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A regulatory journey from PDUFA, FDASIA, and Guidances for standardized study data

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PhUSE CSS, September 13, 2021

Agenda



- PDUFA and 745A
- Data Standards Requirements
- Study Data Technical Rejection Criteria
- Tools to Help Industry

A Brief History

PDUFA and 745A

Looking back to 2012...

Problem to be Addressed

- The extreme variability and unpredictability of the format and content of submitted application data present a major obstacle to timely, consistent, and efficient review within current PDUFA timeframes
- Lack of standardized clinical data:
 - Limits ability to address in-depth questions and late-emerging issues in a timely manner
 - Impedes timely safety analysis to inform REMS decisions
 - Limits ability to transition to more standardized and quantitative approaches to benefit-risk assessment

Timeline of PDUFA & Guidances



July 9, 2012 –
FDASIA signed

2011

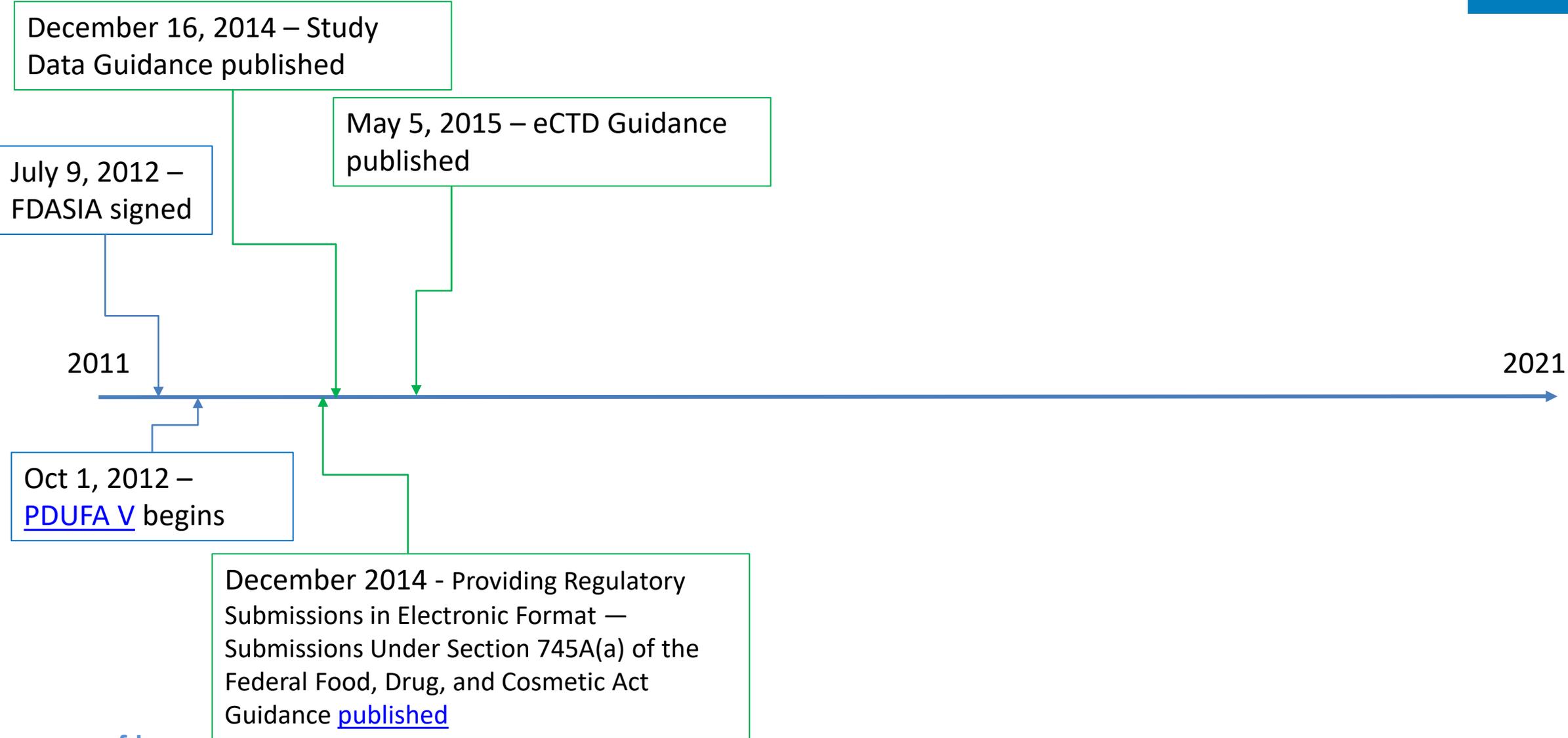
2021

Oct 1, 2012 –
PDUFA V begins

FDASIA/PDUFA V

- [PDUFA V goals](#) include a section “Improving the efficiency of human drug review through required electronic submissions and standardization of electronic drug application data”
- “Section 1136 of FDASIA amended the FD&C Act by adding section 745A, which addresses electronic submissions. ... Section 745A(a)(1) of the FD&C Act describes the general scope of section 745A(a) and provides that submissions under NDAs, ANDAs, BLAs, and INDs must be in electronic format specified in FDA guidance...” [Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A\(a\) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry, Section II](#)

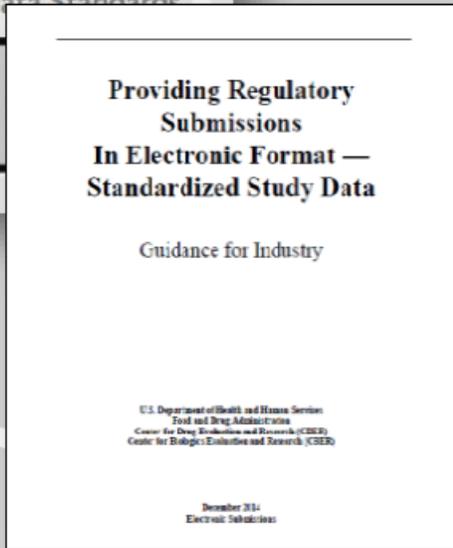
Timeline of PDUFA & Guidances



745A(a) Guidances

- FDA issued [“Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry”](#) in December 2014 (updated in June 2021)
 - Sponsors must conform to standards in the FDA Data Standards Catalog:
 - NDA, certain BLA, ANDA studies that started after December 17th, 2016
 - Commercial IND studies started after December 17th, 2017
- FDA issued [“Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications Guidance for Industry”](#) in May 2015 (updated in February 2020)
 - Sponsors must submit in eCTD format:
 - NDA, certain BLA, ANDA applications starting May 5th, 2017
 - Commercial IND and certain MFs applications starting May 5th, 2018

eStudy Guidance
Binding Guidance— Requires that studies are compliant with the standards outlined in the FDA Data Standards



**December
17
2014**

24 Months*

**December
17
2016**

Compliance

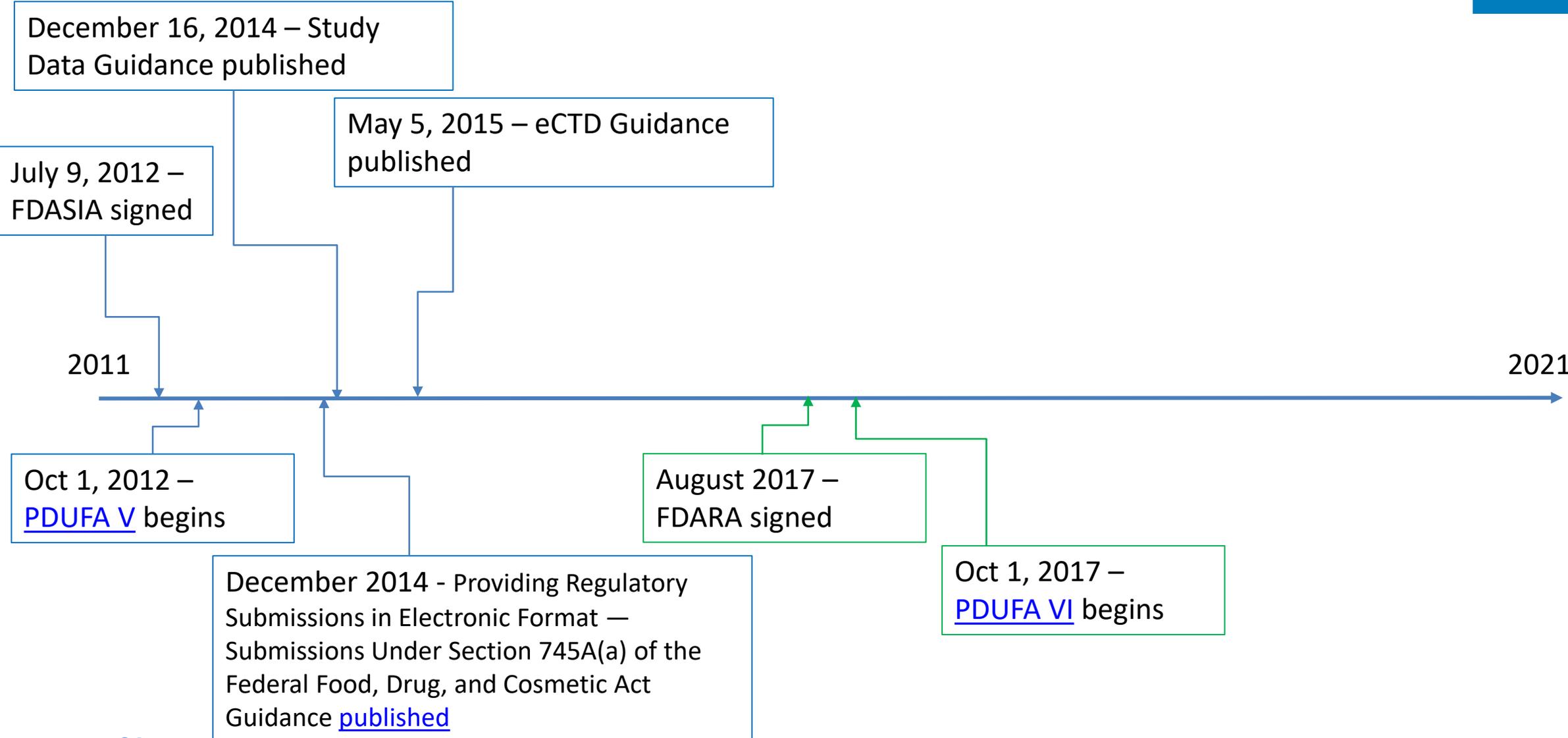


Studies starting after MUST use the standards in the Data Catalog (NDAs, ANDAs, BLAs)**

