Regulatory Submissions, Information, and Document Management Forum

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Technical Rejection Criteria for Study Data

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DIA

Agenda

- FDA’s Study Data Guidance and Requirement
- Study Data Technical Rejection Criteria (SDTRC) and Implementation Timeline
- Study Data Conformance Trends (CY2019 and CY2020)
- Study Data Conformance Analysis (CY2020)
  - CY2020 Error Reasons for Validation Rule 1734
  - CY2020 Error Reasons for Validation Rule 1736
- Summary

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

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 (updated in October 2020)
- **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
- **Sponsors are obligated to meet Technical Rejection Criteria for Study Data which determine whether a submission complies with FDA’s standards for study data**

Warning

Even if your study started prior to the dates above, it will need to include a trial summary file (contains the study start date and/or reason code for standardized data not applicable) if files are submitted under sections listed in the Technical Rejection Criteria for Study Data

FDA Study Data Technical Rejection Criteria (SDTRC)

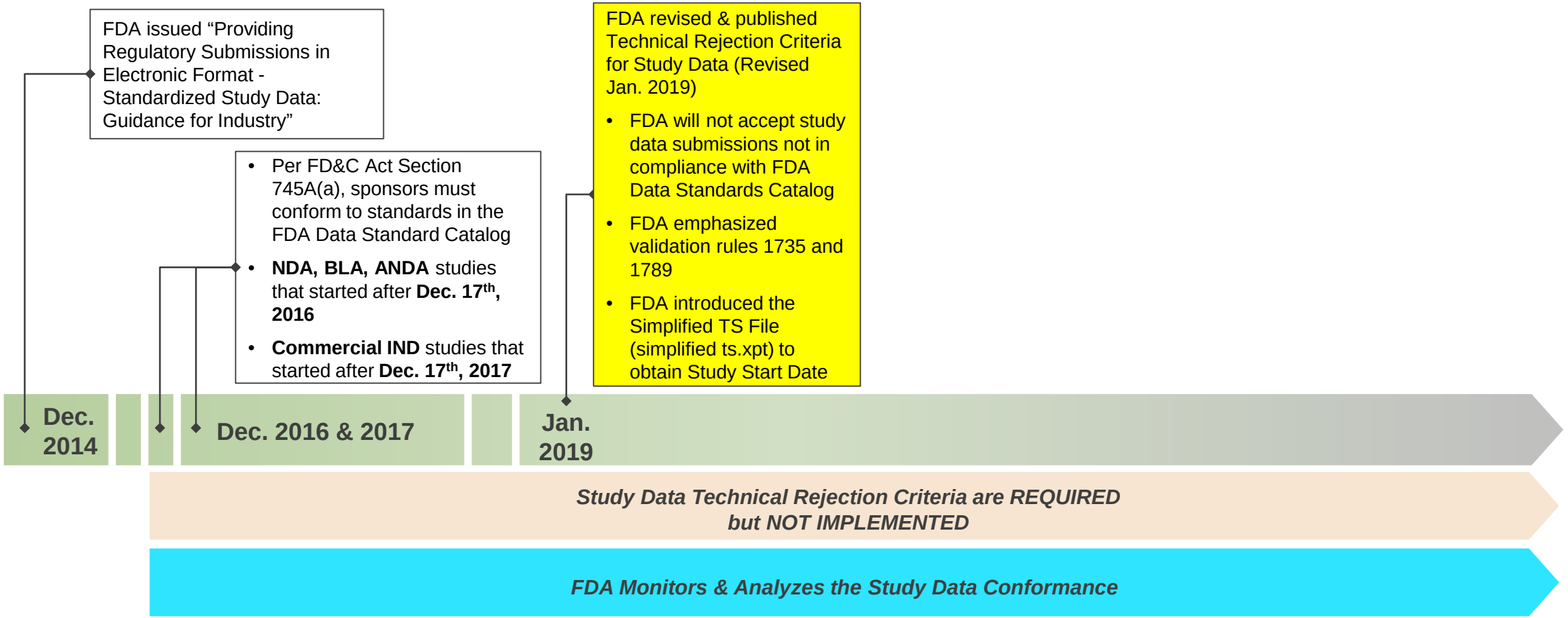
- Study Data Technical Conformance Guide provides technical recommendations for submitting study data according to CDISC standards

- Technical Rejection Criteria for Study Data provides the conditions under which FDA will not accept submissions with study data

Error	Description (Reference to FDA Study Data Technical Rejection Criteria Oct. 2019 version)	Severity Level
1734	A Trial Summary (TS) dataset (ts.xpt) with information on study start date (SSD) must be present for each study in 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). STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references, and 5.3.6 Postmarketing reports	**High**

