER Conformance Analysis including Validation Rules for 1734, 1735, 1736 and 1789

CBER Conformance Analysis: Validation Errors 1734, 1735, 1736 & 1789

- CBER BLA Submissions were assessed for conformance to four high-level errors, 1734, 1735, 1736 and 1789 as defined in the Technical Rejection Criteria for Study Data (Revised Jan. 2019)

	BLA	
	CY2018	CY2019 (Q1)
Total Number of studies with Study Data	6062	1644
Error 1789	6	0
Failure Rate (% among studies with Study Data)	**0.1%**	**0%**

	BLA	
	CY2018	CY2019 (Q1)
Total Number of studies with Study Data	49	12
Total Number of Submissions with Study Data in TRC Applicable Sections		12
Total Number studies with Critical Errors	15	6
Error 1734	14	5
Error 1735	3	1
Error 1736	1	1
Failure Rate (% among studies with Study Data)	**30.6%**	**50.0%**
Failure Rate (% among submissions with Study Data in TRC Applicable Sections)		**50.0%**

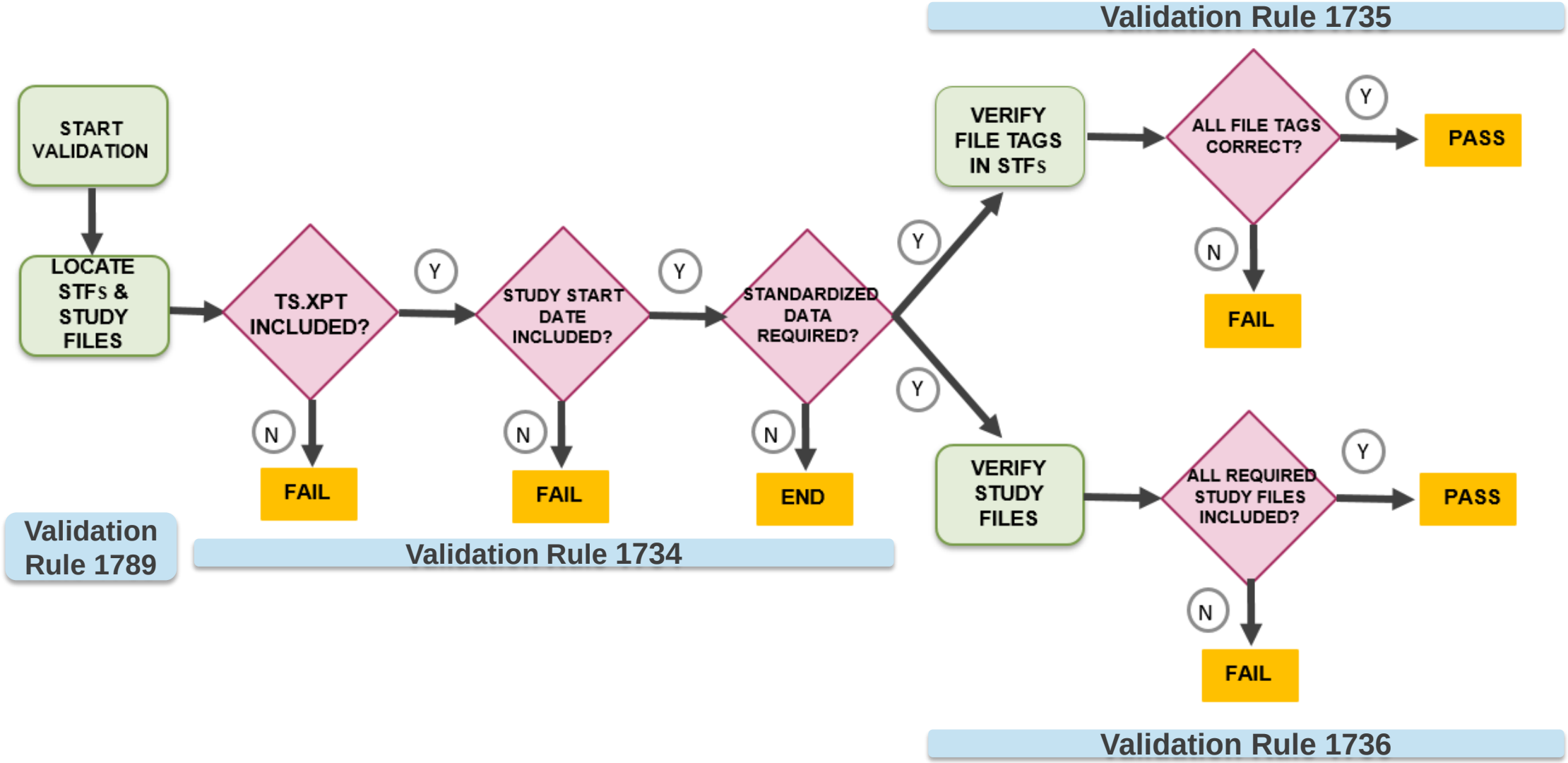
Notes:

