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

Heather Crandall

Operations Research Analyst, DDMSS, OBI, OSP, CDER, FDA

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

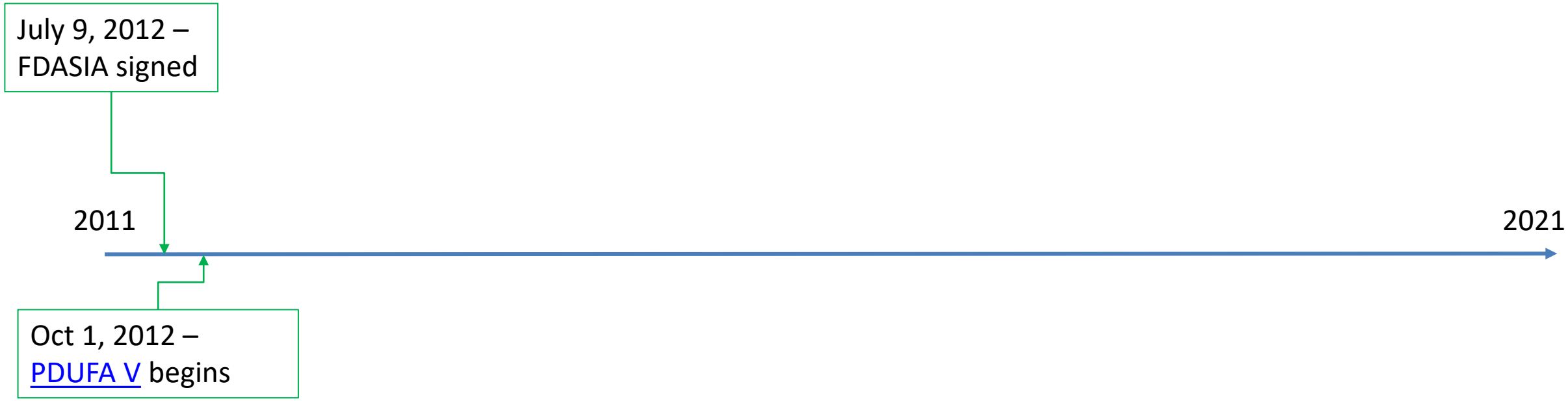
Looking back to 2012…

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

From Theresa Mullin, "Prescription Drug User Fee Act Reauthorization (PDUFA V) What's Next?," PhUSE CSS, March 19-20, 2012.