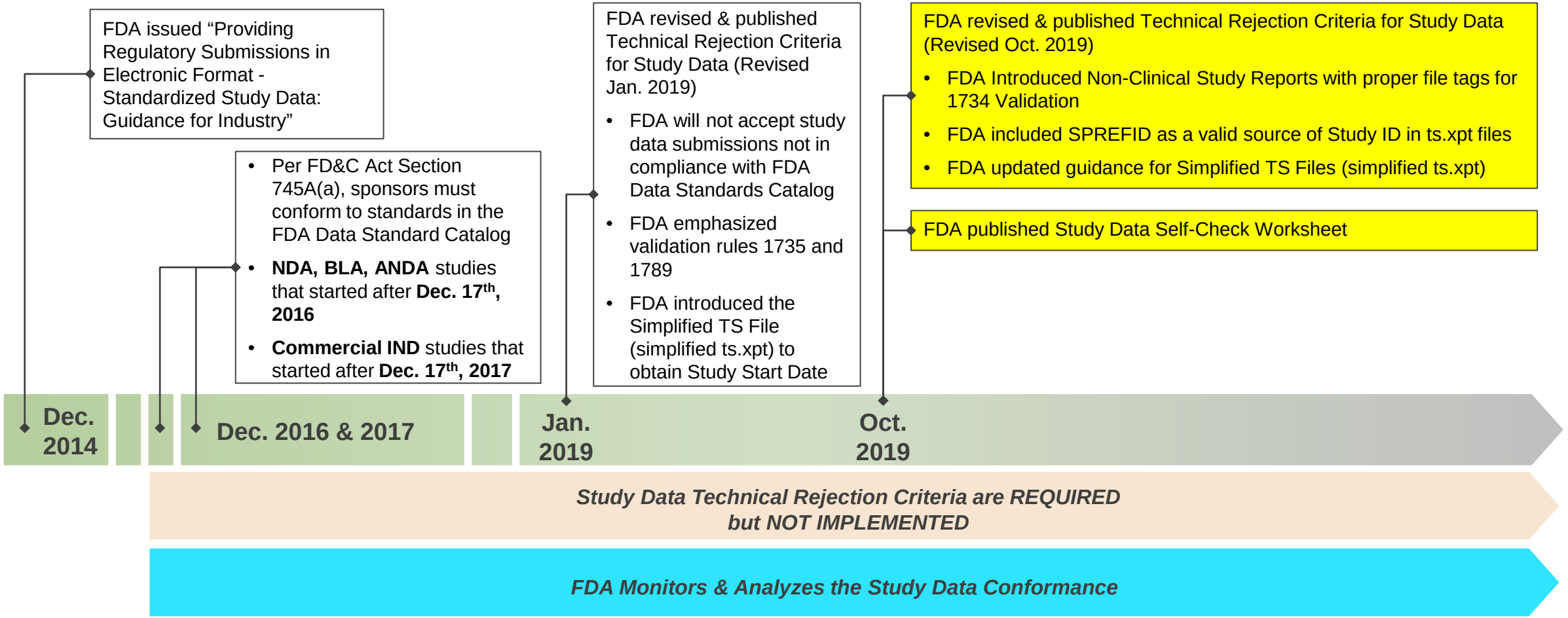
Technical Rejection Criteria Revisions Timeline