1) One drug application could contain multiple submissions throughout its review life-cycle, such as original, supplements, and amendments
2) Analysis includes BLA submissions received by CBER between 1/1/2018 to 3/31/2019
3) Analysis is conducted according to the revised TRC
4) Submission with multiple studies can report both Errors 1734, 1735 and 1736
5) Validation of errors 1735 and 1736 are not performed if a study has Error 1734

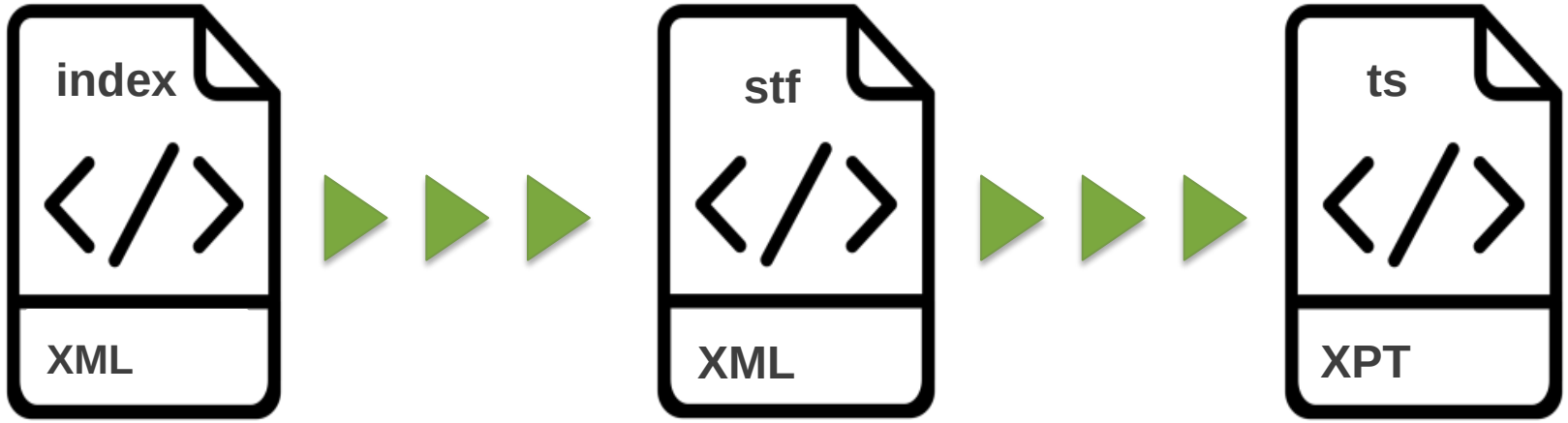
Reference: FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

Top Error Examples

SDTRC High Level Validation Process (Revised Jan. 2019)



eCTD Backbone Files

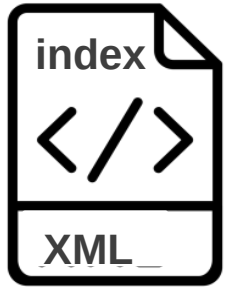


- Leaf ID
- File Path
- File Name

- Leaf ID
- STF Study ID
- File-Tag

- TS Study ID
- Study Start Date

eCTD Backbone Files (index.xml)