Timeline of PDUFA & Guidances

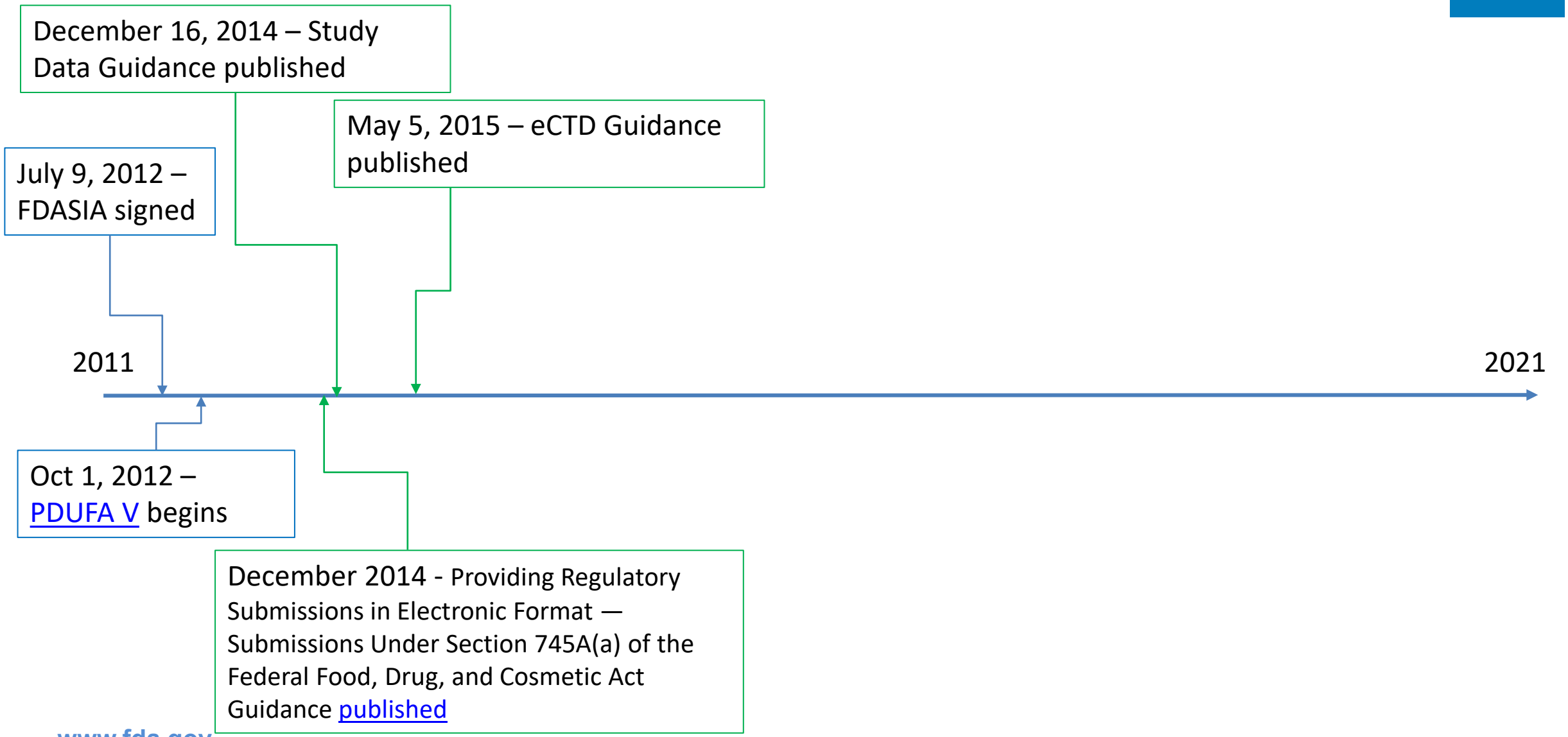


FDASIA/PDUFA V

- 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

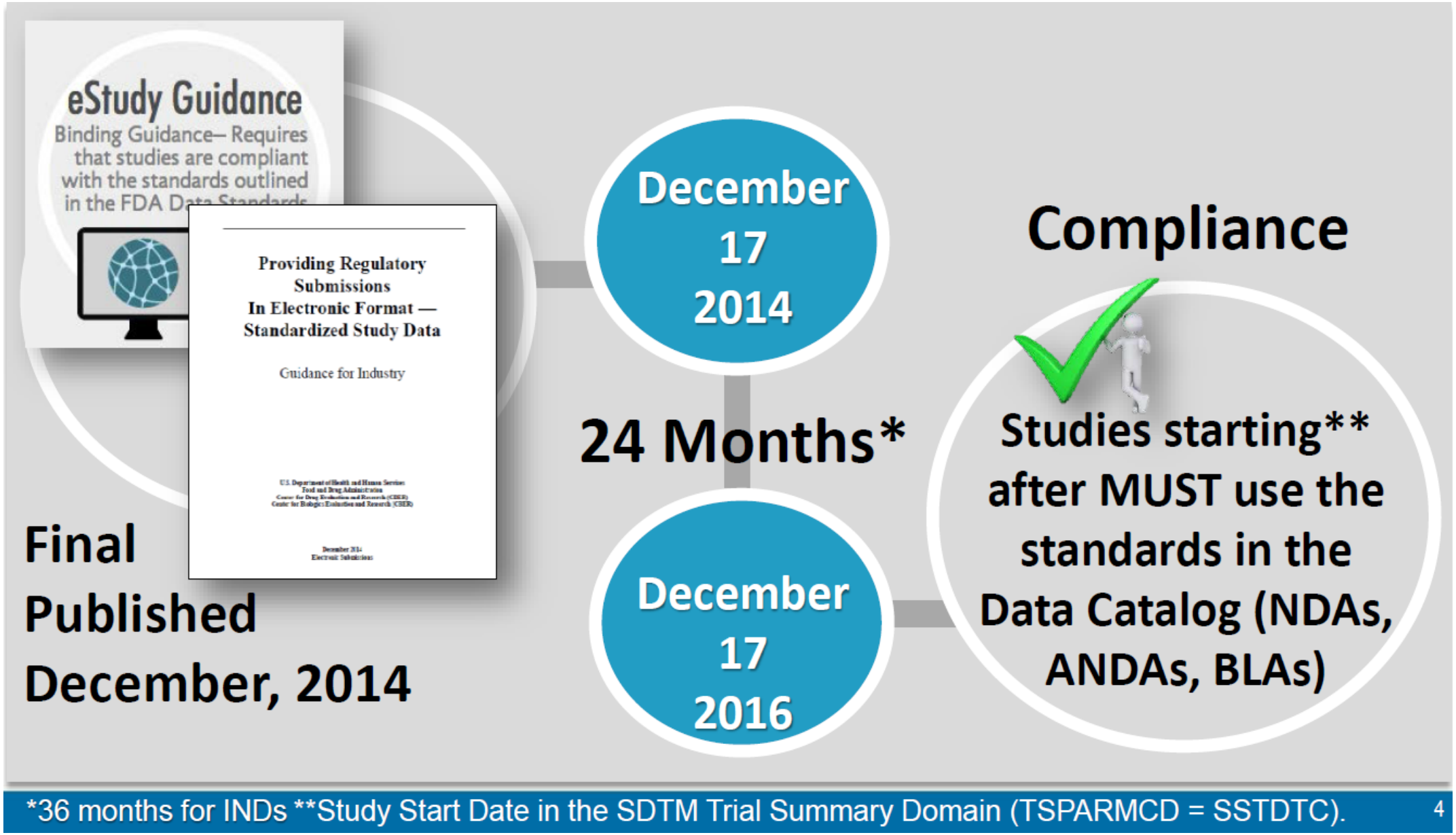
Timeline of PDUFA & Guidances



745A(a) Guidances

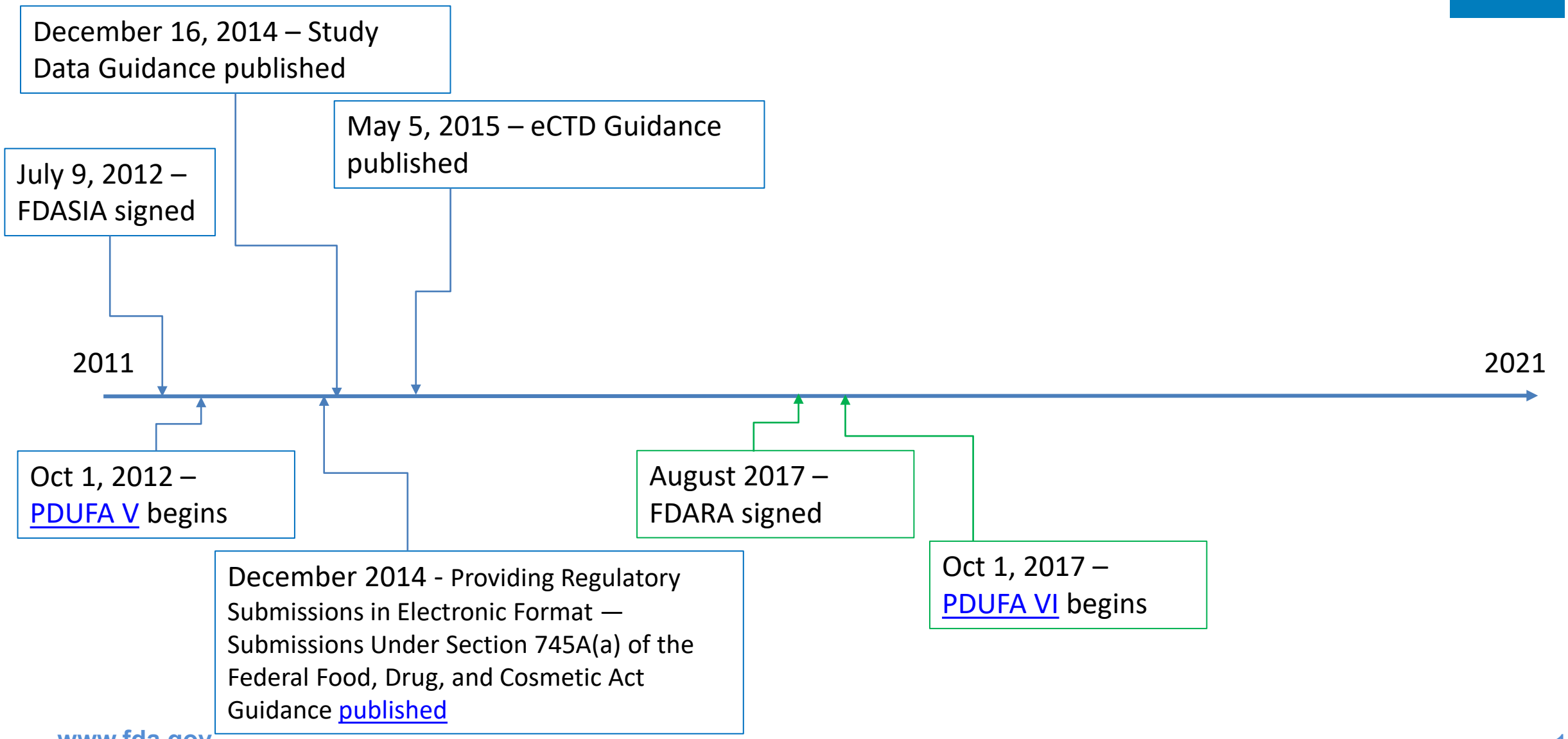
- FDA issued "Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry" in December 2014 (updated in June 2021)
  - Sponsors must conform to standards in the FDA Data Standards Catalog:
    - NDA, certain BLA, ANDA studies that started after December 17th, 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



From Ron Fitzmartin, "Electronic Submissions – The Requirement for Standardized Study Data," PhUSE CSS, March 17, 2015.

Timeline of PDUFA & Guidances



FDARA/PDUFA VI

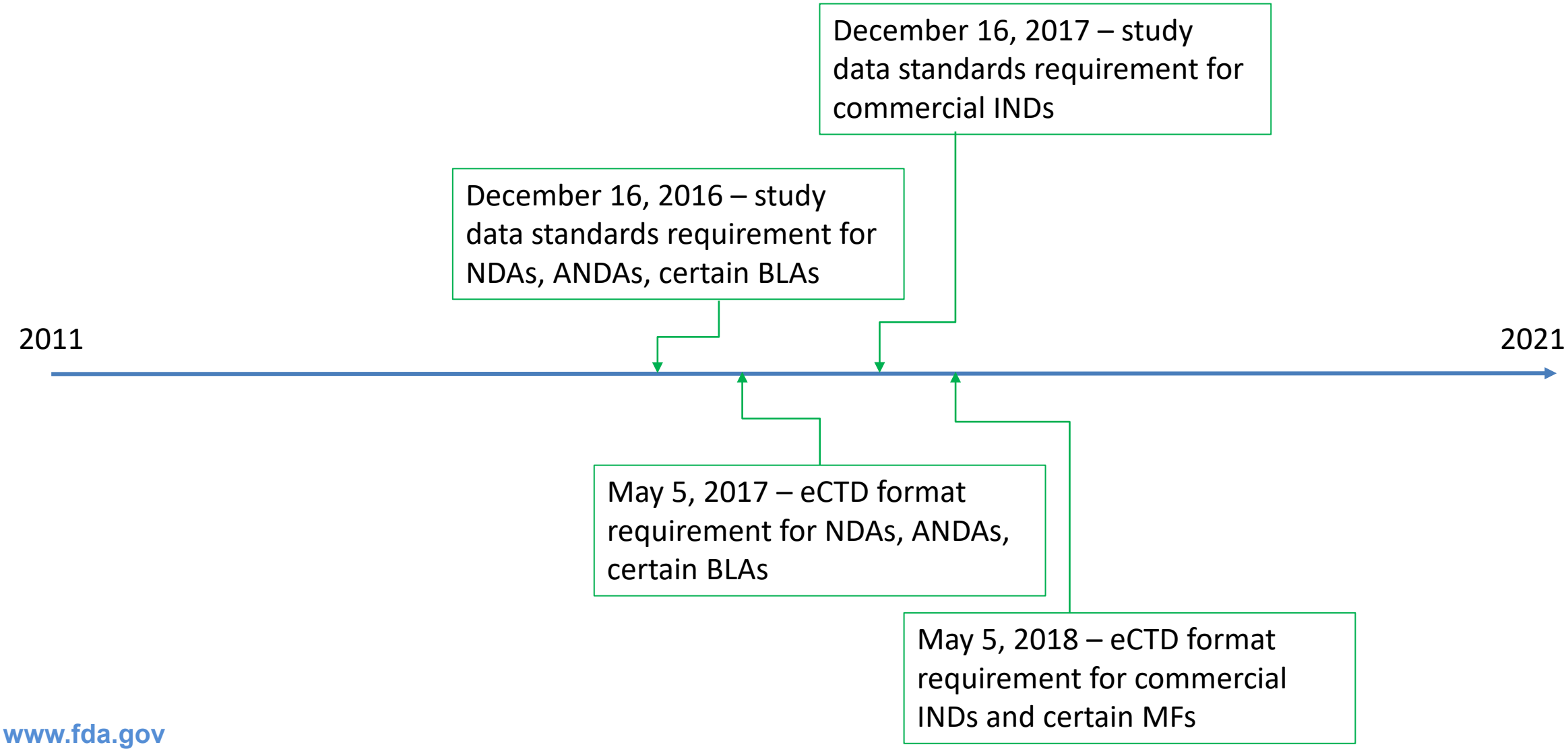
- PDUFA VI goals include a section “Enhance transparency and accountability of FDA electronic submission and data standards activities”