January 2019: FDA published Revised Study Data Technical Rejection Criteria



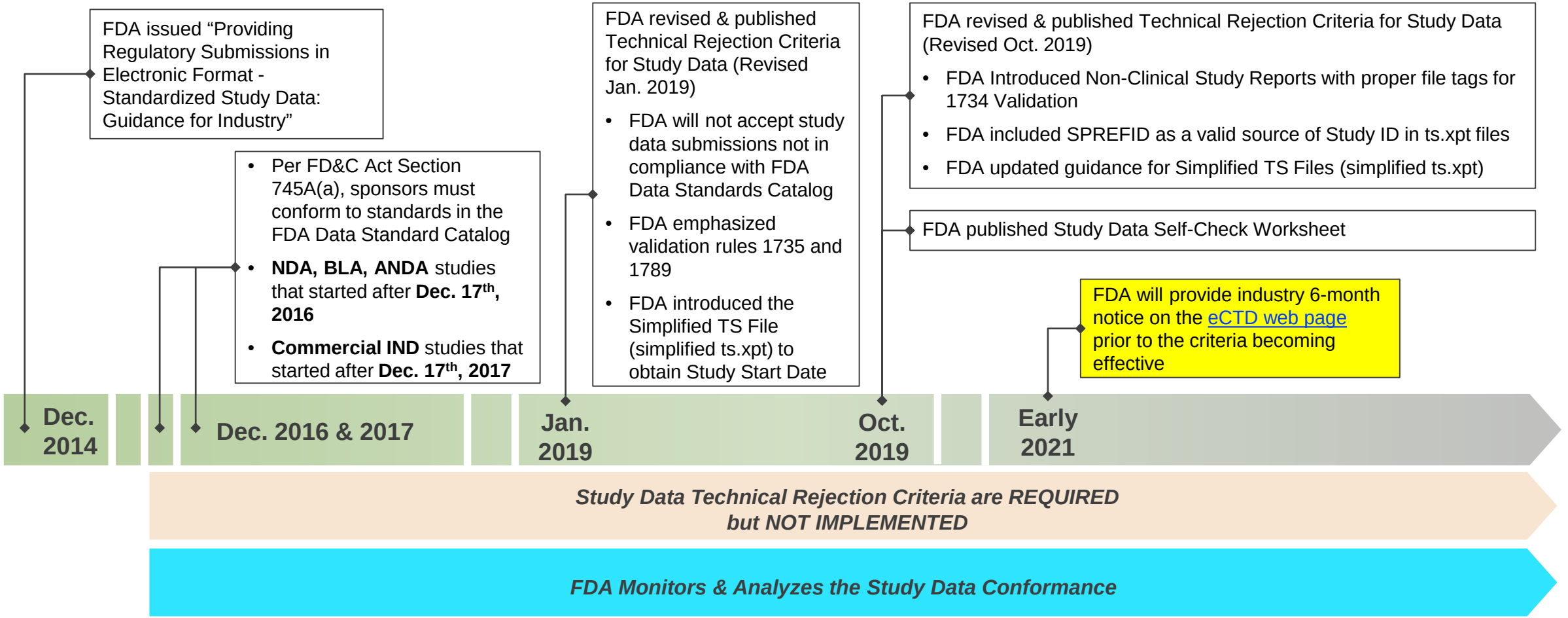
Technical Rejection Criteria Revisions Timeline

October 2019: FDA published Revised Study Data Technical Rejection Criteria and the Study Data Self-Check Worksheet to assist sponsors with TRC conformance



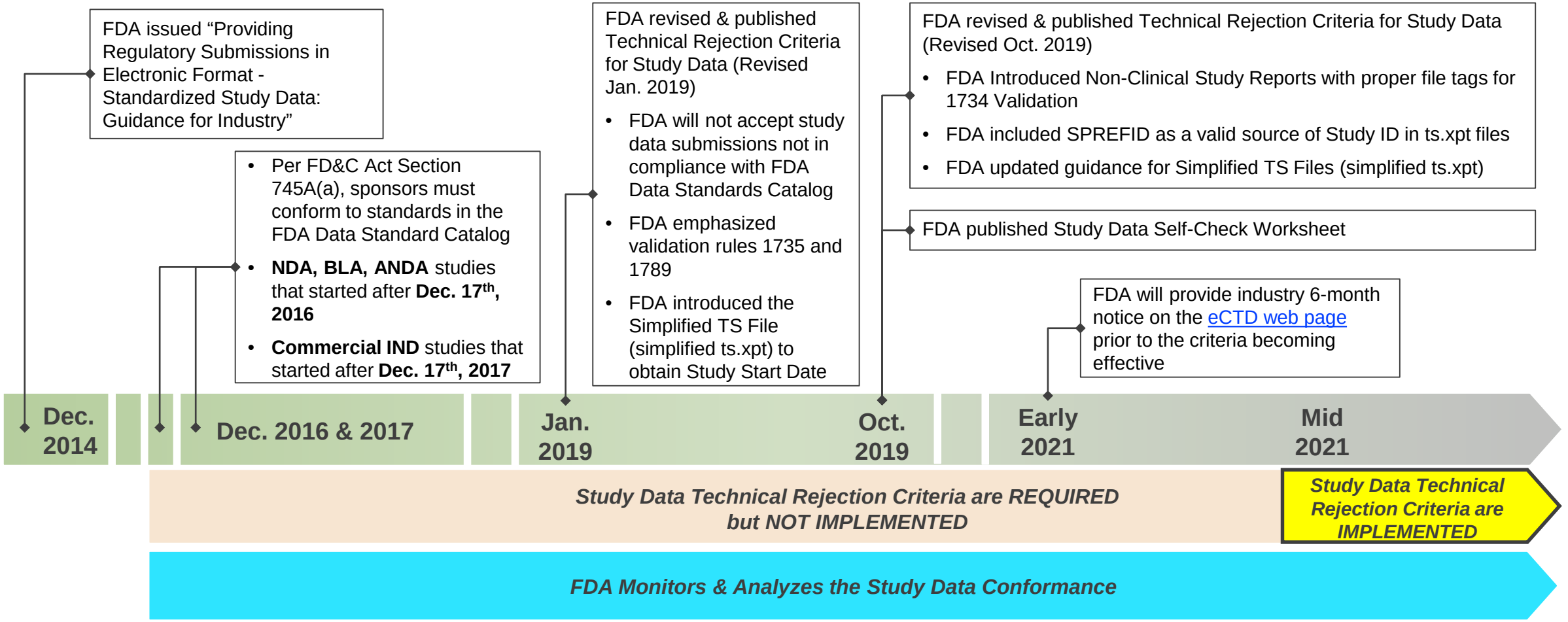
Technical Rejection Criteria Revisions Timeline