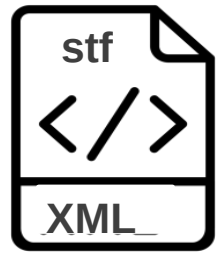

```
<m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
 <leaf checksum-type="MD5"
   xlink:type="simple"
   checksum="98723f7594b5500a861509547c384e46" operation="new"
   xlink:href="m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-repcontr/study-s107/ts.xpt"
   application-version="PDF 1.4"
   ID="a103">
     <title>S107 ts.xpt</title>
 </leaf>
<leaf checksum-type="MD5"
  xlink:type="simple"
  checksum="25d3b246313a9dbf688a48da2295260e" operation="new"
  xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-repcontr/study-s107/stf-s107.xml"
  version="stf version 2.2"
  ID="a104">
    <title>Study Tagging File for S107</title>
 </leaf>
</m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
```

INDEX LEAF ID

FILE PATH FROM INDEX

FILE NAME FROM INDEX

eCTD Backbone Files (stf.xml)



- From Index.xml
  - Leaf ID
  - File Path
  - File Name

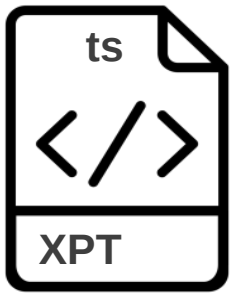
```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="../../../../util/style/ich-stf-stylesheet.xsl"?>
<!DOCTYPE ectd:study SYSTEM "../../../../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xml:lang="en" dtd-version="2.2"
xmlns:xlink="http://www.w3.org/1999/xlink">
  <study-identifier>
  <title>Wonderdrug Study S107</title>
  <study-id>S107</study-id>
  <category name="type-of-control" info-type="ich">no-treatment</category>
  </study-identifier>
  <study-document>
  <doc-content xlink:href="../../../../../index.xml#a103">
  <file-tag name="data-tabulation-dataset-sdtm" info-type="ich"/>
  </doc-content>
  </study-document>
</ectd:study>
```

STF STUDY ID

Index.xml LEAF ID

FILE TAG ASSOCIATED TO STUDY DOCUMENT

eCTD Backbone Files (ts.xpt)



- From Index.xml
  - Leaf ID
  - File Path
  - File Name
- From STF.xml
  - Leaf ID
  - STF Study ID
  - File-Tag

Library | Properties | ts.xpt

Freeze | Hide | Show... | Format | Filter... | Font... | Find

Table | View

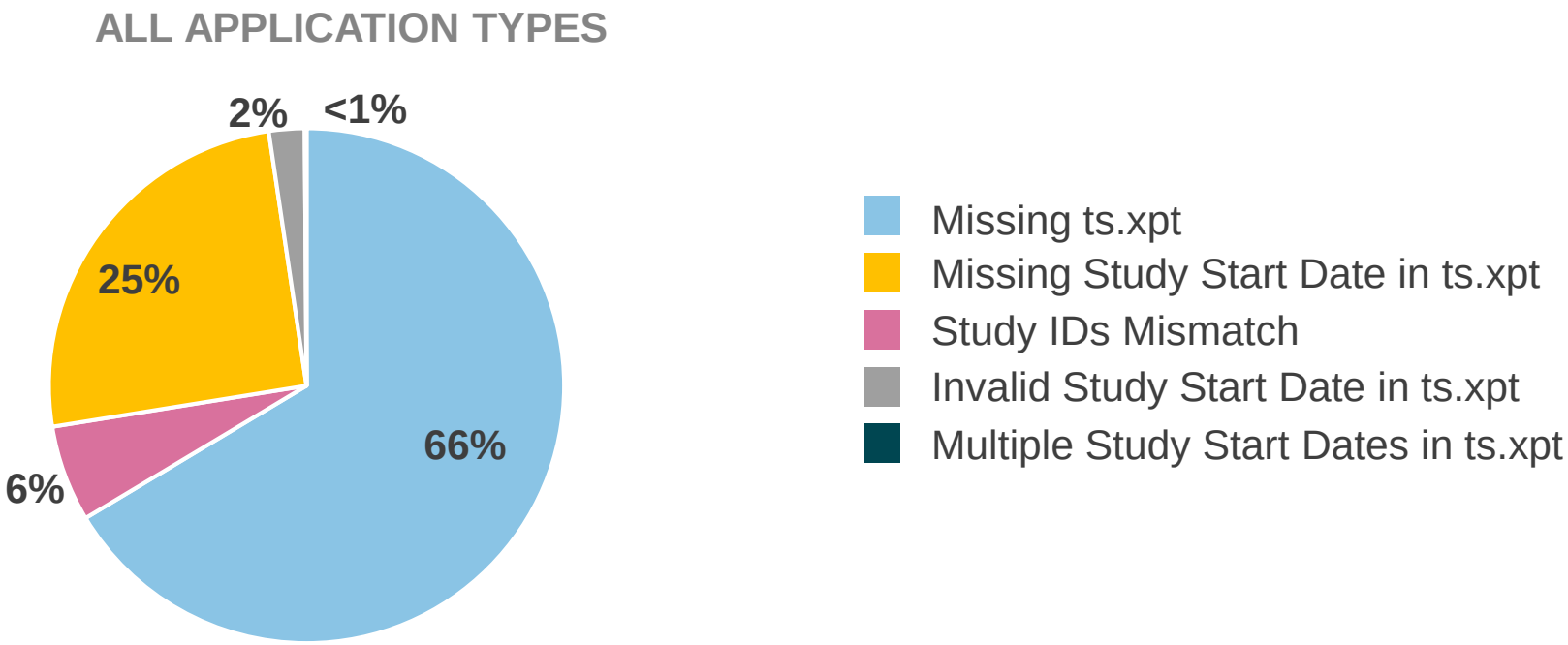
	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	S107	SSTDTC	2019-01-01	