**Final
Published
December, 2014**

*36 months for INDs **Study Start Date in the SDTM Trial Summary Domain (TSPARMCD = SSTDTC). 4

Timeline of PDUFA & Guidances



December 16, 2014 – Study Data Guidance published

May 5, 2015 – eCTD Guidance published

July 9, 2012 – FDASIA signed

2011

2021

Oct 1, 2012 – [PDUFA V](#) begins

August 2017 – FDARA signed

December 2014 - Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act Guidance [published](#)

Oct 1, 2017 – [PDUFA VI](#) begins

FDARA/PDUFA VI

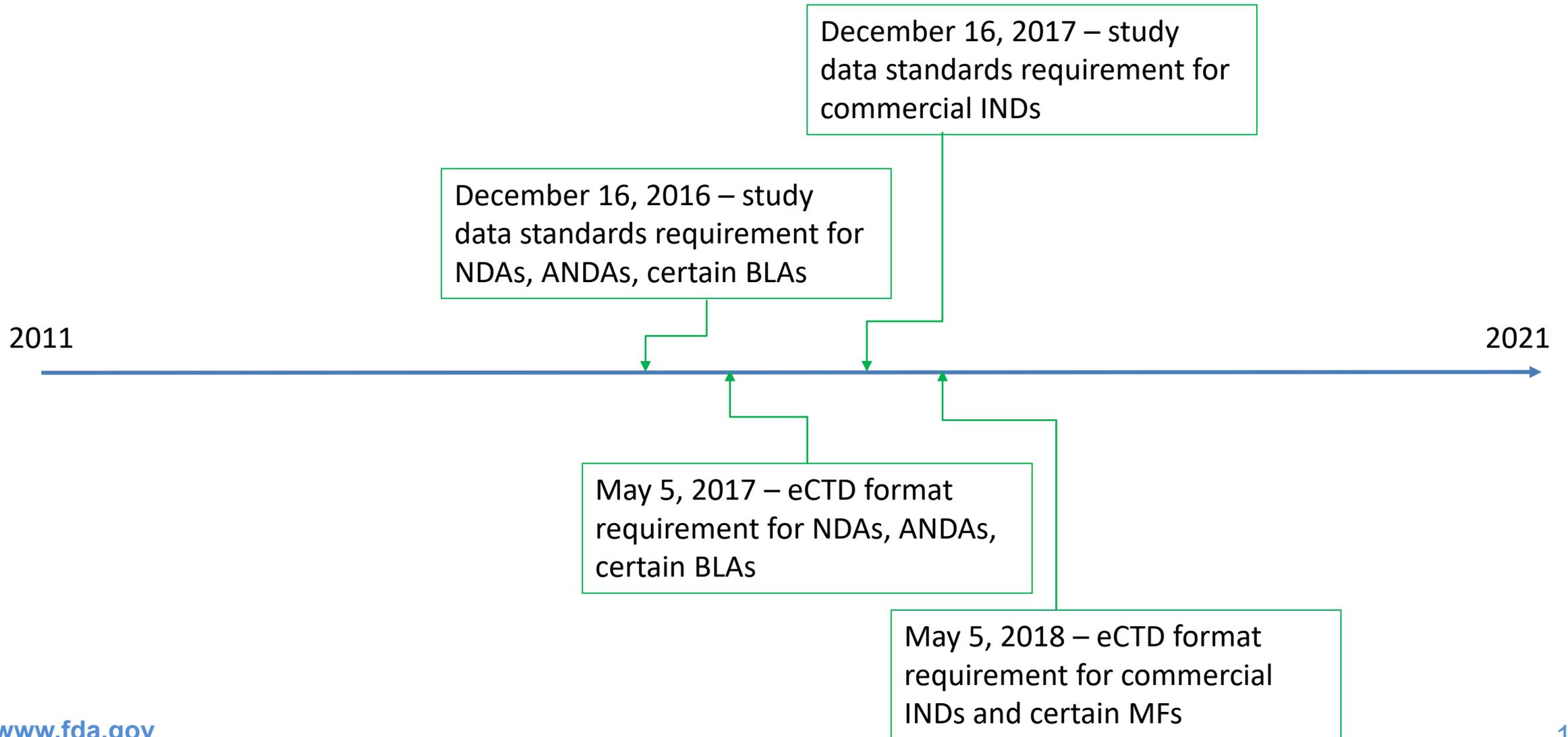


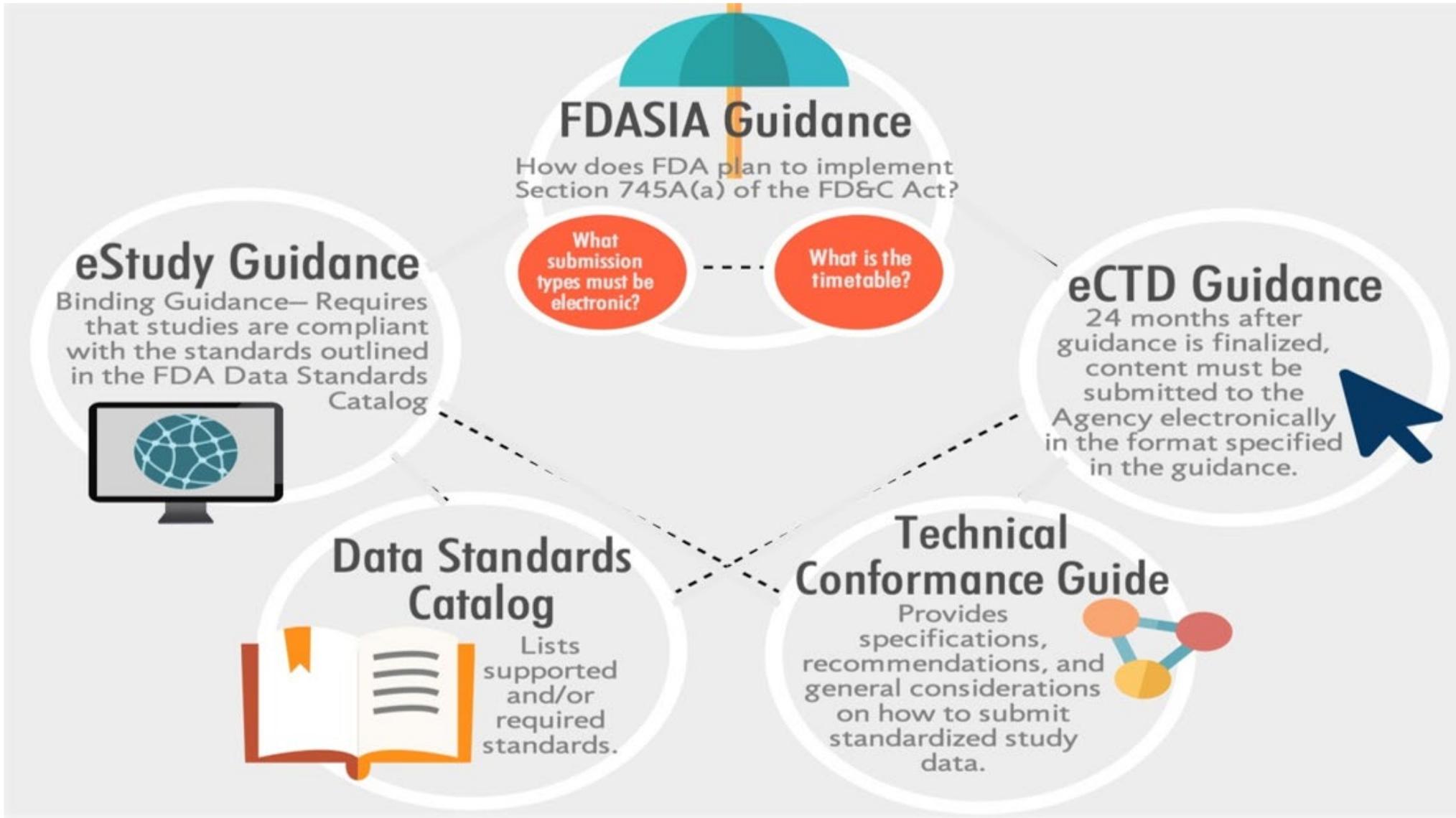
- [PDUFA VI goals](#) include a section “Enhance transparency and accountability of FDA electronic submission and data standards activities”
- [Deliverables](#) include:
 - Public Meetings for Electronic Submissions and Data Standards
 - CBER-CDER Data Standards Program Action Plan
 - FDA Data Standards Catalog
 - Joint Quarterly Meetings to Enhance Transparency and Accountability of FDA Electronic Submission and Data Standards Activities

How does it all connect?