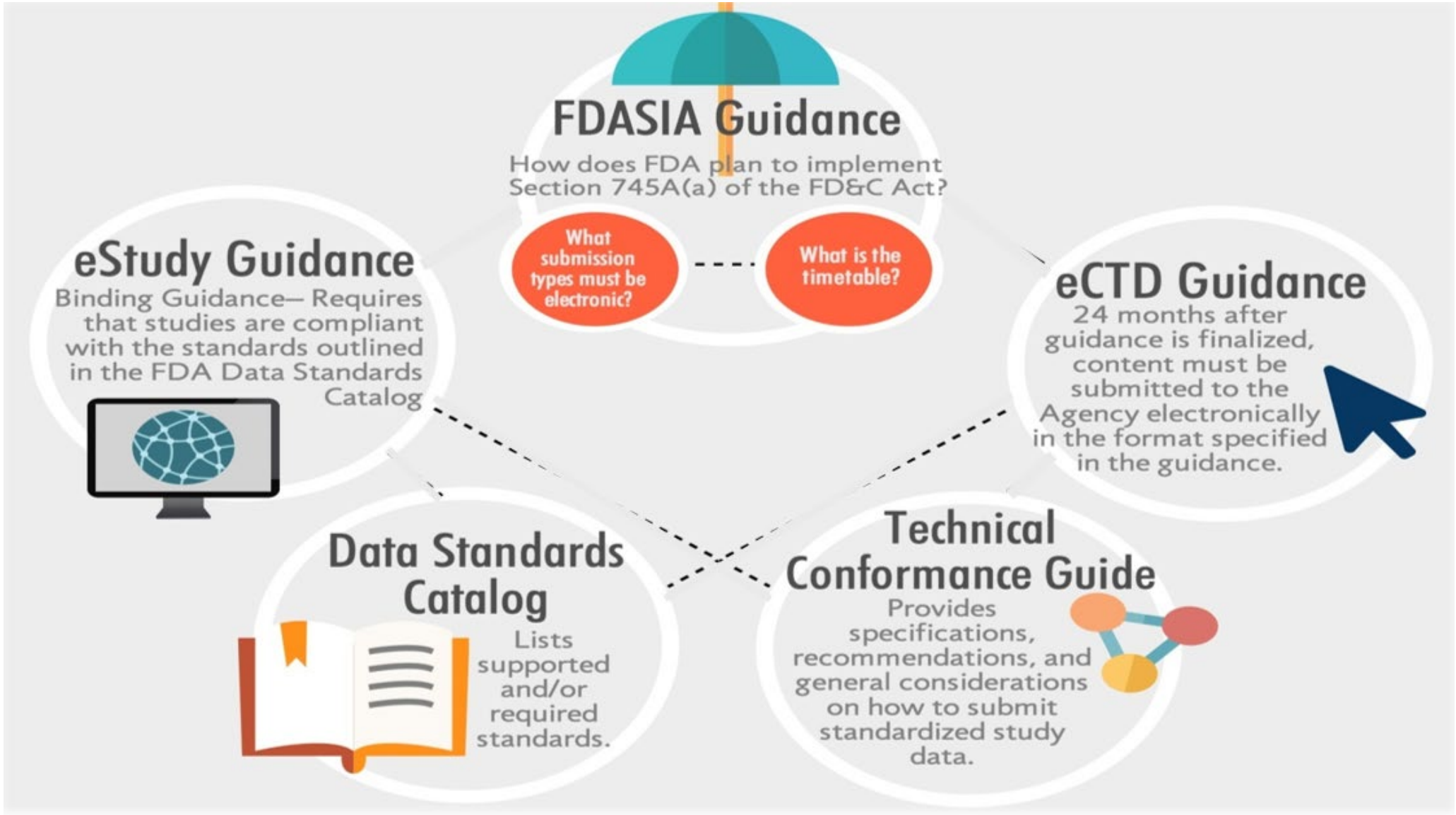
- Deliverables include:
  - Public Meetings for Electronic Submissions and Data Standards
  - CBER-CDER Data Standards Program Action Plan
  - FDA Data Standards Catalog
  - Joint Quarterly Meetings to Enhance Transparency and Accountability of FDA Electronic Submission and Data Standards Activities

How does it all connect?

Data Standards Requirements

Timeline of data standards

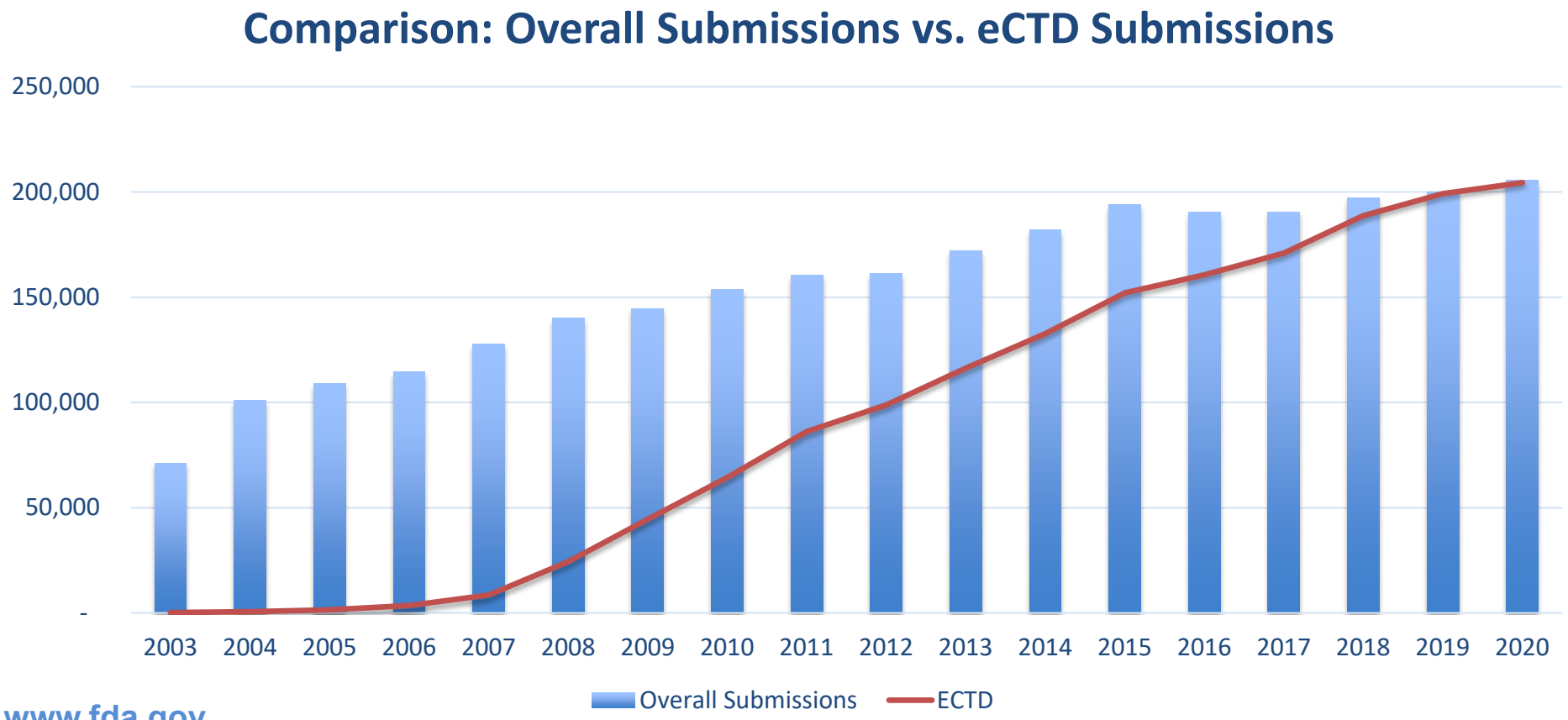




From Colleen Ratliffe, “eStudy Guidance and Technical Conformance Guide: Are you Ready?,” PhUSE CSS, March 13-15, 2016.