TS Study ID

Study Start Date

CY2018 CDER Error Reasons for Validation Rule 1734

- A dataset named ts.xpt with information on Study Start Date (SSD) 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
- **Common error reason across all application types:**
  - a missing ts.xpt file (66% of studies with error 1734)
  - a missing study start date in the ts.xpt (25% of studies with error 1734)



Top Error for Rule 1734: Missing ts.xpt

- A missing ts.xpt file (66% of studies with error 1734)

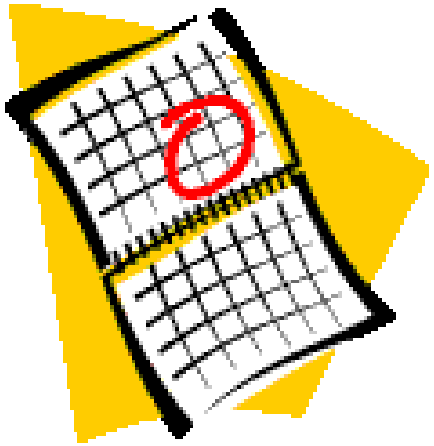
Study Start Date	Application Type	Data Type	Study Sections	Expectation by Center	
				CDER	CBER
Prior to or on 17-Dec-2017	Commercial INDs	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; submit a simplified TS whether or not the study contains an xpt dataset (other than the 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	
After 17-Dec-2017	Commercial INDs	Nonclinical	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	
Prior to or on 17-Dec-2016	NDA, BLA, ANDA	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; 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)	
After 17-Dec-2016	NDA, BLA, ANDA	Nonclinical	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	

Top Error for Rule 1734: Incorrect Study Start Date Format in ts.xpt

- A missing study start date (TSVAL) in the ts.xpt (25% of studies with error 1734)