Data Standards Requirements

Timeline of data standards



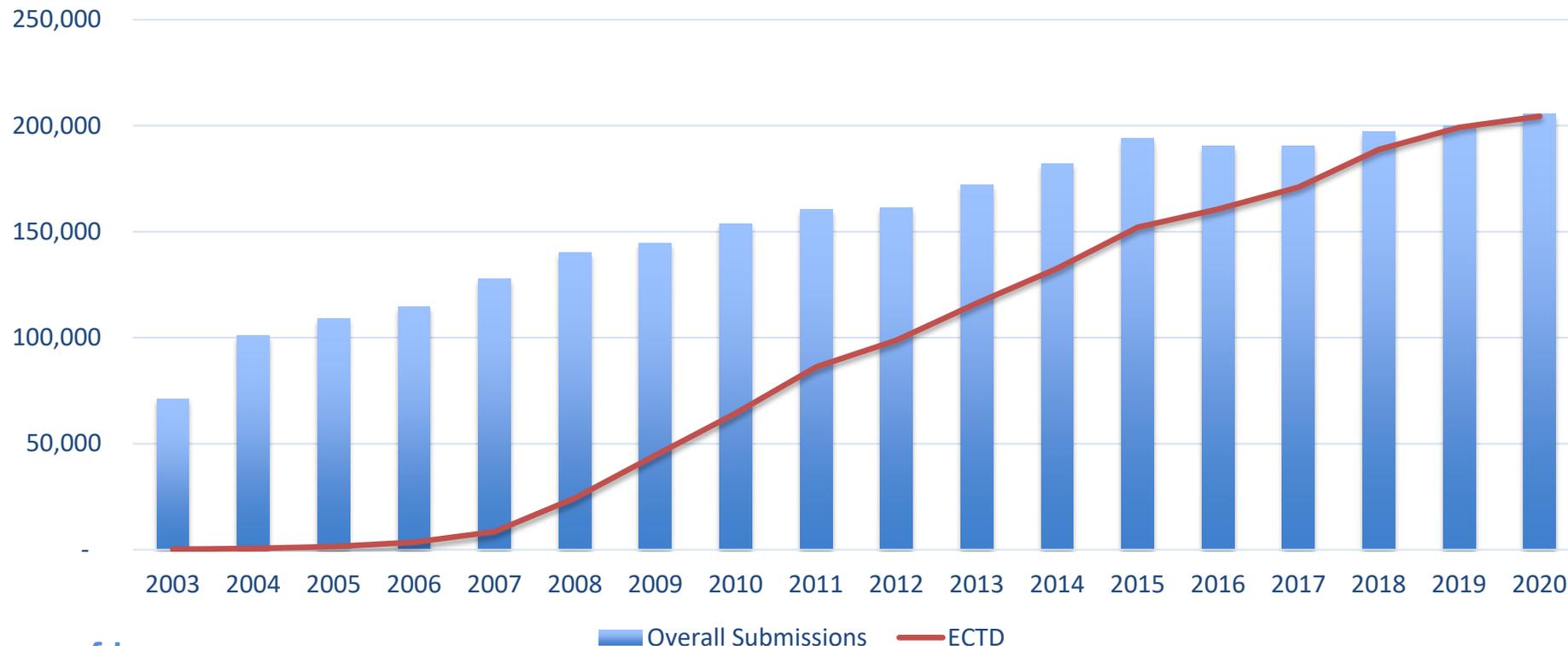




eCTD Submission Metrics 2003 - 2020

CDER received approximately 205,000* electronic submissions via ESG in FY 2020. Nearly all were in eCTD.

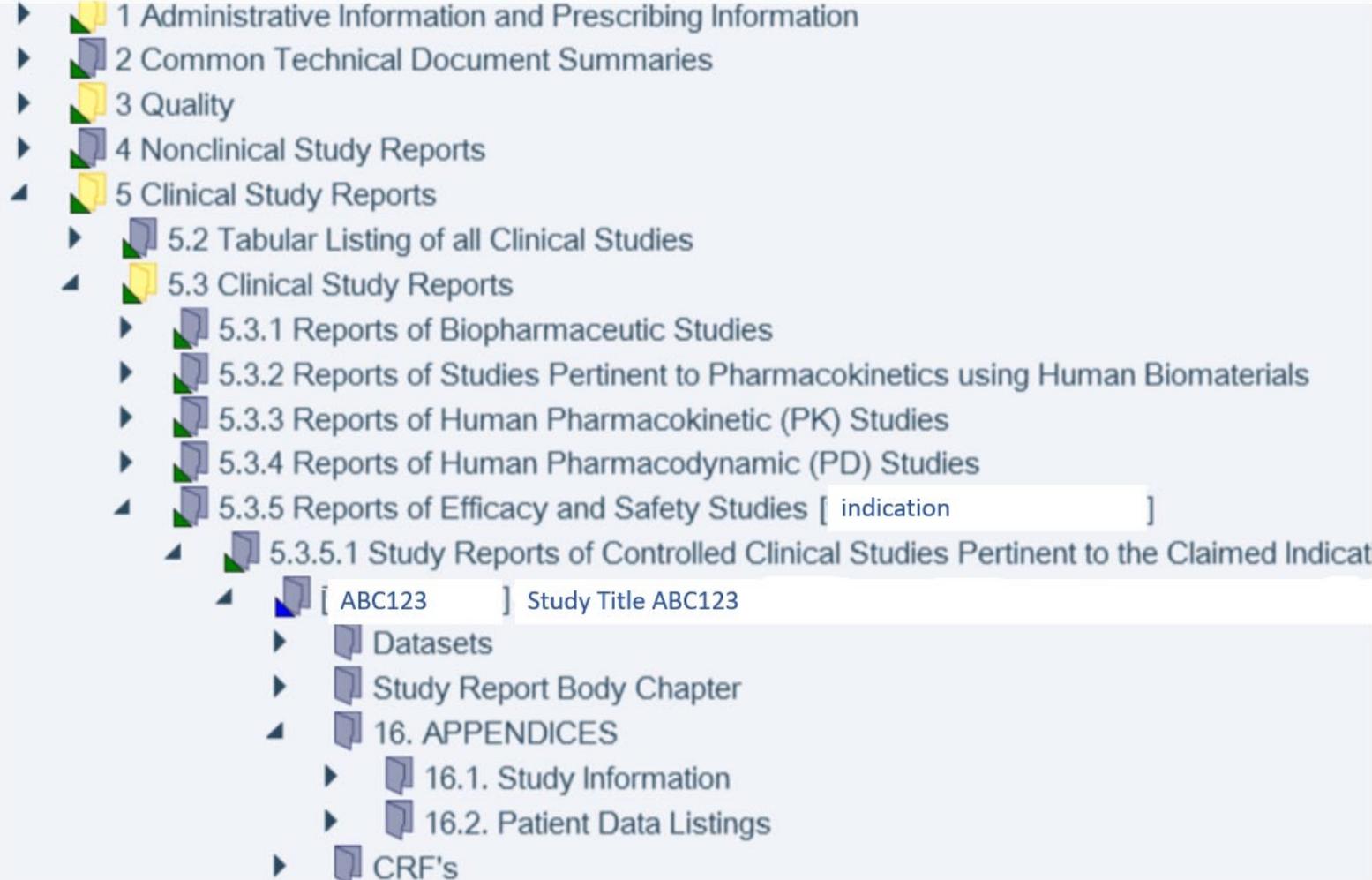
Comparison: Overall Submissions vs. eCTD Submissions



*excludes Non-Commercial IND and DMF Type III

Review of eCTD Submissions

FDA uses Lorenz docuBridge to support the review of eCTD formatted submissions



The screenshot shows a hierarchical tree structure of an eCTD submission. The root level includes sections 1 through 5. Section 5, 'Clinical Study Reports', is expanded to show sub-sections 5.2 and 5.3. Section 5.3, 'Clinical Study Reports', is further expanded to show sub-sections 5.3.1 through 5.3.5. Section 5.3.5, 'Reports of Efficacy and Safety Studies', is expanded to show a specific study entry: '[ABC123] Study Title ABC123'. This study entry is expanded to show its components: 'Datasets', 'Study Report Body Chapter', '16. APPENDICES', '16.1. Study Information', '16.2. Patient Data Listings', and 'CRF's'.