Early 2021: FDA will provide industry 6-month notice on FDA's eCTD website prior to the criteria becoming effective



Technical Rejection Criteria Revisions Timeline

Mid 2021: FDA will implement the Technical Rejection Criteria and criteria will become effective



Where to find the SD TRC Effective Date ?

The Effective Date for the validation criteria 1734, 1735, 1736, 1737, and 1789 will be added to the "Specifications for eCTD Validation Criteria" document as seen below

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:	TBD

Number:	1735
Group:	STF
Description:	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
Severity Description:	High
US DTD Version	2.01 and 3.3
Effective Date:	TBD

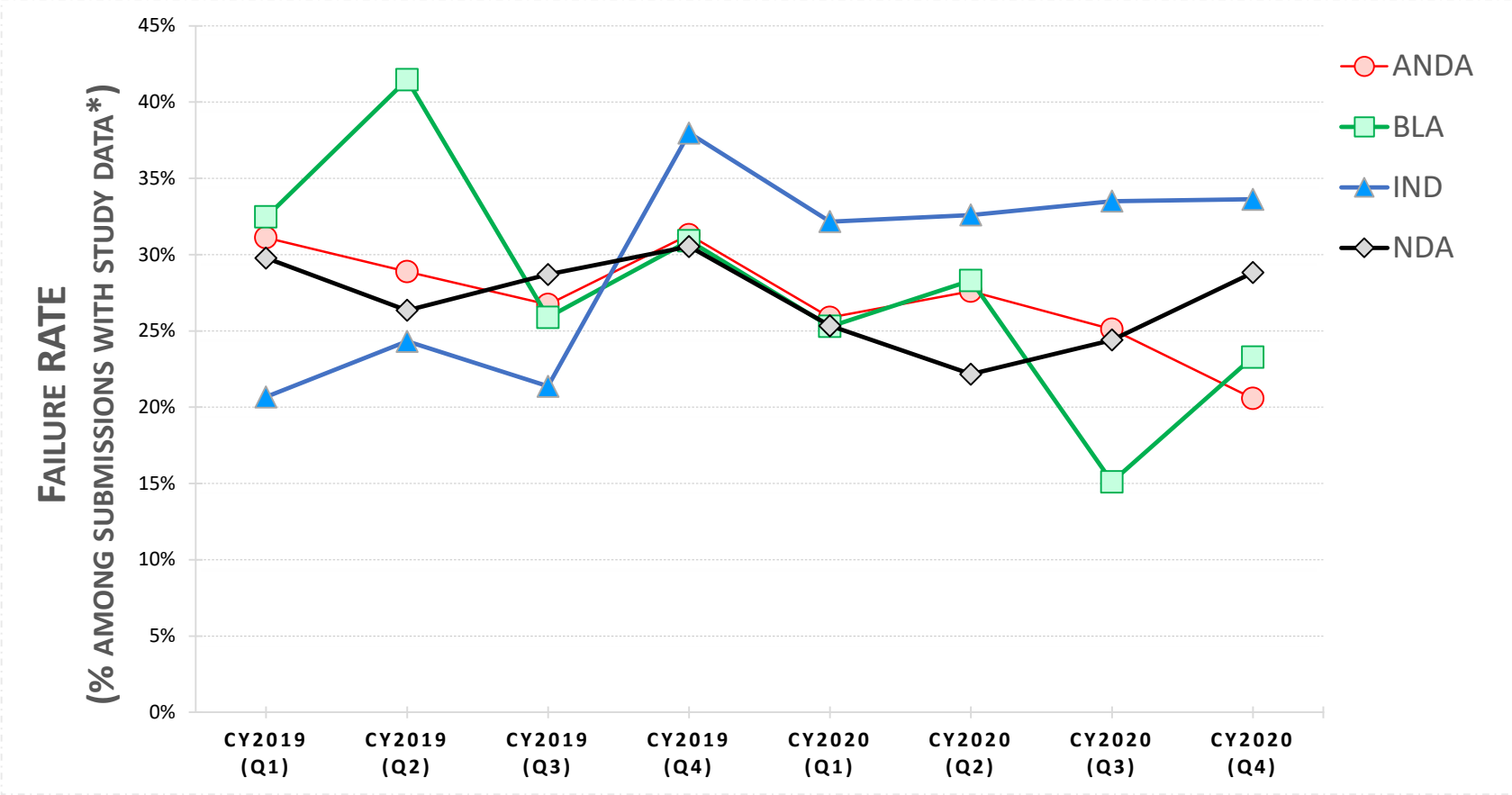
Number:	1736
Group:	General
Description:	For SEND data, a DM dataset and define.xml must be submitted in module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4 For SDTM data, a DM dataset and define.xml must be submitted module 5, sections 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2 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
Severity Description:	High
US DTD Version	2.01 and 3.3
Effective Date:	TBD