Correct Study Start Date Format
yyyy-mm-dd

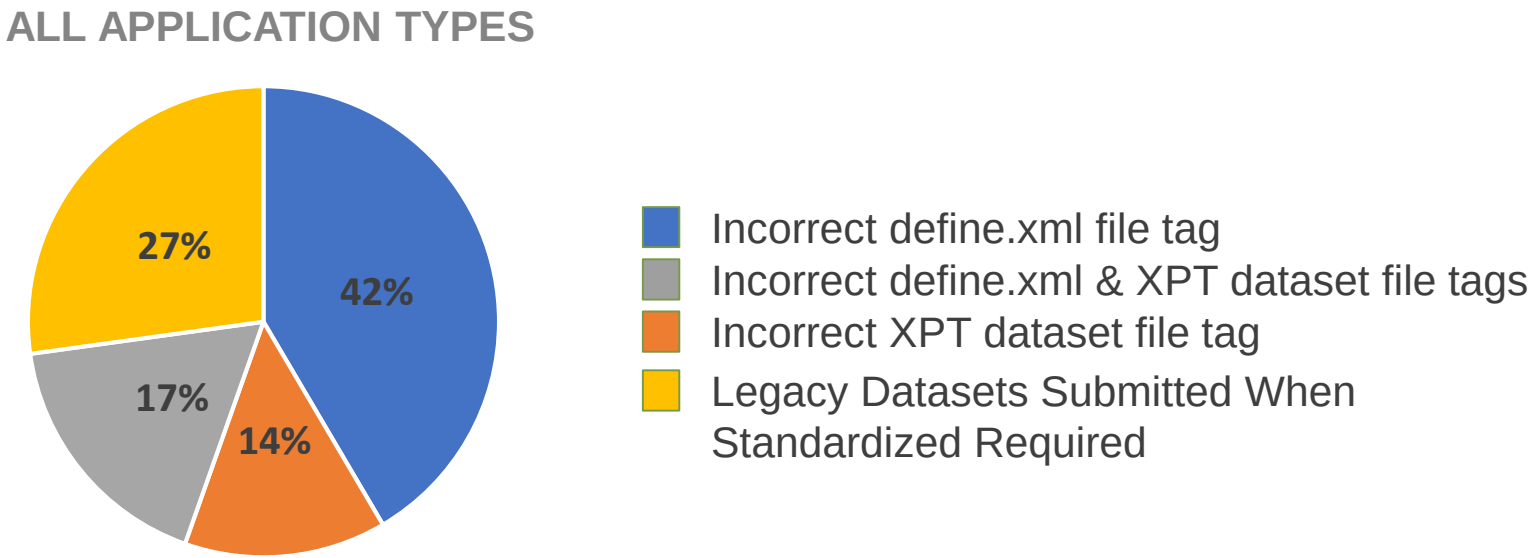
Incorrect Study Start Date Format	
yyyy-mm	dd-mmm-yyyy
SAS Date Format	dd-mm-yyyy
mm/dd/yyyy	ddmmmyyyy
dd-mmm-yy	dd.mm.yyyy
yyyy	month-yyyy
mm/dd/yy	



CY2018 CDER Error Reasons for Validation Rule 1735

- The correct STF file tags must be used for all standardized datasets and corresponding define.xml files 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

- **Common error reason for ANDAs:**
  - an incorrect file tag for a define.xml file (42% of ANDA studies with error 1735)
- **Common error reason for NDAs:**
  - a dataset tagged as legacy when standardized datasets are required (80% of NDA studies with error 1735)



CY2018 CDER Error Reasons for Validation Rule 1735

- The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files 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

INDEX.XML

```
  xlink:href="m5/53-clin-stud-rep/535-rep-effic-safety-stud/
nausea/5351-stud-repcontr/study-s107/define.xml"
  application-version="PDF 1.4"
  ID="a104">
    <title>S107 define.xml</title>
```

STUDY TAGGING FILE: "stf-s107.xml"

```
<doc-content xlink:href="../../../../../index.xml#a104">
<file-tag name="data-tabulation-dataset-sdtm" info-type=ich"/>
```

You have submitted XPT files or define.xml files without correct file tag.

Valid file tags for XPT files are:
data-tabulation-dataset-sdtm
data-tabulation-dataset-send
analysis-dataset-adam

Valid file tags for corresponding define.xml files are:
data-tabulation-data-definition
analysis-data-definition