- ▶ 1 Administrative Information and Prescribing Information
- ▶ 2 Common Technical Document Summaries
- ▶ 3 Quality
- ▶ 4 Nonclinical Study Reports
- ▶ 5 Clinical Study Reports
 - ▶ 5.2 Tabular Listing of all Clinical Studies
 - ▶ 5.3 Clinical Study Reports
 - ▶ 5.3.1 Reports of Biopharmaceutic Studies
 - ▶ 5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials
 - ▶ 5.3.3 Reports of Human Pharmacokinetic (PK) Studies
 - ▶ 5.3.4 Reports of Human Pharmacodynamic (PD) Studies
 - ▶ 5.3.5 Reports of Efficacy and Safety Studies [indication]
 - ▶ 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
 - ▶ [ABC123] Study Title ABC123
 - ▶ Datasets
 - ▶ Study Report Body Chapter
 - ▶ 16. APPENDICES
 - ▶ 16.1. Study Information
 - ▶ 16.2. Patient Data Listings
 - ▶ CRF's

Data Standards Catalog



FDA Data Standards Catalog v7.2 (07-01-2021) - Supported and Required Standards

For full description of column headings, see Instr. & Column Descriptions tab

Use	Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Supported Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY) [1]	Date Requirement Ends (MM/DD/YYYY)	Statutory, Regulatory, or Guidance Authority	Information Sources
Clinical study datasets	SDTM	XPT	CDISC	1.2	3.1.2	CDER, CBER	10/30/2009	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]	Standardized Study Data	CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.2	Version 3.1.2 Amendment 1	CDER, CBER	08/07/2013	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]	Standardized Study Data	CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.3	3.1.3	CDER, CBER	12/01/2012	03/15/2021	12/17/2016 [1] 12/17/2017 [2]	03/15/2021	Standardized Study Data	CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.4	3.2	CDER, CBER	08/17/2015		03/15/2018 [1] 03/15/2019 [2]		Standardized Study Data	CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.7	3.3	CDER, CBER	03/15/2021			03/15/2023	Standardized Study Data	CDISC.org - SDTM
Animal Rule study datasets	SDTM	XPT	CDISC	1.8	SENDIG-AR v1.0	CDER	03/15/2020			3/15/2022 [1] 3/15/2023 [2]	Standardized Study Data	CDISC.org - SDTM
Clinical study datasets	Analysis Data Model (ADaM)	XPT	CDISC	2.1	1.0	CDER, CBER	Ongoing	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]	Standardized Study Data	CDISC.org - ADaM
Clinical study datasets	ADaM	XPT	CDISC	2.1	1.1	CDER, CBER	03/15/2018			03/15/2019 [1] 03/15/2020 [2]	Standardized Study Data	CDISC.org - ADaM
Animal study datasets	Standard for Exchange of Nonclinical Data (SEND)	XPT	CDISC	1.2	3.0	CDER	06/13/2011	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]	Standardized Study Data	CDISC.org - SEND
Animal study datasets	SEND	XPT	CDISC	1.5	3.1	CDER	08/21/2017			03/15/2019 [1] 03/15/2020 [2]	Standardized Study Data	CDISC.org - SEND
Animal study datasets	SEND	XPT	CDISC	1.5	3.1	CBER	03/15/2021			03/15/2023	Standardized Study Data	CDISC.org - SEND
Nonclinical study datasets										03/15/2023 [1]	Standardized Study Data	CDISC.org - SEND

Review of Study Data

FDA also utilizes multiple tools and systems to support analysis of standardized study data:

CDEROne

U.S. FOOD & DRUG ADMINISTRATION | CDEROne Analytics | Reports and Dashboards | Search Engines | Review Explorer | Resources

Clinical Trials

- Disclaimer
- Application Type & Number
- Product/Ingredient Name
- Dosage Form
- Approved ROA
- SNOMED CT
- Study ID
- NCT ID
- Trial Phase
- Study Title
- Trial Type
- Trial Disease/Condition Indication

Diagnosis Group

- Investigational Therapy or Treatment
- Trial Blinding Schema
- Trial is Randomized
- Control Type
- Dose Per Administration
- Dose Units
- Dose Form
- Dosing Frequency
- Objectives and Outcomes
- Planned Number of Subjects
- Actual Number of Subjects
- Countries with Sites

ACTIVE FILTERS

- Diagnosis Group
- Investigational Therapy or Treatment
- Trial Blinding Schema
- Trial is Randomized
- Control Type
- Dose Per Administration
- Dose Units
- Dose Form
- Dosing Frequency
- Objectives and Outcomes
- Planned Number of Subjects
- Actual Number of Subjects
- Countries with Sites

Clinical Trial Details

Application Type & Number	Product Name	Ingredient Name	Dosage Form	Study ID	Study Title
NDA 000000	Product A	Ingredient A	SOLUTION, INJECTION	Study ID STF	Study ABC
NDA 000000	Product A	Ingredient A	SOLUTION, INJECTION	Study ID TS	Study ABC
NDA 000000	Product A	Ingredient A	SOLUTION, INJECTION	NCT ID	00000
NDA 000000	Product A	Ingredient A	SOLUTION, INJECTION	Investigational Therapy	Drug xxx
NDA 000000	Product A	Ingredient A	SOLUTION, INJECTION	STF Study Title	Study ABC – A study that looks at many people taking Drug xxx and how to effects disease xxx in a Phase x Trial
NDA 000000	Product A	Ingredient A	SOLUTION, INJECTION	TS Trial Title	Study ABC – A study that looks at many people taking Drug xxx and how to effects disease xxx in a Phase x Trial
NDA 000000	Product A	Ingredient A	SOLUTION, INJECTION	Trial Phase	Phase x
NDA 000000	Product A	Ingredient A	SOLUTION, INJECTION	Trial Type	A study

M5 Documents

Docu...	Document...	Submissi...	Submission	Seq Num	Module/S...
study report body	Study ABC Synopsis	1/1/2021	ORIGINAL-1	0001	m5-3-3-4-extrinsic-factor-pk-study-reports
study report body	Study ABC Study Report	1/1/2021	ORIGINAL-1	0001	m5-3-3-4-extrinsic-factor-pk-study-reports
study report body	Study ABC Protocol Amendment	1/1/2021	ORIGINAL-1	0001	m5-3-3-4-extrinsic-factor-pk-study-reports
study report body	Study ABC Define.pdf	1/1/2021	ORIGINAL-1	0001	m5-3-3-4-extrinsic-factor-pk-study-reports

M2 Documents

Trial D...	Dataset N...	Submissi...	Submission	Seq Num	Module/S...
analysis dataset adam	AE	1/1/2021	ORIGINAL-1	0001	m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports
data tabulation dataset sdtm	DM	1/1/2021	ORIGINAL-1	0001	m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports
data tabulation dataset sdtm	TS	1/1/2021	ORIGINAL-1	0001	m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports
data tabulation dataset define	Define	1/1/2021	ORIGINAL-1	0001	m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports

An unstandardized study cannot display with the same detailed information as a standardized study

Review of Study Data

FDA also utilizes multiple tools and systems to support analysis of standardized study data:

JANUS NONCLINICAL REVIEW (PREPROD)

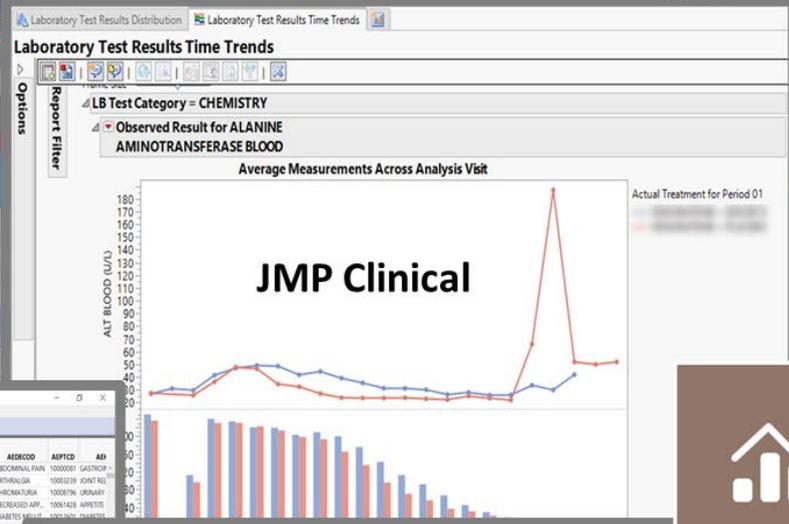
STUDY LIST > DASHBOARD > MICROSCOPIC FINDINGS - GROUPED SUMMARY

AVAILABLE DOMAINS: BG BW CL DD ED LB MA CO DM DS EX SE TA TE

GROUPED SUMMARY | DAILY BY ANIMAL | ANIMAL DETAILS

Filter table data by term: []

Organ/Tissue	Finding	Result Modifier	Severity	Male	Female
SPLEEN	Congest...	2 OF 5	Janus	C1-NP-001:0	C2-NP-001:500
				C3-NP-001:200	C4-NP-001:750
				C5-NP-001:1000	C6-NP-001:1500
				C7-NP-001:2000	C8-NP-001:2500
Total			1 (25.0%)	3 (75.0%)	



OCS Data Central

Locate the Data

Search

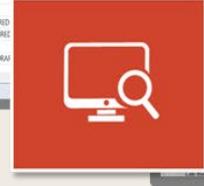
Data Located for: []

Sequence	Study Id	Data Standard	Number of Outcomes	Last Modified Timestamp	Program Submission?	EDR Source Location	Data Central Location
002	W	ACM	2	8/20/2013 4:05 PM	No	COPY	COPY
002	W	ACM	2	8/20/2013 4:05 PM	No	COPY	COPY
004	W	ACM	2	3/24/2012 3:44 PM	No	COPY	COPY
004	W	ACM	1	1/21/2012 10:28 PM	No	COPY	COPY
ACM			13	1/20/2019 1:28 AM	No	COPY	COPY