Number:	1789
Group:	STF
Description:	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
Severity Description:	High
US DTD Version	2.01 and 3.3
Effective Date:	TBD

Number:	1737
Group:	General
Description:	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, no more than one dataset of the same name should be submitted as new
Severity Description:	Medium
US DTD Version	2.01 and 3.3
Effective Date:	TBD

Study Data Technical Rejection Criteria Conformance Statistics and Trend

CDER CY2019 & CY2020 Conformance Trend for TRC Validation Errors 1734 & 1736



Notes:

1) CY2019 and CY2020 analysis was conducted according to the TRC (Revised Oct. 2019)
2) Analysis includes NDA, BLA, ANDA and Commercial IND Sequence received by CDER between 1/1/2018 and 12/31/2020
3) Validation of error 1736 is not performed if a study has Error 1734
4) *M4 Definition of Study Data - .xpt files and/or a Study Report tagged as pre-clinical-study-report, legacy-clinical-study-report, or study-report-body present in eCTD module 4
5) *M5 Definition of Study Data - .xpt files present in eCTD module 5

CDER CY2020 Submission Level Conformance for Validation Errors 1734 & 1736

- ANDA, NDA, BLA, and Commercial IND Submissions received by CDER between 1/1/2020 and 12/31/2020, were assessed for conformance to the two high-level errors as revised in the Technical Rejection Criteria for Study Data (Revised Jan. 2019)

		ANDA	BLA	NDA	Comm. IND**	All
a	**Total Number of Submissions**	**61,525**	**19,808**	**55,817**	**95,222**	**232,372**
b	**Total Number of Submissions with Study Data***	704	388	1073	3291	5456
c	**Total Number of Submissions with Study Data* in TRC Applicable Sections**	635	268	693	1907	3503
d	**Total Number Submissions with Critical Errors (e or f)**	**175**	**90**	**271**	**1086**	**1622**
e	**Error 1734**	164	87	263	1045	1559
f	**Error 1736**	28	7	21	62	118
g	**Failure Rate (% among submissions with Study Data* in TRC Applicable Sections) [d/c]**	27.56%	33.58%	39.11%	56.95%	46.30%
h	**Failure Rate (% among submissions with Study Data*) [d/b]**	**24.86%**	**23.20%**	**25.26%**	**33.00%**	**29.73%**
i	**Failure Rate (% among all submissions) [d/a]**	0.28%	0.45%	0.49%	1.14%	0.70%

Notes:

1) CY2020 analysis was conducted according to the TRC (Revised Oct. 2019)
2) Analysis includes NDA, BLA, ANDA and Commercial IND Sequence received by CDER between 1/1/2020 and 12/31/2020
3) Validation of error 1736 is not performed if a study has Error 1734
4) * M4 Definition of Study Data - .xpt files and/or a Study Report tagged as pre-clinical-study-report, legacy-clinical-study-report, or study-report-body present in eCTD module 4
5) * M5 Definition of Study Data - .xpt files present in eCTD module 5
6) **Comm. IND Clinical studies are included in this analysis which constitutes a very small fraction of the total submissions with critical errors. Comm. IND clinical studies are not subject to errors 1734, 1735, 1736, or 1737

CDER CY2020 Study Level Conformance for Validation Errors 1734 & 1736

- A high number of non-clinical (m4) studies fail Validation Rule 1734 because of a missing trial summary dataset
- A trial summary dataset (ts.xpt) is required when a non-clinical study report is submitted (TRC Revised Oct. 2019)