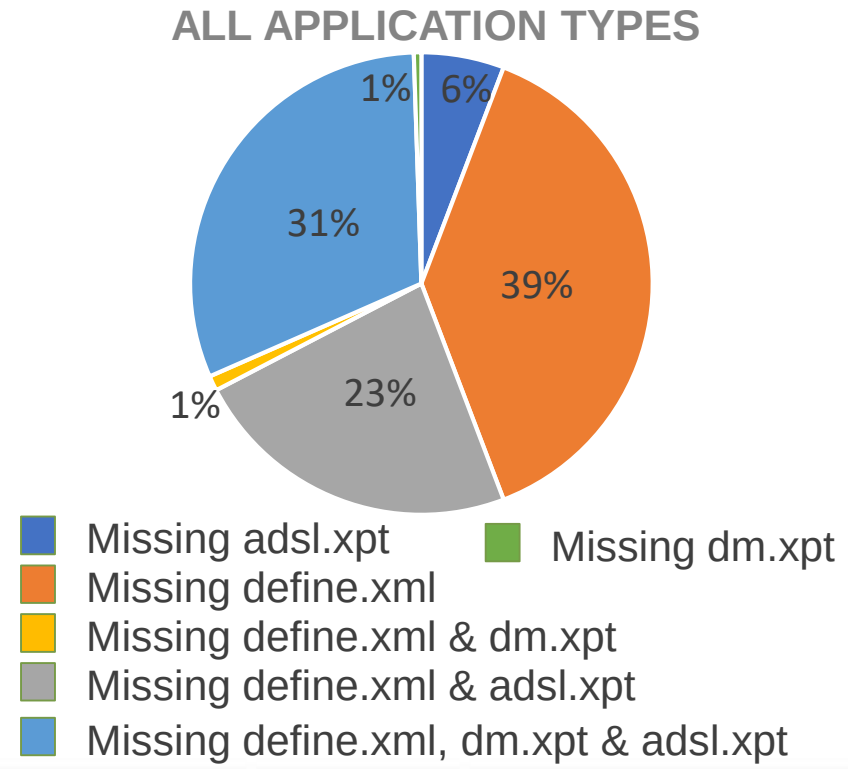
define.xml is tagged as "data-tabulation-dataset-sdtm". It should be "**data-tabulation-data-definition**"

Fail Rule 1735

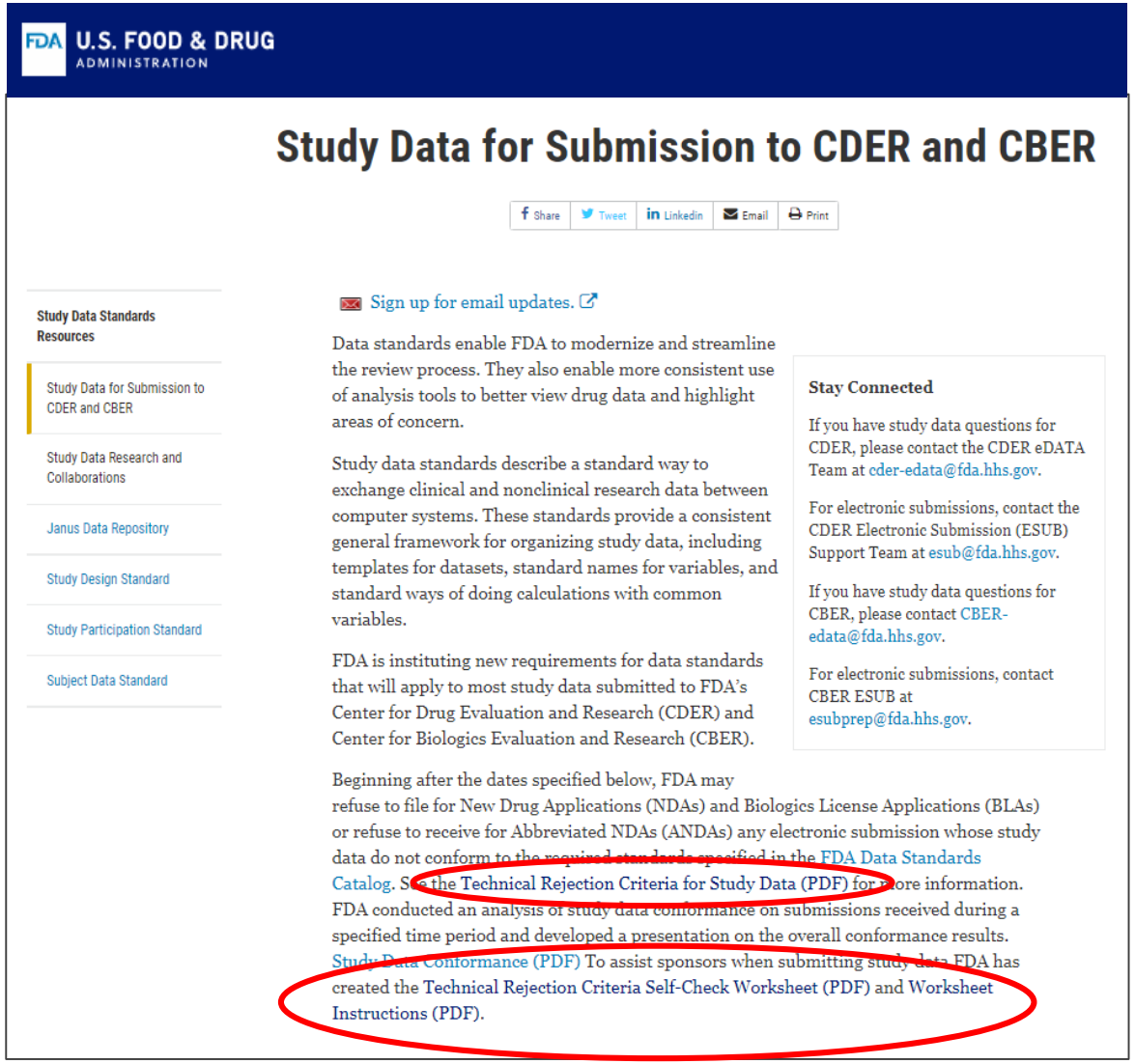
CY2018 CDER Error Reasons for Validation Rule 1736