JMP

STUDIOD	D	USURID	ASRQ	ASPD	AETERM	AEMOOPY	AELLT	AELLTCD	AEDECO	AEPYCD	AEI
1	AE		1	#AIDE-015240	PAIN-ABDOMINAL	PAIN-ABDOMINAL	1003374	ABDOMINAL PAIN	1000081	GASTROI...	
2	AE		2	#AIDE-015240	ASTHENOIA	ASTHENOIA	1003379	ASTHENOIA	1003379	JOINT P...	
3	AE		3	#AIDE-015240	URINE-DISCOLOR	URINE-DISCOLOR	1006428	CHROMATURIA	1008796	URINARY	
4	AE		4	#AIDE-015240	ANOREXIA	ANOREXIA	1002446	DECREASED APP...	1008428	APPETITE	
5	AE		5	#AIDE-015240	DIABETES MELLIT.	DIABETES MELLIT.	1001261	DIABETES MELLIT.	1001261	DIABETES	
6	AE		6	#AIDE-015240	DARRHNOIA	DARRHNOIA	1001277	DARRHNOIA	1001277	DARRHNOIA	
7	AE		7	#AIDE-015240	INDIGESTION	INDIGESTION	1002796	INDIGESTION	1002796	INDIGESTION	
8	AE		8	#AIDE-015240	FATIGUE	FATIGUE	1001626	FATIGUE	1001626	FATIGUE	
9	AE		9	#AIDE-015240	FOLLICULITIS	FOLLICULITIS	1001838	FOLLICULITIS	1001838	FOLLICULITIS	
10	AE		10	#AIDE-015240	HYPERTHYROIDISM	HYPERTHYROIDISM	1000939	HYPERTHYROIDISM	1000939	HYPERTHYROIDISM	
11	AE		11	#AIDE-015240	FULLY EMPTY	FULLY EMPTY	1001291	FULLY EMPTY	1001291	MILLURIA	
12	AE		12	#AIDE-015240	ISCHEMIA	ISCHEMIA	1002247	ISCHEMIA	1002247	ISCHEMIA	
13	AE		13	#AIDE-015240	NAUSEA	NAUSEA	1000813	NAUSEA	1000813	NAUSEA	
14	AE		14	#AIDE-015240	PHOTODIAGNOSIS	PHOTODIAGNOSIS	1003466	PHOTODIAGNOSIS	1003466	PHOTODIAGNOSIS	
15	AE		15	#AIDE-015240	PHOTODIAGNOSIS	PHOTODIAGNOSIS	1003466	PHOTODIAGNOSIS	1003466	PHOTODIAGNOSIS	
16	AE		16	#AIDE-015240	INFECTION-SEIN	INFECTION-SEIN	1003542	POSITIVE	1003542	PROSTATE	
17	AE		17	#AIDE-015240	ELEVATED PSA-L	ELEVATED PROST.	1001484	PROSTATE	1001484	PROSTATE	
18	AE		18	#AIDE-015240	PROTEINURIA	PROTEINURIA	1001032	PROTEINURIA	1001032	PROTEINURIA	
19	AE		19	#AIDE-015240	PURITUS-URIN	PURITUS-URIN	1001787	PURITUS-URIN	1001787	PURITUS-URIN	
20	AE		20	#AIDE-015240	RASH-NON-AC	RASH-NON-AC	1001784	RASH	1001784	RASH	
21	AE		21	#AIDE-015240	MUCOSITIS-ORAL	MUCOSITIS-ORAL	1003130	STOMACH	1003130	STOMACH	
22	AE		22	#AIDE-015240	URINARY RETENT.	URINARY RETENT.	1003130	STOMACH	1003130	STOMACH	
23	AE		23	#AIDE-015240	PHOTODIAGNOSIS	PHOTODIAGNOSIS	1003466	PHOTODIAGNOSIS	1003466	PHOTODIAGNOSIS	
24	AE		24	#AIDE-015240	IMPAIRED/BLUR	IMPAIRED/BLUR	1003466	PHOTODIAGNOSIS	1003466	PHOTODIAGNOSIS	
25	AE		25	#AIDE-015240	IMPAIRED/BLUR	IMPAIRED/BLUR	1003466	PHOTODIAGNOSIS	1003466	PHOTODIAGNOSIS	
26	AE		26	#AIDE-015240	ACUTE RECURRE.	ACUTE RECURRE.	1003466	PHOTODIAGNOSIS	1003466	PHOTODIAGNOSIS	
27	AE		27	#AIDE-015240	VERRUCA/VIRUS-L	VERRUCA/VIRUS-L	1003466	PHOTODIAGNOSIS	1003466	PHOTODIAGNOSIS	
28	AE		28	#AIDE-015240	ARTHRALGIA	ARTHRALGIA	1003466	PHOTODIAGNOSIS	1003466	PHOTODIAGNOSIS	



Analysis Studio

Analysis Studio interface showing a scatter plot and a line graph. The scatter plot displays data points in red and blue, with axes labeled 'Peak On Treatment ACT or AST' and 'Peak On Treatment ACT or AST'. The line graph shows 'Peak On Treatment ACT or AST' over 'Study Day'.



CoreDF

Generated: 2020-01-06T13:45:10 | Version: 2.3.1

Demographics

- 38 (5.0%) of RACE values not found in CDISC code list
- 25 (6.4%) of screen failure subjects do not have information in Inclusion/Exclusion Criteria Not Met (IE) domain

Disposition

- 761 (3.7%) of disposition events are missing Start Date/Time of Disposition Event (DSDTIC) and Study Day of Exposure

Exposure

- No significant findings

Adverse Events

- 5 (1.3%) of adverse events have started after the last disposition date
- 1 (0.4%) of adverse events have neither severity or toxicity grade populated

Laboratory

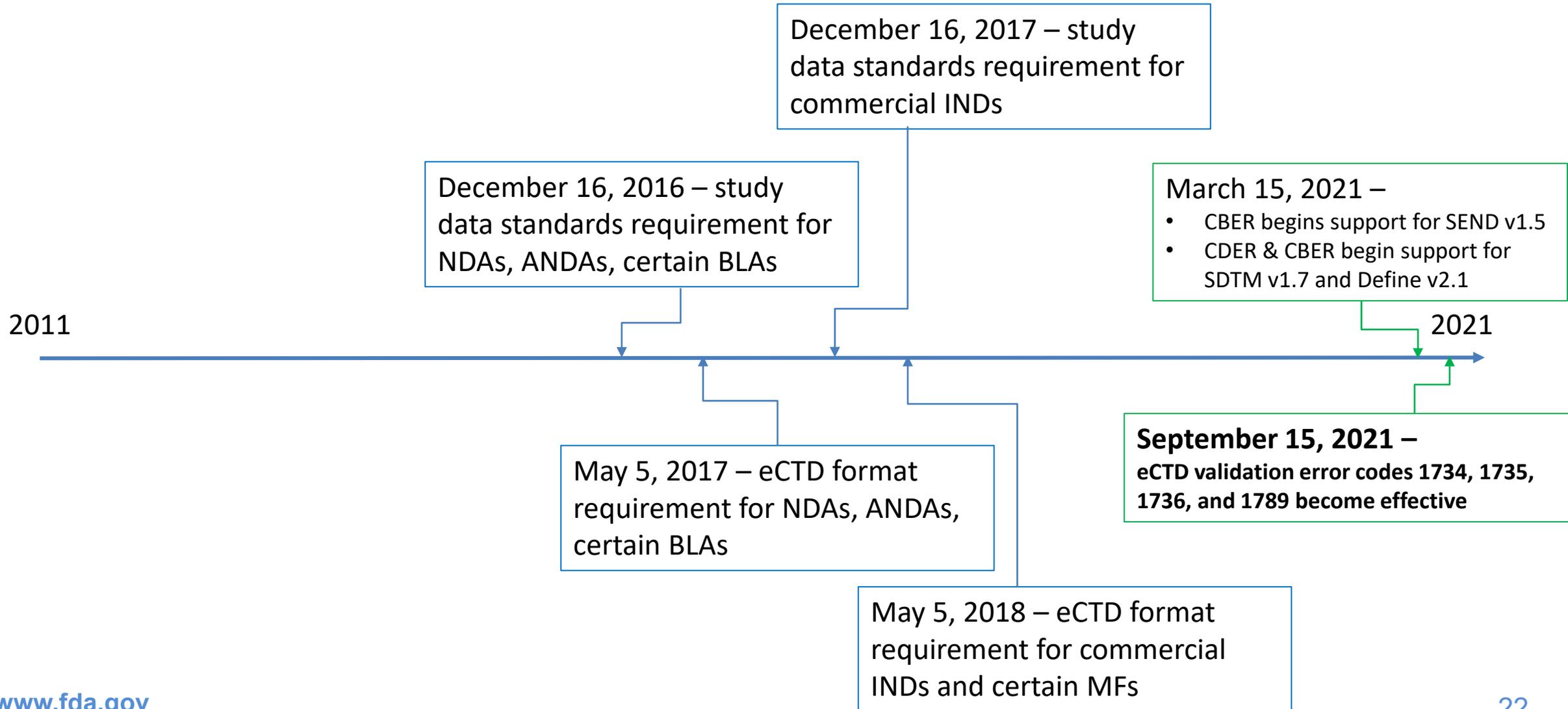
- 240 (5.1%) of laboratory test results are potential duplicates

Potential Data Quality Issues

- Coding
- Supplqual
- Non-standard DM.RACE values
- Missing IE



Timeline of data standards



How are we checking the Study Data Guidance requirements?