		ANDA		BLA		NDA		Comm. IND	
		m4	m5	m4	m5	m4	m5	m4	m5**
a	**Total Number of Studies***	45	1398	1041	796	5477	2556	33534	328
b	**Total Number of Studies* in TRC Applicable Sections**	15	1222	136	453	868	1645	5619	291
c	**Total Number Studies with Critical Errors (d or f)**	**12**	**342**	**82**	**109**	**349**	**334**	**3272**	**45**
d	**Error 1734**	12	277	82	104	348	333	3173	40
f	**Error 1736**	0	65	0	5	1	24	99	5
g	**Error Rate (% among failed studies with Study Data* Data in TRC Applicable Sections**) [c/b]**	80.0%	28.0%	60.3%	24.1%	40.2%	20.3%	58.2%	15.5%
h	**Error Rate (% among Total Number of Studies) [c/a]**	**26.7%**	**24.5%**	**7.9%**	**13.7%**	**6.4%**	**13.1%**	**9.8%**	**13.7%**

Notes:

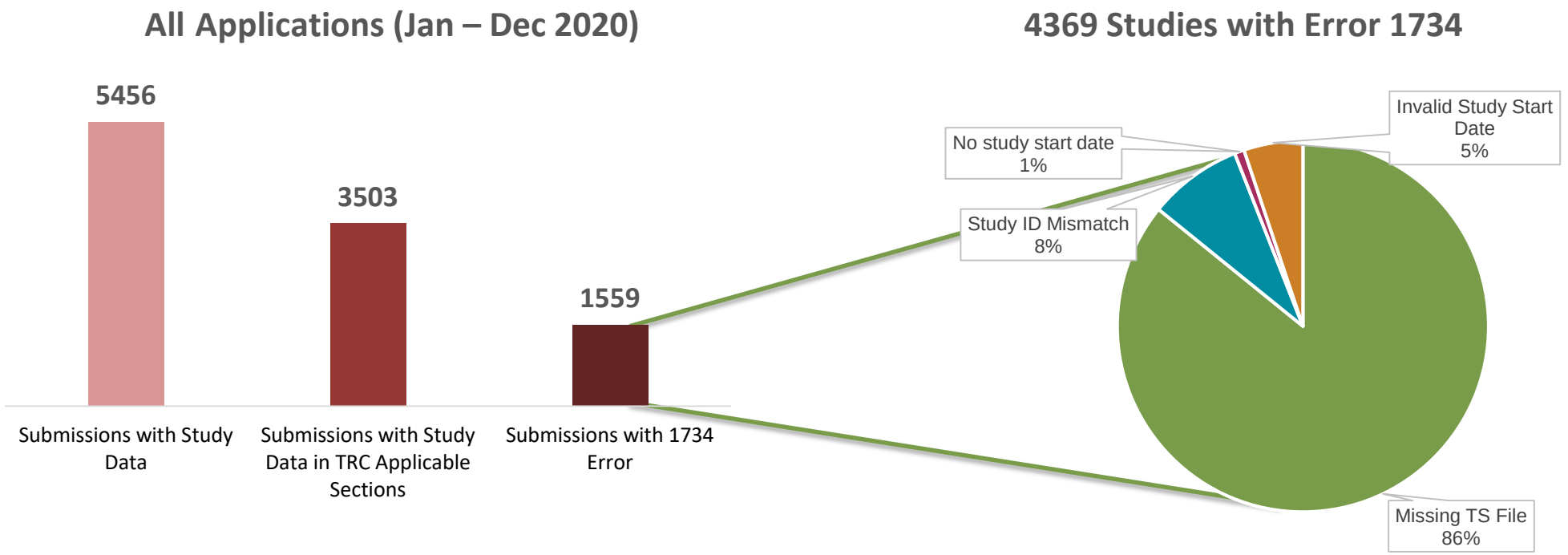
(1) CY2020 analysis was conducted according to the TRC (Revised Oct. 2019)
(2) Validation of errors 1736 is not performed if a study has Error 1734
(3) *M4 Definition of Study - .xpt files and/or a Study Report tagged as pre-clinical-study-report, legacy-clinical-study-report, or study-report-body present in TRC applicable sections
(4) *M5 Definition of Study - .xpt files present in TRC applicable sections
(5) ** Comm. IND clinical studies are not subject to errors 1734, 1735, 1736, or 1737

Top Error Reason for TRC Rule 1734

CY2020 Error Reasons for Validation Rule 1734

Error	Description
1734	Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections*

- **Common error reason for all application type:**
  - A missing ts.xpt file
  - Study ID Mismatch between TS and STF



1734 Most Common Error Reason: Missing TS File

Study Report File Tag Criteria					
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 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, 5.3.3.1z, 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 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)	

1734 Most Common Error Reason: Missing TS File

- A Simplified ts.xpt file would be expected when a non-clinical study report is submitted but SEND datasets are not required