eCTD Submission Metrics 2003 - 2020

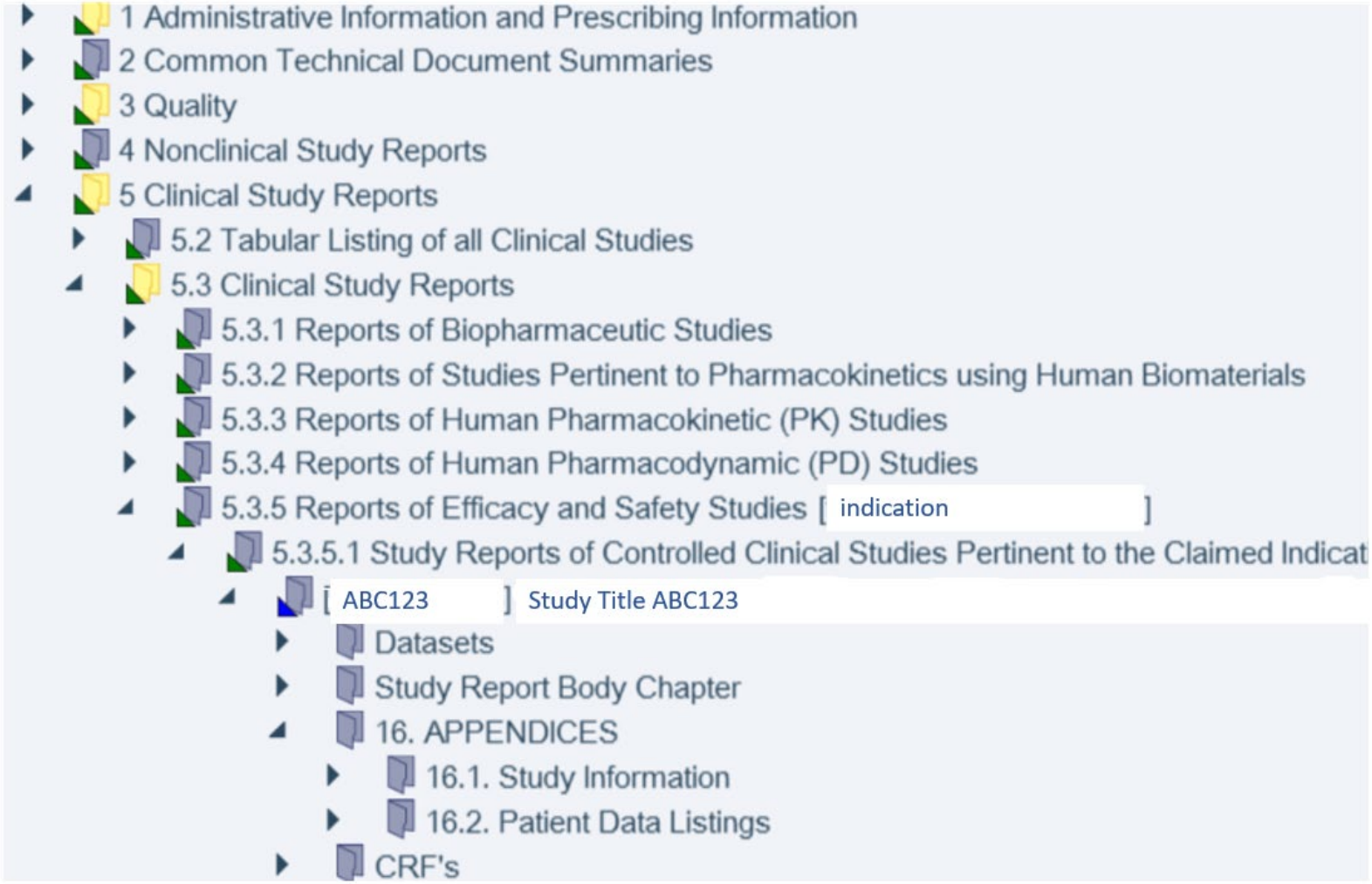
CDER received approximately 205,000* electronic submissions via ESG in FY 2020. Nearly all were in eCTD.

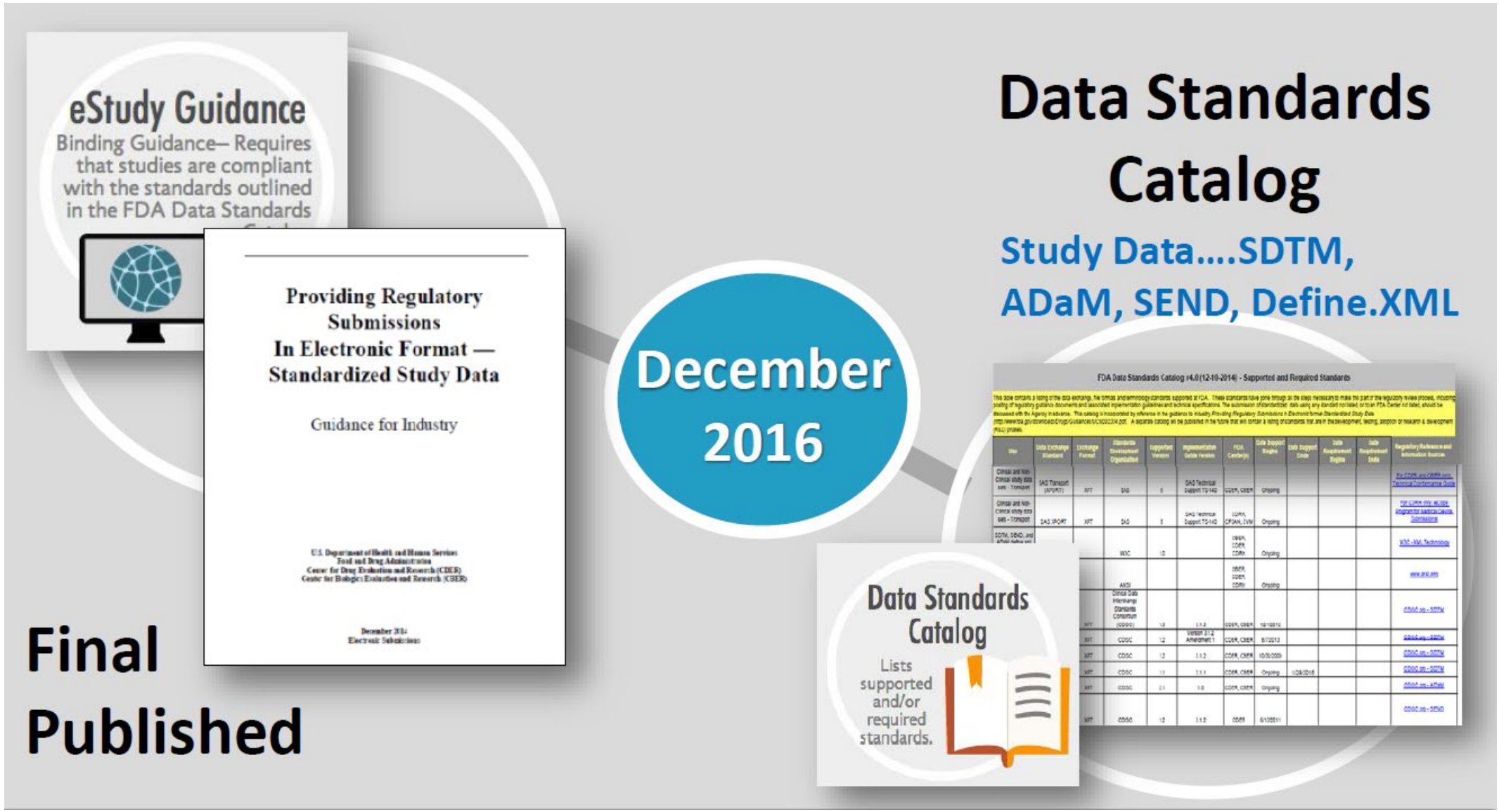


*excludes Non-Commercial IND and DMF Type III

Review of eCTD Submissions

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





From Ron Fitzmartin, "Electronic Submissions – The Requirement for Standardized Study Data," PhUSE CSS, March 17, 2015.