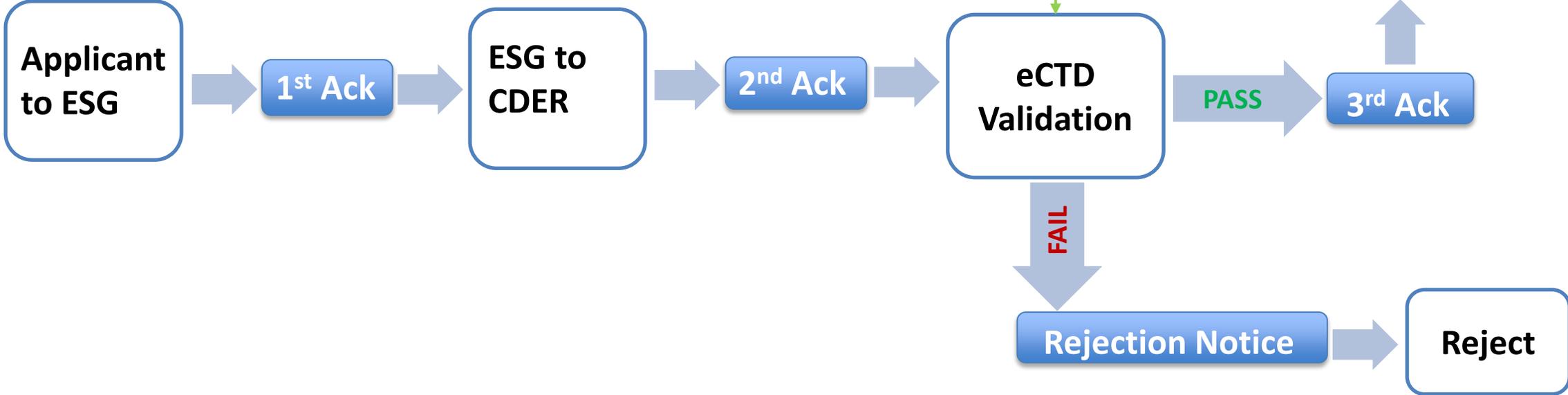
Specifications for eCTD Validation Criteria
US Food and Drug Administration

Specifications for eCTD Validation Criteria

Revision History

Date	Description	Version
2008-03-10	Initial Release of eCTD Validation Criteria	1.0
2010-12-10	eCTD Validation Criteria updated including additions and deletions of error codes - DRAFT	2.0
2011-12-20	eCTD Validation Criteria updated including clarifications and deletions of error codes - FINAL	2.1
2013-04-30	eCTD Validation Criteria effective dates updated - FINAL	2.2
2013-08-23	eCTD Validation Criteria added and existing criteria updated to incorporate changes for US eCTD Module 1 (using DTD version 3.2) - FINAL	3.0
2014-02-07	Updated DTD version 3.2 references to 3.3; DTD 2.01 added to the applicable DTD versions for error 2001; updated guidance sources where applicable - FINAL . <small>Note: On 2014-03-07, corrections were made to a date and the descriptions in the last two rows of this Revision History.</small>	3.1
2016-09-21	eCTD Validation Criteria added to support Study Data Technical Conformance Guide	3.2
2016-11-07	Update to the descriptions of the eCTD Validation Criteria which support the Study Data Technical Conformance Guide	3.3
2017-03-02	Update to the descriptions of the eCTD Validation Criteria which support the Study Data Technical Conformance Guide	3.4
2017-03-29	Update to the descriptions of the eCTD Validation Criteria which support the Study Data Technical Conformance Guide	3.5

Validation, as listed in the [Specification for eCTD Validation Criteria](#), occurs during this step (including 1734, 1735, and 1736)



Are You Ready?

Study Data Technical Rejection Criteria

Overview of TRC Errors



- 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 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*	High	
	For Study Data Tabulation Model (SDTM) data, a DM dataset and define.xml must be submitted in Module 5 required sections* 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*		
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	

* 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

Relationship between the Technical Rejection Criteria for Study Data and the Specification for eCTD Validation Criteria

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 enforce the deadlines below² and will become effective on September 15, 2021.

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.³

The standards apply to the following types of submissions to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER):

- New drug applications (NDAs), abbreviated new drug applications (ANDAs), certain biologics license applications (BLAs), and all subsequent submissions to these types of applications, including amendments, supplements, and reports, even if the original submission was filed before the requirements went into effect.
- Commercial investigational new drug applications (INDs) (for products that are intended to be distributed commercially).

Deadlines: Sponsors whose studies started after December 17, 2016, must use the data standards listed in the FDA Data Standards Catalog for NDAs, BLAs and ANDAs. For Commercial INDs, the requirement applies to studies started after December 17, 2017.

FDA implemented an approach to determine compliance with the requirement to submit electronic standardized study data. The technical rejection criteria are automated validations by the Center (CDER or CBER) submittal processing systems using the FDA Specifications for eCTD Validation Criteria as described below.

This document focuses on the criteria used for the automated validation process. In order for the FDA automated eCTD validation process to determine the study start date (SSD) for the submitted study, FDA relies on the SSD value provided in the Trial Summary dataset (ts.xml) that is referenced in the Study Tagging File (STF).⁴ This validation confirms the submission of a valid STF (see validation code 1789) and a Trial Summary (TS) domain (see validation code 1734). For a study that contains a study report with file tags "pre-clinical-study-report," "legacy-clinical-study-report," or "study-report-body," and/or an xml formatted dataset, the expectation for content in the TS domain (simplified or full)⁵ depends on whether the study is submitted in compliance with a Clinical Data Interchange Standards Consortium (CDISC) standard. FDA's Study Data Technical Conformance Guide provides the appropriate content.

¹ This requirement is discussed in the guidance *In-Industry Preclinical Regulatory Submissions in Electronic Format—Standardized Study Data*, available on the FDA guidance web page at <https://www.fda.gov/regulatory-information/ucm464641.htm> and on the FDA Study Data Standards Resources web page at <https://www.fda.gov/oc/industry/industry-standards/industry-standards.html>. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page.

² See page 6-8.

³ Available on the FDA Study Data Standards Resources web page.

⁴ The Study Start Date (SSD) should follow the ISO 8601 standard that provides, at minimum, the year, month, and day for the study start date.

⁵ Please refer to Appendix 2 of this document for more information on the simplified TS file and the Study Data Technical Conformance Guide on the FDA Study Data Standards Resources web page for more information on the full TS file.

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Revised 03/15/21



is a subset of

Specifications for eCTD Validation Criteria
US Food and Drug Administration

Specifications for eCTD Validation Criteria

Revision History

Date	Description	Version
2008-03-10	Initial Release of eCTD Validation Criteria	1.0
2010-12-10	eCTD Validation Criteria updated including additions and deletions of error codes - DRAFT	2.0
2011-12-20	eCTD Validation Criteria updated including clarifications and deletions of error codes - FINAL	2.1
2013-04-30	eCTD Validation Criteria effective dates updated - FINAL	2.2
2013-08-23	eCTD Validation Criteria added and existing criteria updated to incorporate changes for US eCTD Module 1 (using DTD version 3.2) - FINAL	3.0
2014-02-07	Updated DTD version 3.2 references to 3.3; DTD 2.01 added to the applicable DTD versions for error 2001; updated guidance sources where applicable - FINAL Note: On 2014-03-07, corrections were made to a date and the descriptions in the last two rows of this Revision History.	3.1
2016-09-21	eCTD Validation Criteria added to support Study Data Technical Conformance Guide	3.2
2016-11-07	Update to the descriptions of the eCTD Validation Criteria which support the Study Data Technical Conformance Guide	3.3
2017-03-02	Update to the descriptions of the eCTD Validation Criteria which support the Study Data Technical Conformance Guide	3.4
2017-03-29	Update to the descriptions of the eCTD Validation Criteria which support the Study Data Technical Conformance Guide	3.5

FDA

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The Specification for eCTD Validation Criteria contains a total of 161 validations