- For SEND data, a DM dataset and define.xml must be submitted in module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4
- For SDTM data, a DM dataset and define.xml must be submitted 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
- For ADaM data, an ADSL dataset and define.xml must be submitted 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

- **Common reason across all application types:**
  - a missing define.xml file (39% of studies)
  - a missing define.xml, dm.xpt, and adsl.xpt files (31% of studies)
- **Common error reason for NDAs:**
  - missing define.xml and adsl.xpt files



Published Technical Rejection Criteria for Study Data & Self-Check Worksheet



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Study Data for Submission to CDER and CBER

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Study Data Standards Resources

- Study Data for Submission to CDER and CBER
- Study Data Research and Collaborations
- Janus Data Repository
- Study Design Standard
- Study Participation Standard
- Subject Data Standard

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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).

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.

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 specified time period and developed a presentation on the overall conformance results. Study Data Conformance (PDF) To assist sponsors when submitting study data, FDA has created the Technical Rejection Criteria Self-Check Worksheet (PDF) and Worksheet Instructions (PDF).

"Technical Rejection Criteria for Study Data"
https://www.fda.gov/media/100743/download

"Technical Rejection Criteria Self-Check Worksheet"
https://www.fda.gov/media/123098/download

"Technical Rejection Criteria Self-Check Worksheet Instructions"
https://www.fda.gov/media/123099/download