Data Standards Catalog

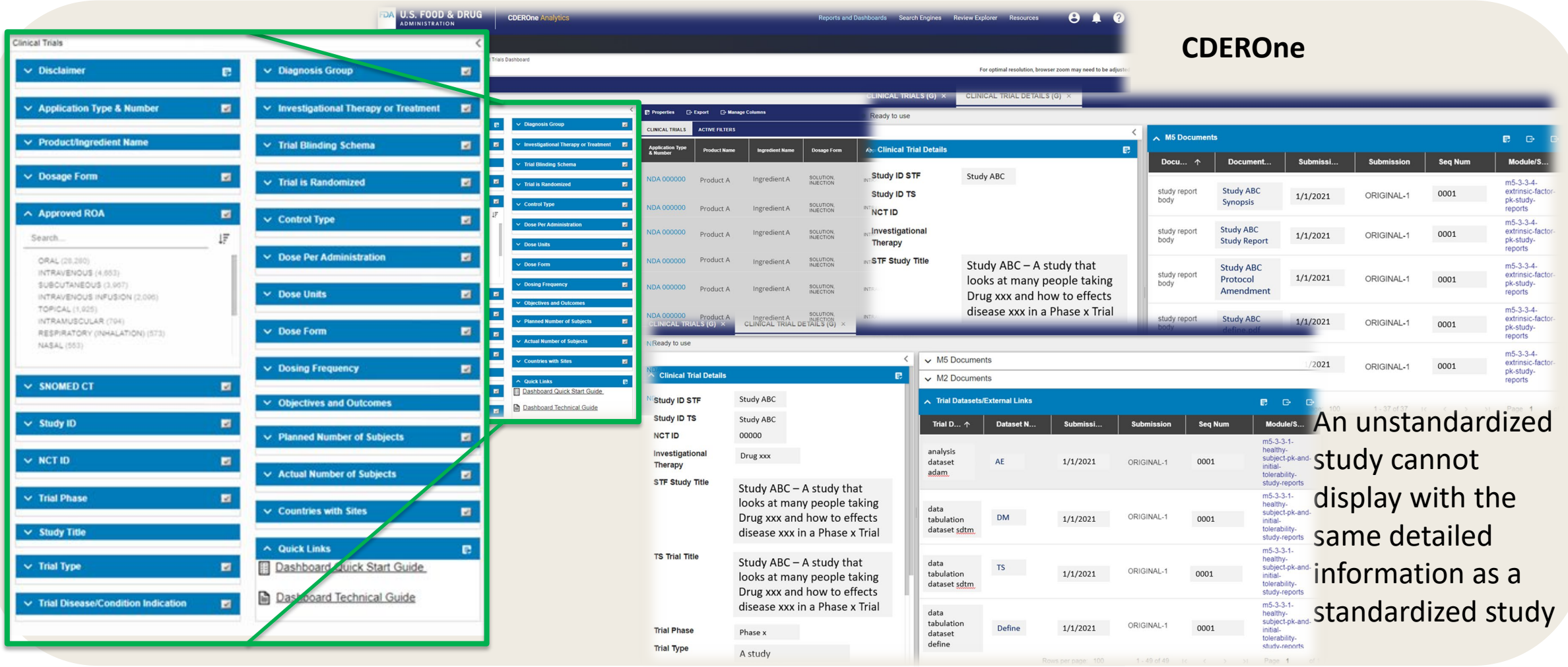
FDA Data Standards Catalog v7.2 (07-01-2021) - Supported and Required Standards

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

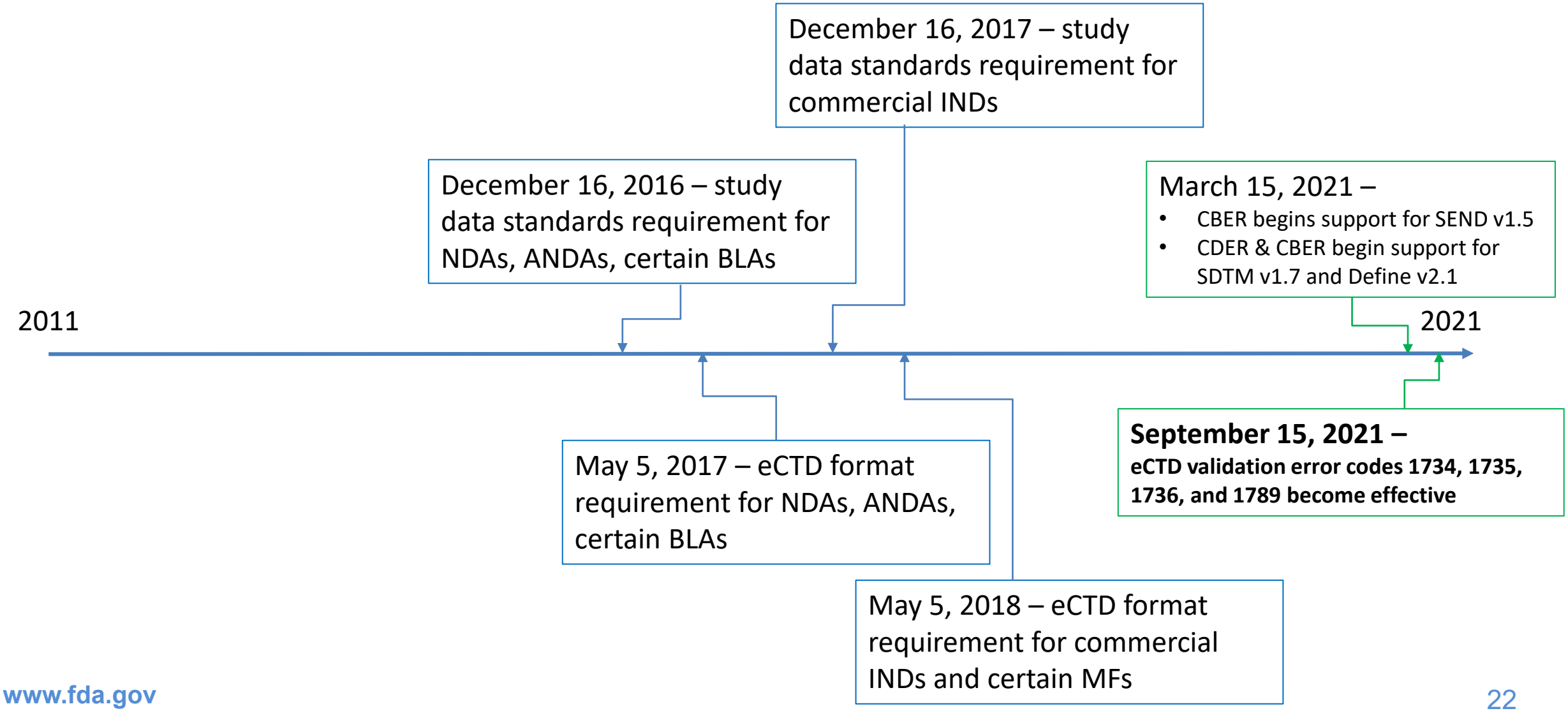
FDA also utilizes multiple tools and systems to support analysis of standardized study data:



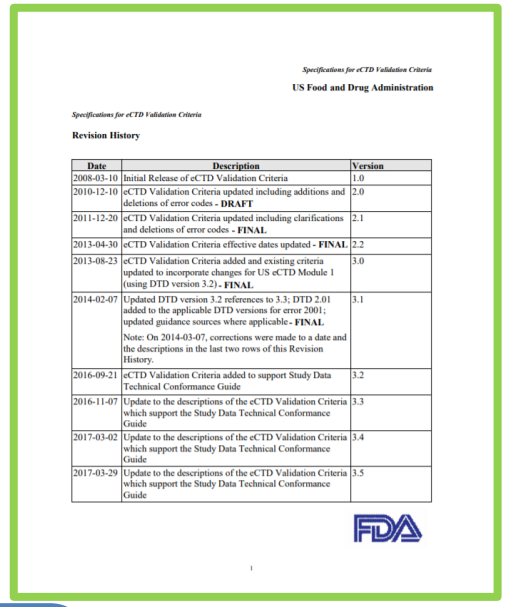
Review of Study Data

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

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** 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

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

Applicant to ESG → **1st Ack** → **ESG to CDER** → **2nd Ack** → **eCTD Validation**

eCTD Validation → PASS → **3rd Ack** → **Review Division**

eCTD Validation → FAIL → **Rejection Notice** → **Reject**

Are You Ready?