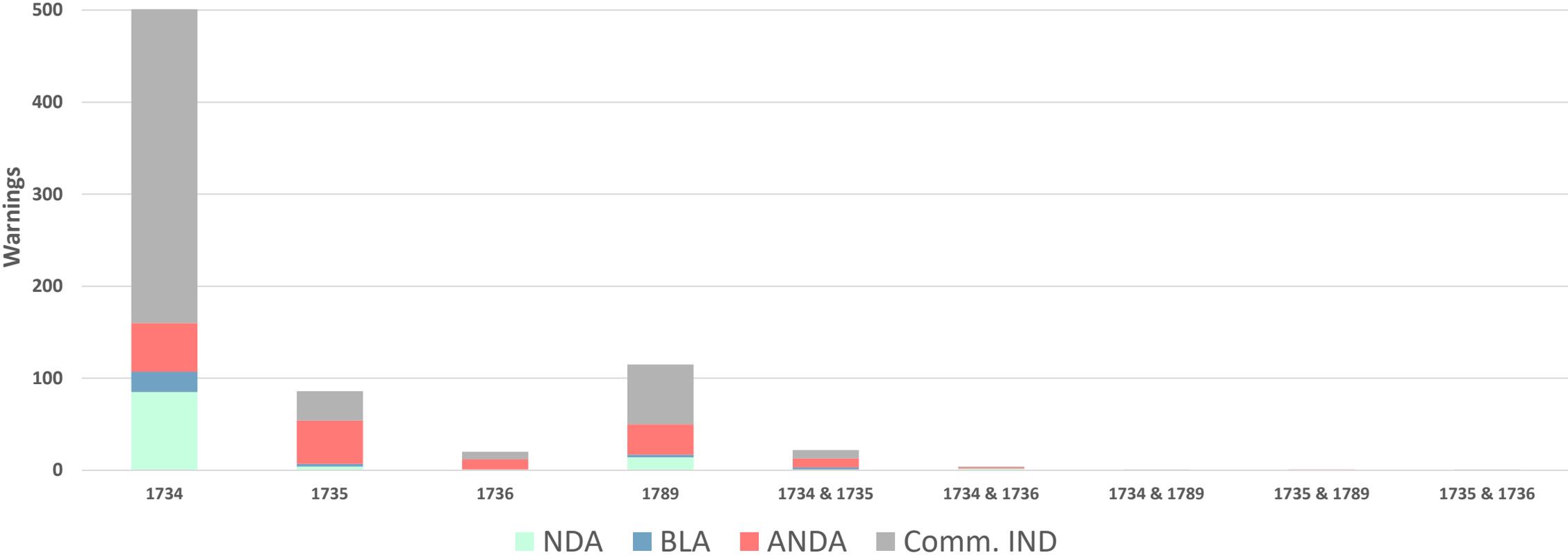
46 are High severity, meaning failure of that validation leads to rejection

The Technical Rejection Criteria for Study Data provides additional detail on 4 of these validations (1734, 1735, 1736, 1789) to help industry understand under what conditions submission of study files will trigger them and criteria to pass



TRC Warning Notices (March 15 – August 15, 2021)

- 1734 is the most common failure reason, especially for Commercial IND submissions
- 1789 is the second largest failure reason and is particularly high for Commercial IND submissions

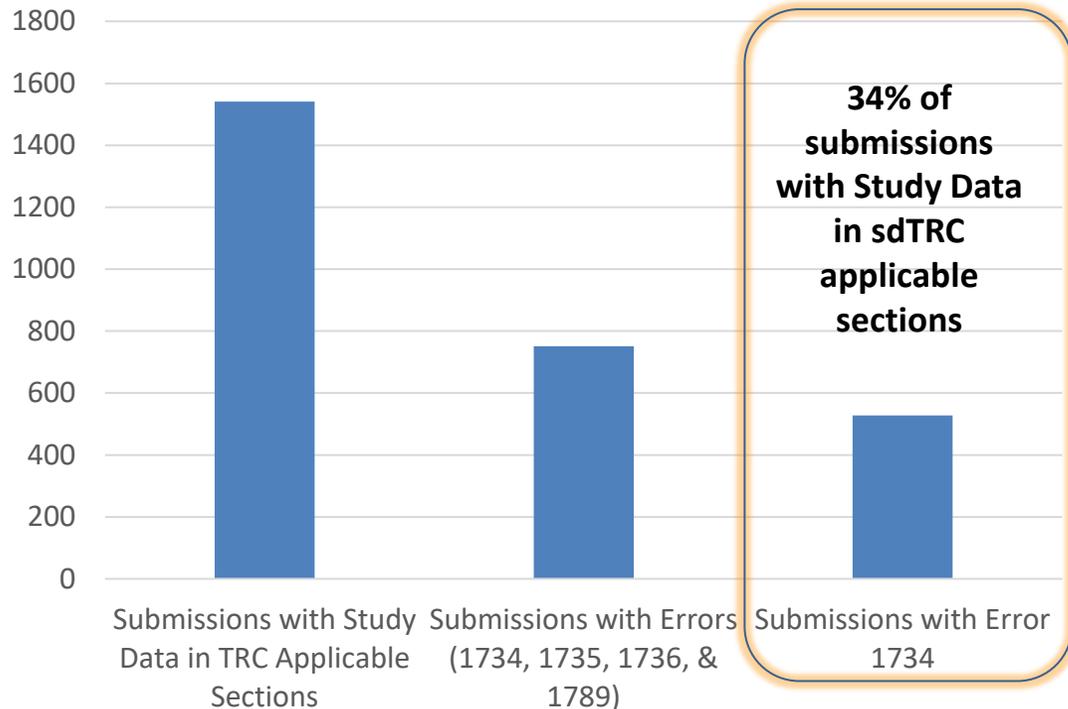


Validation Rule 1734

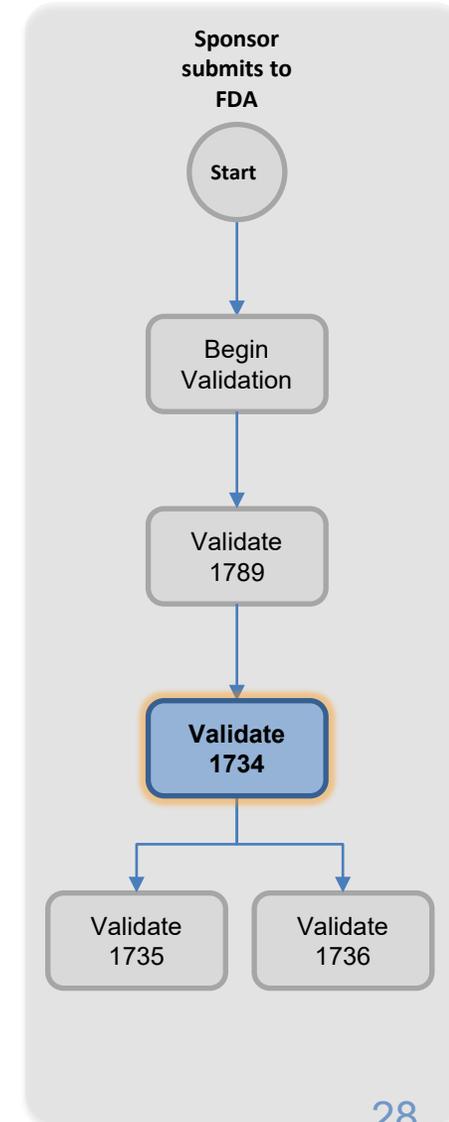
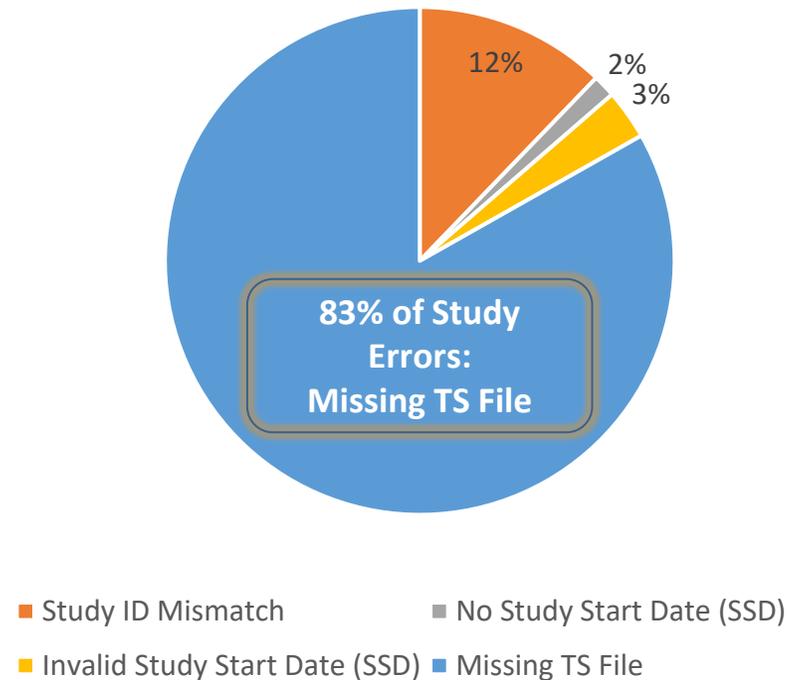
A dataset named ts.xpt with information on study start date must be present for each study in required sections*

- ✓ 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

Submissions CY2021 (March 15 – August 15, 2021)