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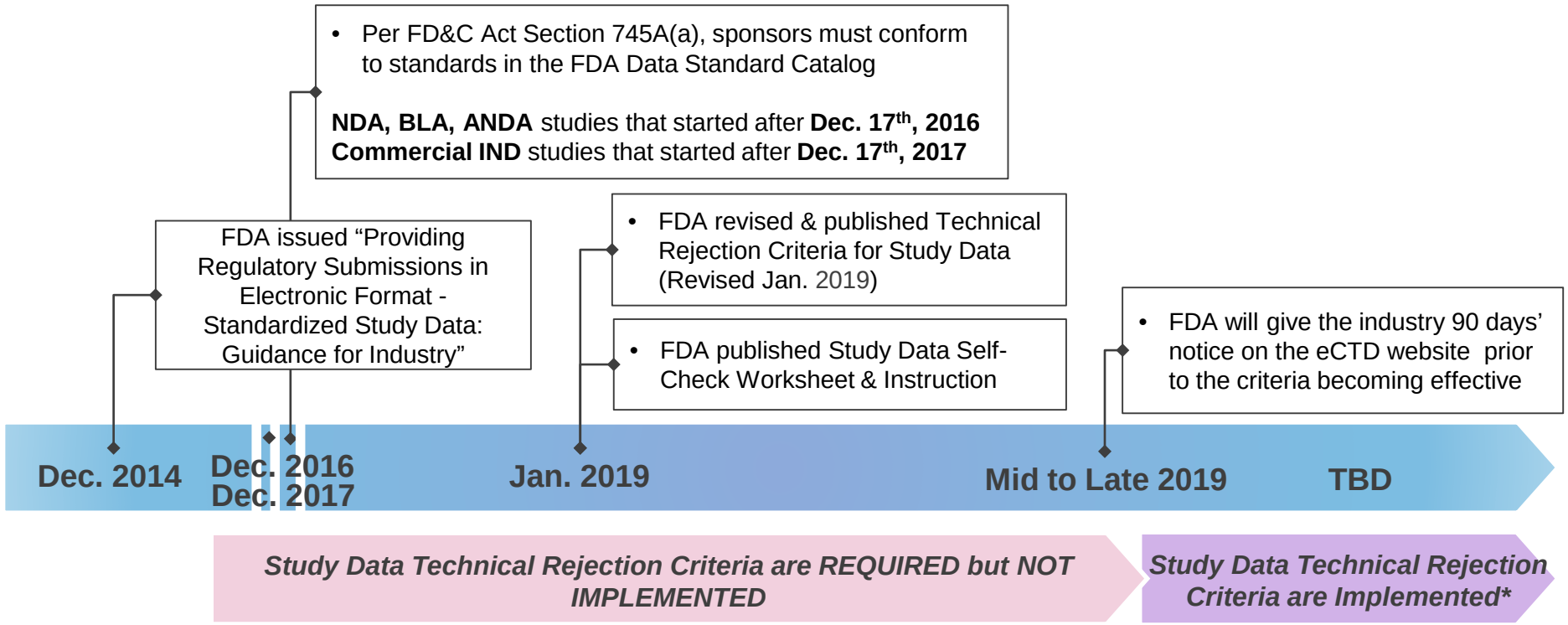
Implementation Timeline

Implementation Timeline

- FDA published Revised Study Data Technical Rejection Criteria (Revised Jan. 2019) and Study Data Self-Check Worksheet to assist sponsors with the TRC Conformance



** Note: When a submission is technically-rejected, the submission sequence is not transferred into the FDA electronic document rooms*

Summary

Summary

- Based on the revised TRC, about **40%** all submissions were received with non-critical errors for 1734, 1735, and 1736
- FDA requires the submission of standardized Study Data as defined in the FDA Data Standard Catalog
- FDA has not rejected any submission that contains errors as reflected in this analysis
- FDA plans to use technical rejection criteria to identify applications that are not fulfilling this requirement.

TIP

To avoid validation errors, it is important for sponsors and applicants to understand the requirements specified in guidance and recommendations for submitting study data in the Study Data Technical Conformance Guide.

Questions

- For questions about submitting study data please contact:
  - CDER – edata@fda.hhs.gov
  - CBER – cber.cdisc@fda.hhs.gov

- For questions about eCTD, including stf.xml and file-tags, please contact:
  - CDER - esub@fda.hhs.gov
  - CBER – esubprep@fda.hhs.gov

References

- "Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry" https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf
- "Providing Regulatory Submissions In Electronic Format - Submissions Under Section 745a(a) Of The FD&C Act: Guidance For Industry" https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384686.pdf
- "Technical Rejection Criteria For Study Data" https://www.fda.gov/media/100743/download
- "Study Data Technical Conformance Guide" https://www.fda.gov/media/88173/download
- "FDA Data Standards Catalog" https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
- "Technical Denunciation Criteria Self-Check Worksheet" https://www.fda.gov/media/123098/download
- "Technical Rejection Criteria Self-Check Worksheet Instructions" https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630733.pdf
- For FDA instruction of Study Data submission, see the FDA "Study Data for Submission to CDER and CBER" https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
- For the full list of Study Data standards, see the FDA "Study Data Standards Resources" http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards

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Thank You

Heather Crandall

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