Study Data Technical Rejection Criteria

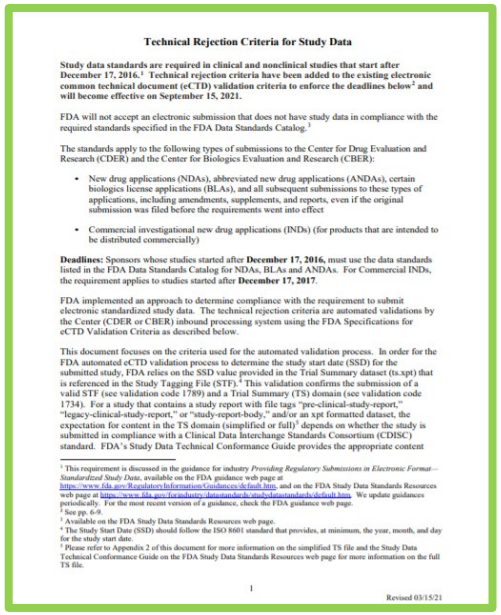
Overview of TRC Errors

- 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* 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*	High	
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 below[2] 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) inbound processing system 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.xpt) 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 xpt 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

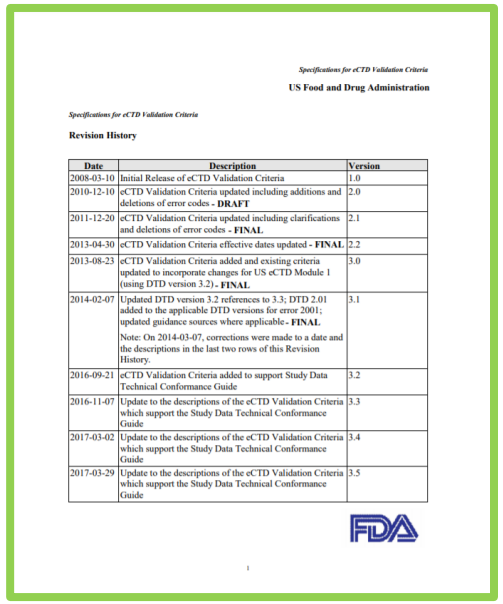
[1] This requirement is discussed in the guidance for industry *Providing Regulatory Submissions in Electronic Format—Standardized Study Data*, available on the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm, and on the FDA Study Data Standards Resources web page at https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page.
[2] See pp. 6-9.
[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.

1

Revised 03/15/21

⊂

is a subset of



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2017-03-29	Update to the descriptions of the eCTD Validation Criteria which support the Study Data Technical Conformance Guide	3.5

1

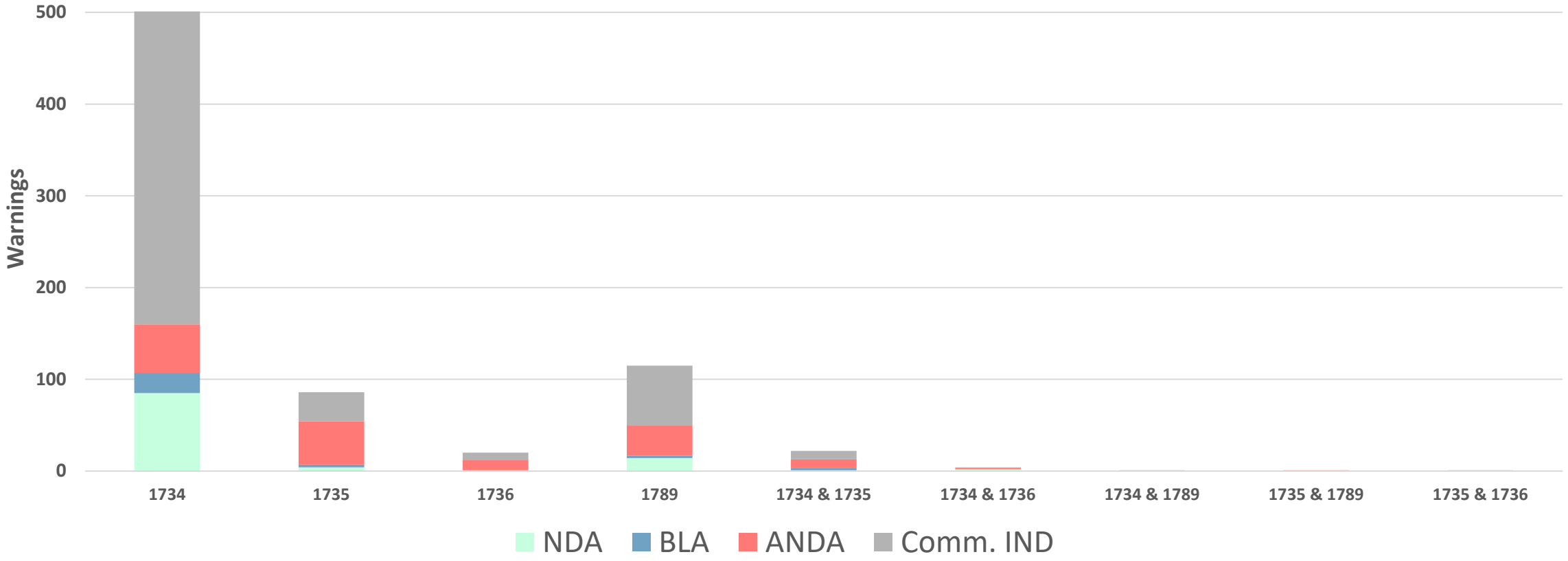
The Specification for eCTD Validation Criteria contains **a total of 161 validations**