1734 Error Reasons**



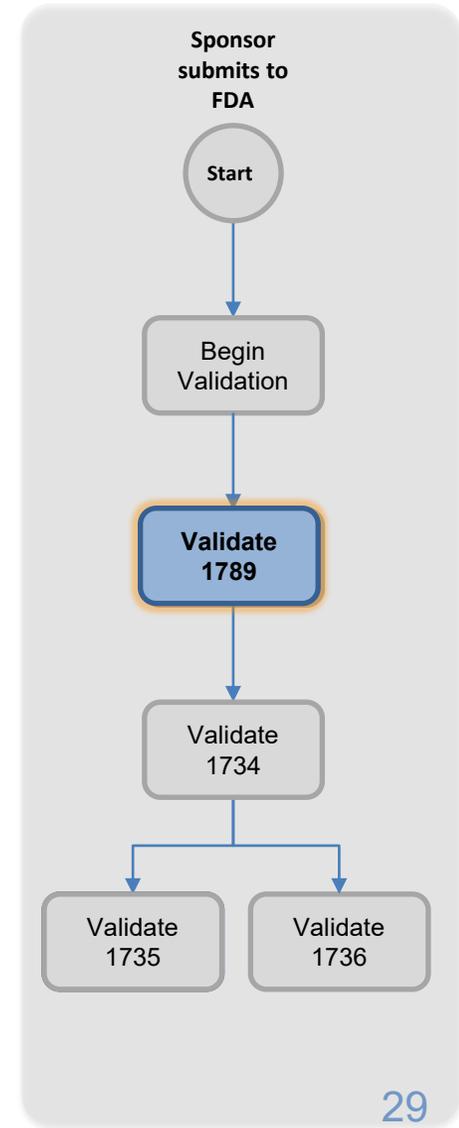
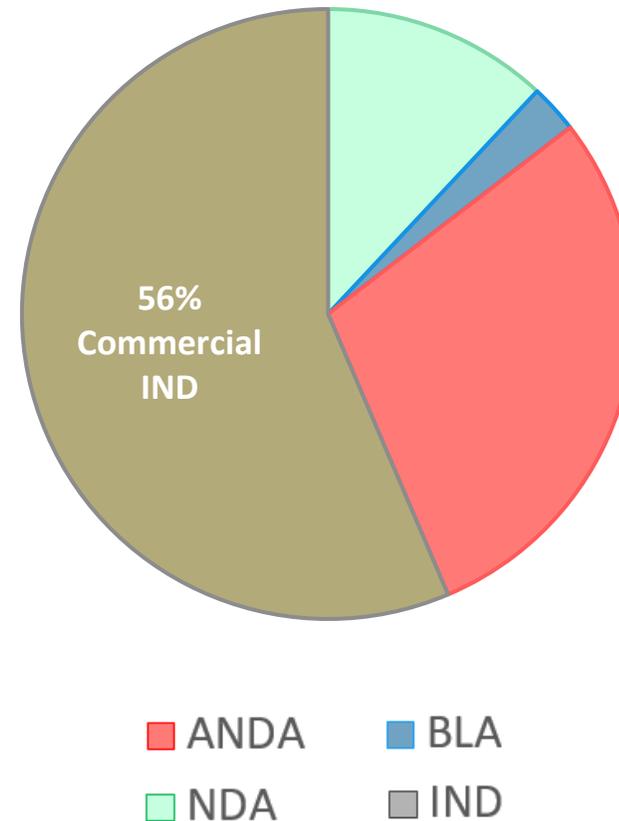
Validation Rule 1789

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).

✓ All study files are included in a Study Tagging File (STF)

1789 errors are the second largest source of sdTRC failures*

Submission Types for 1789 Errors*



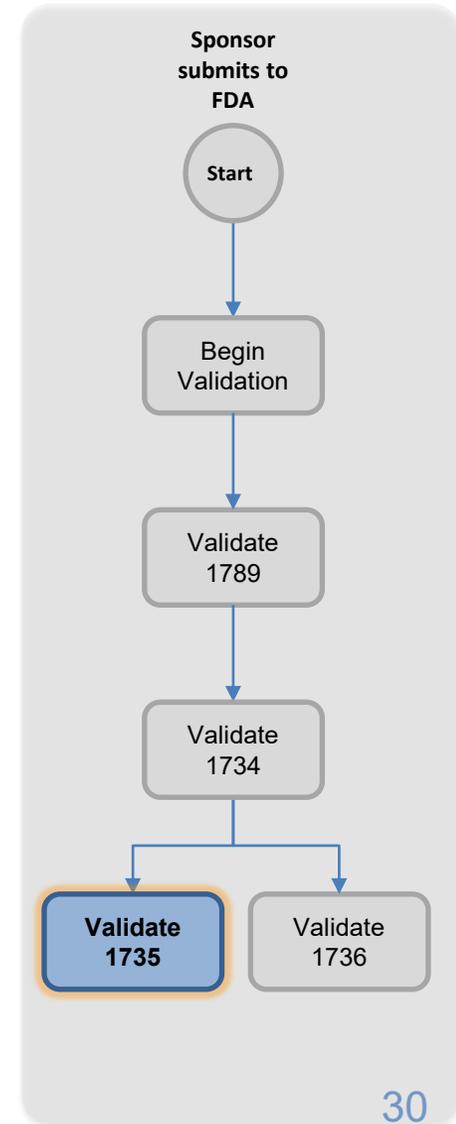
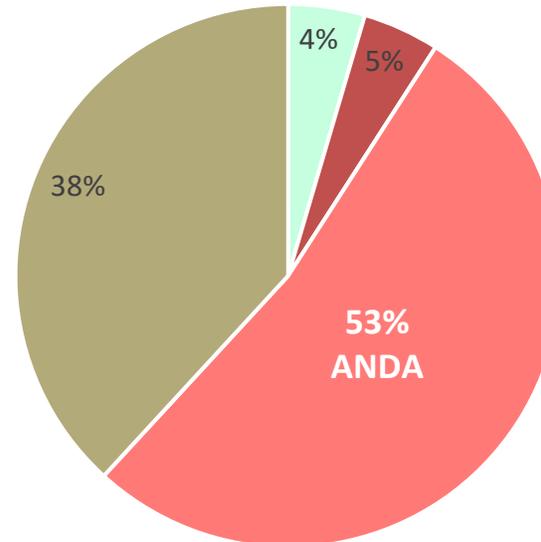
Validation Rule 1735

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

- ✓ Standardized dataset domains (e.g., adsl.xpt, dm.xpt) are tagged as:
 - “data-tabulation-dataset-sdtm” for SDTM
 - “analysis-dataset-adam” for ADaM
 - “data-tabulation-dataset-send” for SEND
- ✓ Define.xml files are tagged as:
 - “data-tabulation-data-definition” for SDTM & SEND
 - “analysis-data-definition” for ADaM

ANDA submissions have the highest number of 1735 errors*

Submission Types for 1735 Errors*





Tools to Help Industry

The Self-Check Worksheet

- Designed to walk sponsors through each step of sdTRC validation process
- Dynamically guides sponsors through study data requirements based on study information entered
- Helps sponsors prepare study data to submit to the FDA for the first time

[Demonstration Videos & Other Supporting Material](#)

[Technical Rejection Criteria Self-Check Worksheet](#)

[Self-Check Worksheet Instructions](#)

		DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration		
SELF-CHECK WORKSHEET FOR STUDY DATA PREPARATION				
<p>Note: This self-check Worksheet is not required for submissions of study data and is designed to help prepare newly submitted study data to FDA, i.e. studies for which no files have been previously submitted.</p> <p>*Required Field</p>				
Section 1: Application & Submission Information				
1a. FDA Center* <input type="checkbox"/> CDER <input type="checkbox"/> CBER		1b. Application Type* <input type="checkbox"/> NDA <input type="checkbox"/> BLA <input type="checkbox"/> ANDA <input type="checkbox"/> Commercial IND		1c. Application Number* <input type="text"/>
1d. eCTD Sequence Number <input type="text"/>	1e. eCTD Submission Type <input type="text"/>		1f. eCTD Submission Sub Type <input type="text"/>	
<p>Note: Repeat Sections 2 through 5 for each study included in the submission.</p>				
Section 2: Study Information				
2a. Study ID* <input type="text"/> <p><i>(Study ID is the unique identifier across application documents. Therefore, the study ID must be consistent across all the files being submitted for the same study, i.e. STF File, ts.xpt, dm.xpt, etc.)</i></p>				
2b. Is This the First Time Study Data is Being Submitted for This Study as Part of This Application?*				
<input type="checkbox"/> Yes <input type="checkbox"/> No <i>If you answered "No" in Field 2b, do not proceed. This self-check worksheet is designed for newly submitted study data.</i>				
2c. Title of the Study <input type="text"/>				
2d. Study Section - eCTD Heading (Example: m4-2-1-1)* <input type="text"/>				
2e. Module* <input type="checkbox"/> Nonclinical (m4) <input type="checkbox"/> Clinical (m5)				
2f. Study Dataset Type(s)* <input type="checkbox"/> Tabulation <input type="checkbox"/> Analysis <input type="checkbox"/> Other <p><i>If you are submitting tabulation data select "Tabulation." If you are submitting analysis data, select "Analysis." For other types of data, such as Listings datasets, when tabulation or analysis data is not being submitted, select "Other." Additional details and examples are included in the Study Data Self-Check Worksheet Instructions.</i></p>				
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References

- ❖ **Study Data Standards Resources** [<https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>]
 - Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [June 2021]
 - Study Data Technical Conformance Guide [August 2021]
 - FDA Data Standards Catalog [March 2021]
- ❖ **Study Data for Submission to CDER and CBER** [<https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>]
 - Technical Rejection Criteria For Study Data [August 2021]
 - Technical Rejection Criteria Self-Check Worksheet
 - Technical Rejection Criteria Self-Check Worksheet Instructions
- ❖ **Electronic Common Technical Document (eCTD)** [<https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/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 [August 2021]
 - Specifications for eCTD Validation Criteria [August 2021]
- ❖ **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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