- Simplified ts.xpt:
  - Sponsors should submit a dataset named ‘ts.xpt’ with four variables: STUDYID, TSPARMCD, TSVAL, and TSVALNF

Example of Simplified ts.xpt Dataset:

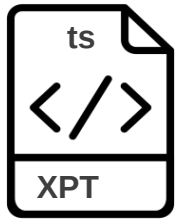
STUDYID	TSPARMCD	TSVAL	TSVALNF
• Study ID in STF File	• SSTDTC for a clinical study • STSTDTC for a nonclinical study	• Format: yyyy-mm-dd • Left blank when study start date is not available or relevant	• Left blank when study start date is provided in TSVAL • “NA”

References:
FDA Study Data Technical Conformance Guide (Appendices F & G; Version 4.4, Oct 2019)
FDA Study Data Technical Rejection Criteria (Revised Oct. 2019)

Example: Simplified TS Files

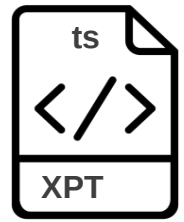
- Example of a Simplified TS file submitted for a non-clinical study with study-id “S107” in the STF file

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	S107	STSTDTC	2014-10-26	



Example of a Simplified TS file submitted for a non-clinical study with study-id “S107” in the STF file without a study start date

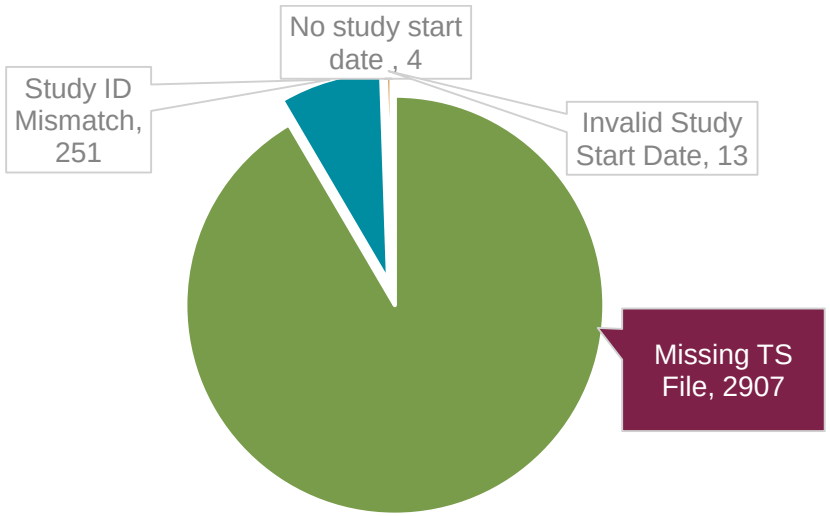
	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	S107	STSTDTC		NA



CY2020 -1734 common error reason for non-clinical studies - A missing ts.xpt file

- 3173 non-clinical studies from IND application fail for TRC rule 1734 out of which 2907 studies fail due to a missing ts.xpt

CY2020 Non-Clinical IND Studies 1734 Error Reason



Total = 3173

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

2907 IND non-clinical studies were missing the ts.xpt

	Count
Studies with study data or reports	2907
Studies with only study reports	2807

72.5% of the 2907 non-clinical studies with missing ts.xpt are in the repeat dose toxicology eCTD section

Toxicology Sections	Count
Repeat dose toxicology (m4.2.3.2)	2115
Single dose toxicology (m4.2.3.1)	621
Carcinogenicity (m4.2.3.4)	171