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

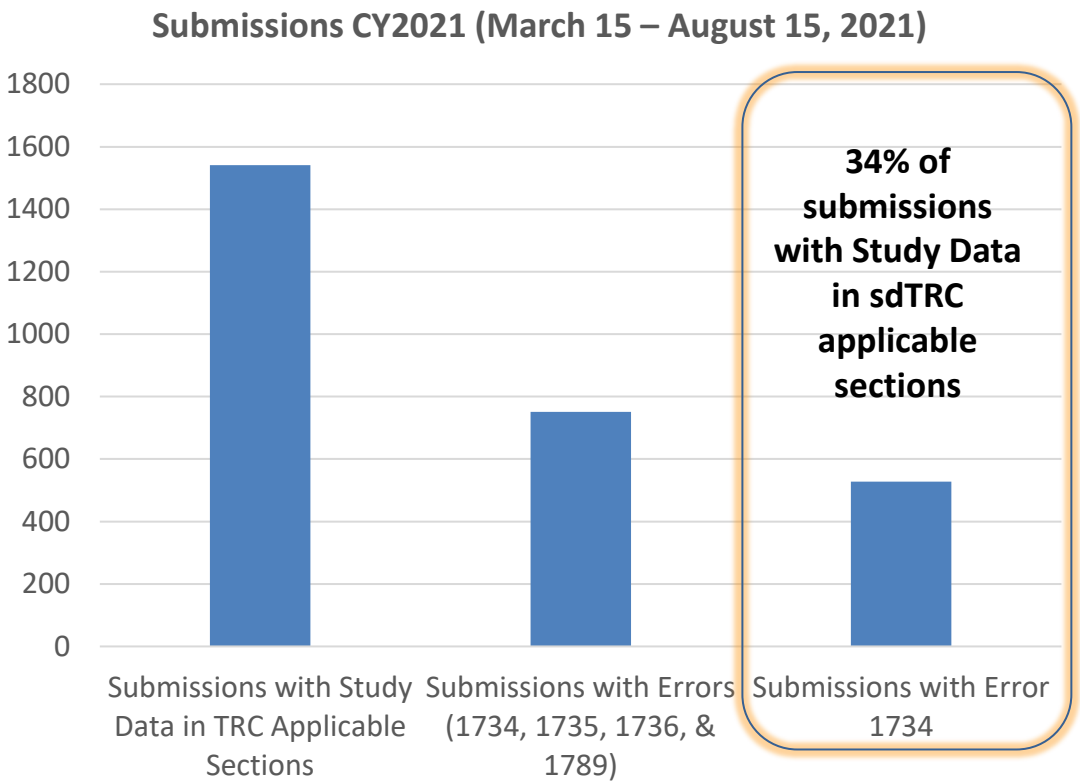


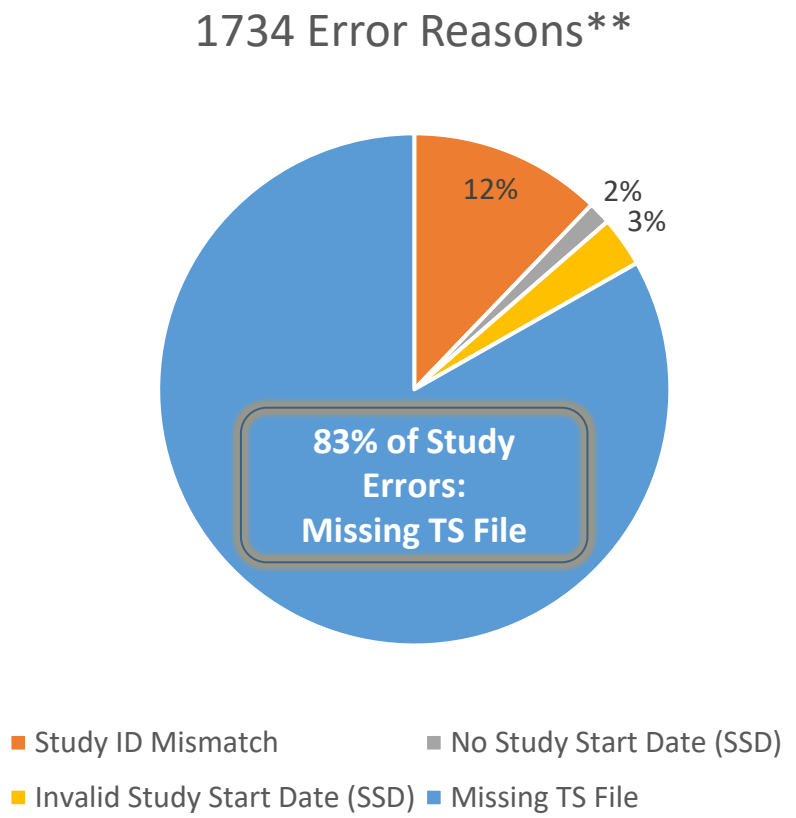
Note: Warnings generated by CDER between March 15th and August 15th, 2021

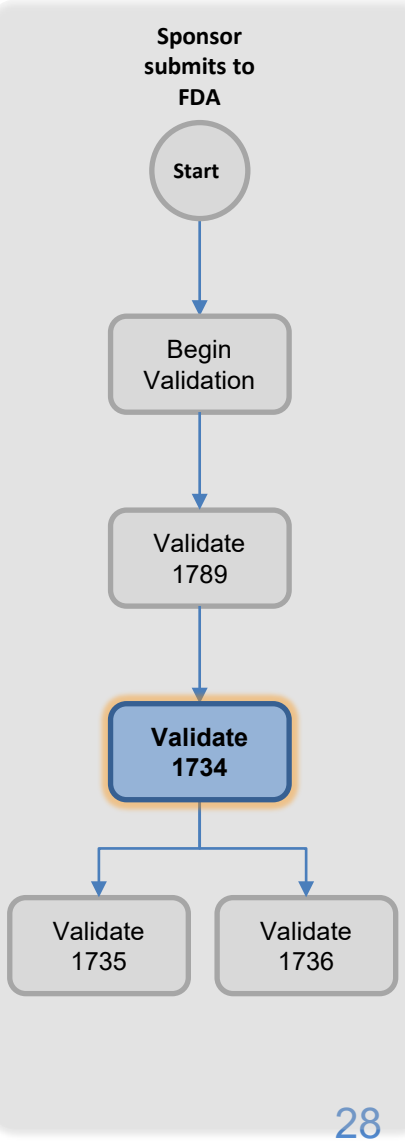
Validation Rule 1734

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 TSVALNF = NA)
- ✓ Study start date is in a valid format







** 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

***1388 Studies in 528 Submissions with Error 1734 between March 15, 2021 and August 15, 2021*

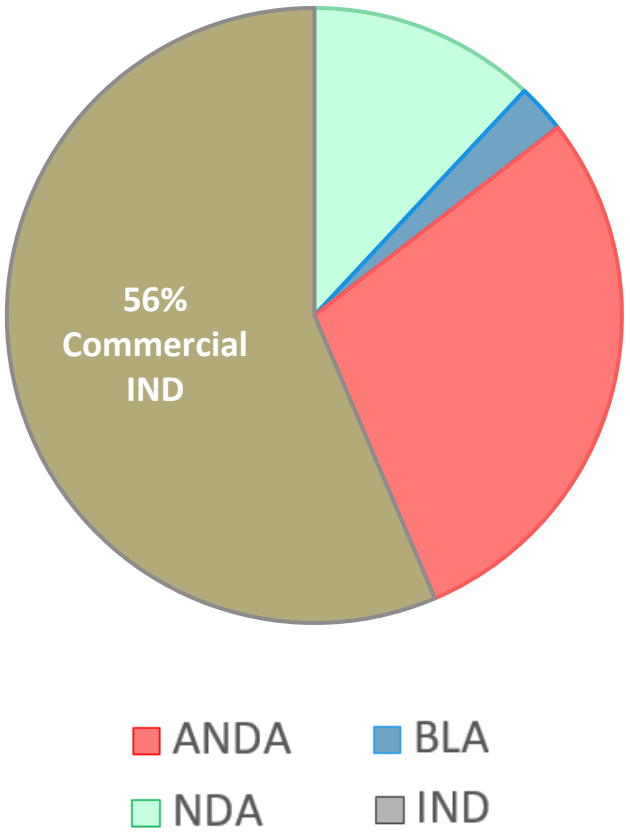
Validation Rule 1789

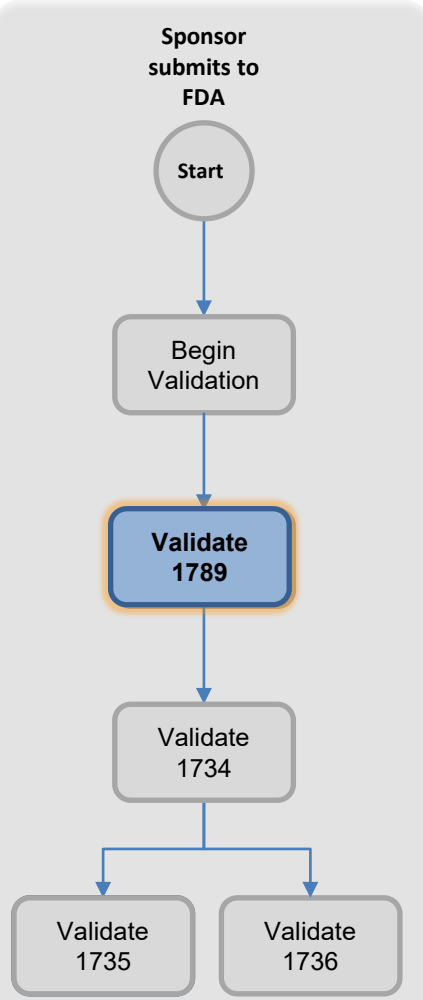
A file has been submitted in a study section without providing an STF file (STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports).