Note - 2 error reasons were counted for one IND non-clinical study

How to identify and create a simplified ts.xpt

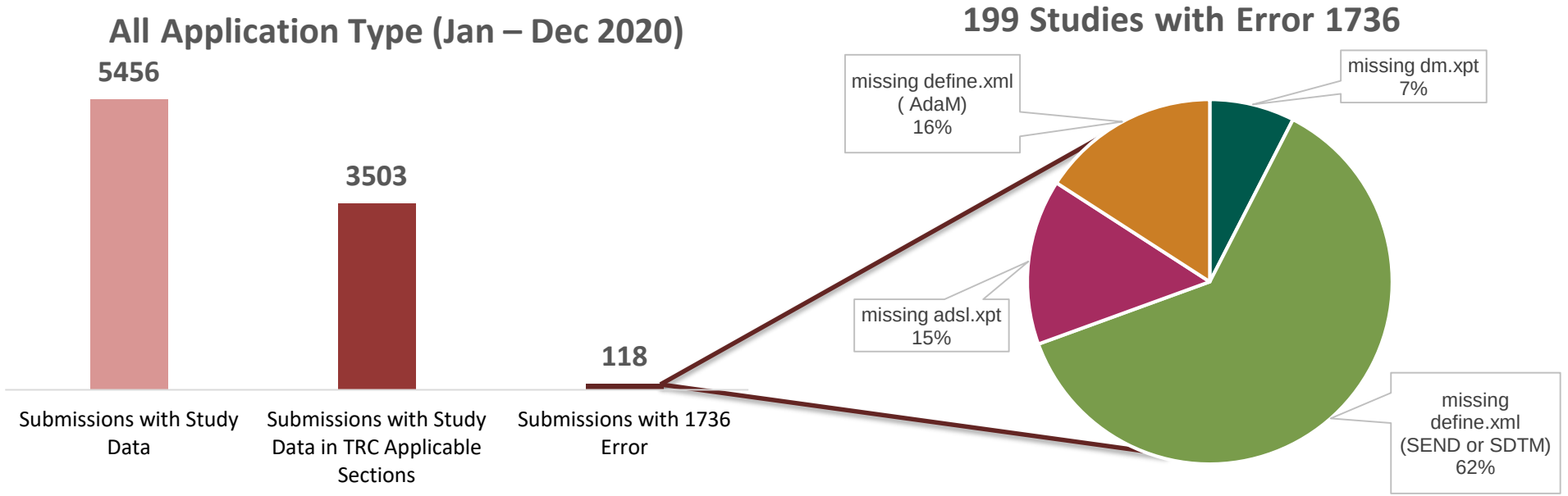
- **Sponsors should submit a simplified ts.xpt even if datasets are not submitted for a non-clinical study**
- **Sponsor should submit a ts.xpt file for clinical studies that contain .xpt file/s**
- To understand if a simplified ts.xpt file is required, please review the TRC Self-check worksheet.
- FDA has created a step-by-step Simplified ts.xpt Creation Guide on how to create a simplified ts.xpt using free and open source tools such as R or Python.
- There's also a PHUSE Utility to assist in generating a simplified ts.xpt file

Top Error Reason for TRC Rule 1736

CY2020 CDER Error Reasons for Validation Rule 1736

Error	Description
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*

- **Common error reason for all application types:**
  - A missing define.xml file
  - A missing define.xml, dm.xpt, and/or adsl.xpt files



Self-Check Worksheet Example

- **Section 5** in the Self-Check Worksheet Provides more guidance to sponsors/applicants to check for the DM and/or ADSL for standardized dataset as well as the associated Define file

Verify DM and Define for SEND

Nonclinical (m4)

Tabulation (SEND datasets)

5b. Is DM File Included?* ☒ Yes ☐ No

5c. Is Define File Included?* ☒ Yes ☐ No

Referenced Validation Error Number 1736

*If you answered "No" in **Fields 5b or 5c**, Validation Rule 1736 FAILS. Proceed to **Fields 5d and 5e** for Validation Rule 1735.*

Verify DM and Define for SDTM

Clinical (m5)

Tabulation (SDTM datasets)

5f. Is DM File Included?* ☒ Yes ☐ No

5g. Is Define File Included?* ☒ Yes ☐ No

Referenced Validation Error Number 1736

*If you answered "No" in **Fields 5f or 5g**, Validation Rule 1736 FAILS. Proceed to Fields **5h and 5i** for Validation Rule 1735.*

Verify ADSL and Define for ADaM

Analysis (ADaM datasets)

5j. Is ADSL File Included?* ☒ Yes ☐ No

5k. Is Define File Included?* ☒ Yes ☐ No

Referenced Validation Error Number 1736

*If you answered "No" in **Fields 5j or 5k**, Validation Rule 1736 FAILS. Proceed to **Fields 5l and 5m** for Validation Rule 1735.*

Summary

- Overall Error rate of TRC rule 1734 and 1736 has not significantly reduced from CY2019 to CY2020
- **FDA requires the submission of standardized Study Data as defined in the FDA Data Standard Catalog**
- FDA will provide industry 6-month notice on the eCTD web page prior to the criteria becoming effective
  - The Study Data Technical Rejection criteria will be updated with the actual effective date after the notice
  - After the announcement, FDA plans to provide TRC validation error warning message as part of 3rd acknowledgement
- **Sponsors are obligated to meet Technical Rejection Criteria for Study Data which determine whether a submission complies with FDA's standards for study data**

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.

References

- **Study Data Standards Resources**
  - Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry
  - Study Data Technical Conformance Guide
  - FDA Data Standards Catalog

  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
  - Technical Rejection Criteria Self-Check Worksheet
  - Technical Rejection Criteria Self-Check Worksheet Instructions

  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**

  HTTPS://WWW.FDA.GOV/REGULATORY-INFORMATION/SEARCH-FDA-GUIDANCE-DOCUMENTS

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Questions