✓ 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*





*117 1789 failures out of 751 total warning notices March 15 – August 15, 2021

Validation Rule 1735

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

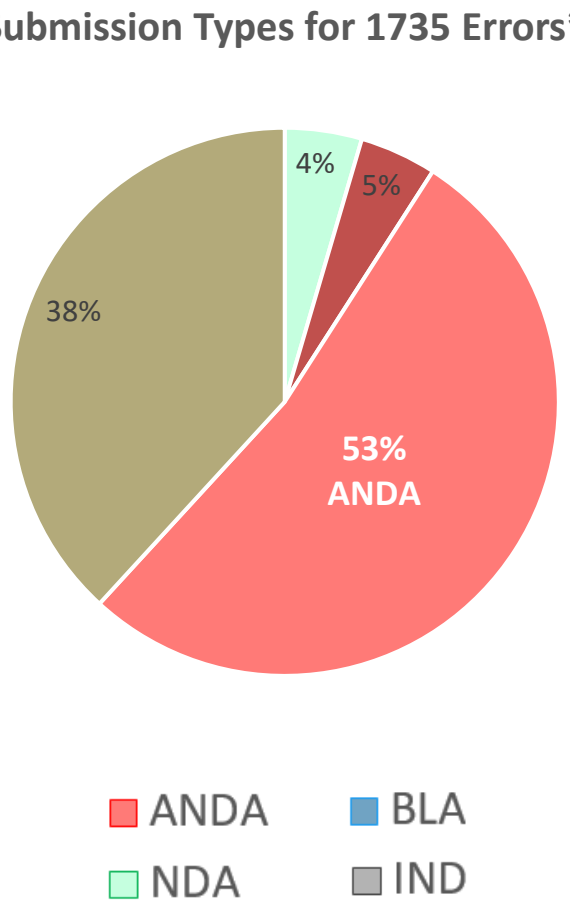
- ✓ Standardized dataset domains

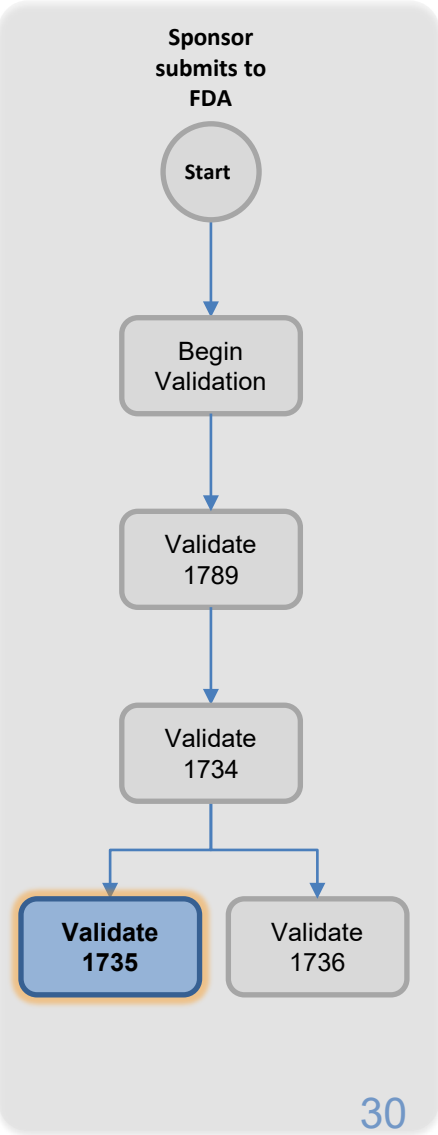
  (e.g., adsl.xpt, dm.xpt) are tagged as:

  - "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*





*110 1735-only failures out of 751 total warning notices March 15 – August 15, 2021

Tools to Help Industry

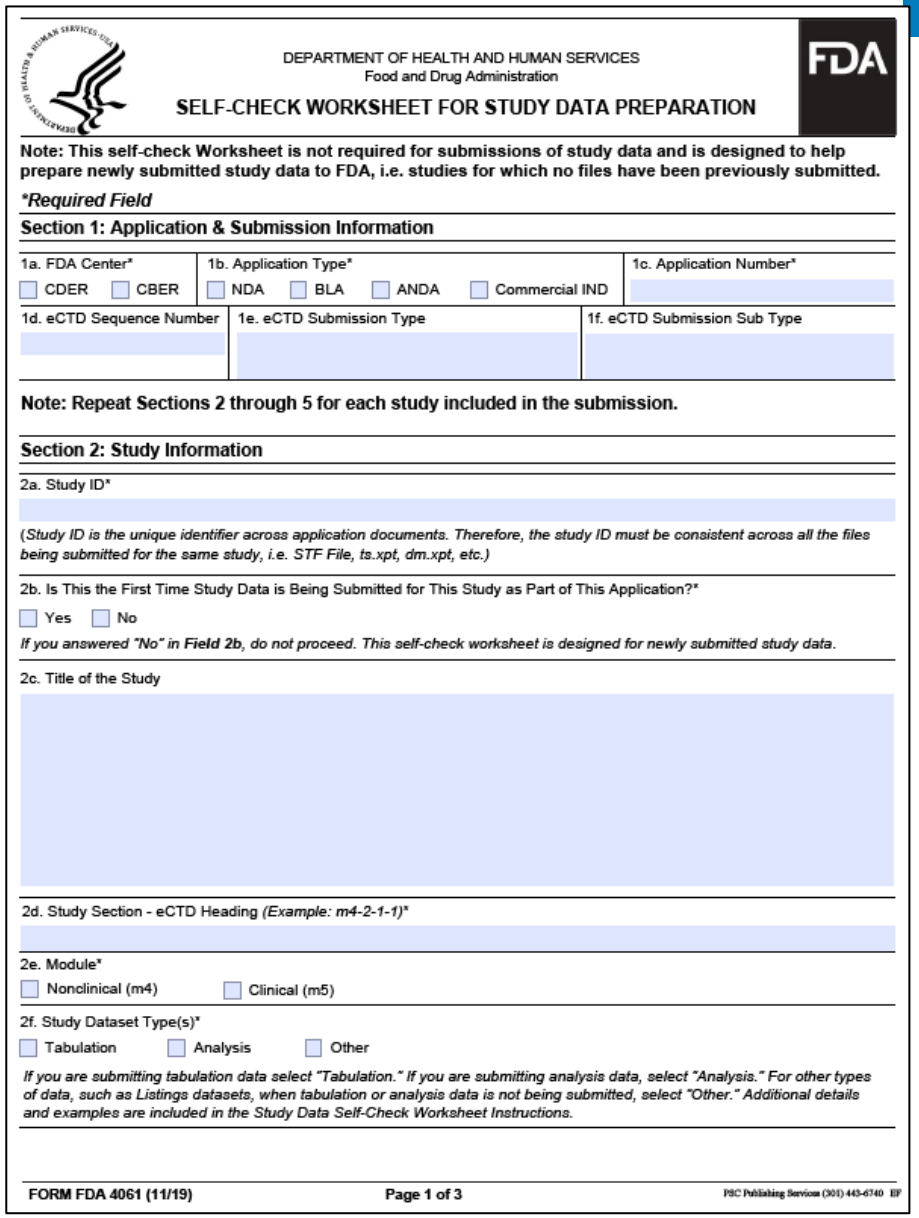
The Self-Check Worksheet

- 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

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.

**Required Field*

Section 1: Application & Submission Information

1a. FDA Center* ☐ CDER ☐ CBER

1b. Application Type* ☐ NDA ☐ BLA ☐ ANDA ☐ Commercial IND

1c. Application Number*

1d. eCTD Sequence Number

1e. eCTD Submission Type

1f. eCTD Submission Sub Type

Note: Repeat Sections 2 through 5 for each study included in the submission.

Section 2: Study Information

2a. Study ID*

(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.)

2b. Is This the First Time Study Data is Being Submitted for This Study as Part of This Application?*

☐ Yes ☐ No

If you answered "No" in Field 2b, do not proceed. This self-check worksheet is designed for newly submitted study data.

2c. Title of the Study

2d. Study Section - eCTD Heading *(Example: m4-2-1-1)**

2e. Module* ☐ Nonclinical (m4) ☐ Clinical (m5)

2f. Study Dataset Type(s)* ☐ Tabulation ☐ Analysis ☐ Other

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.

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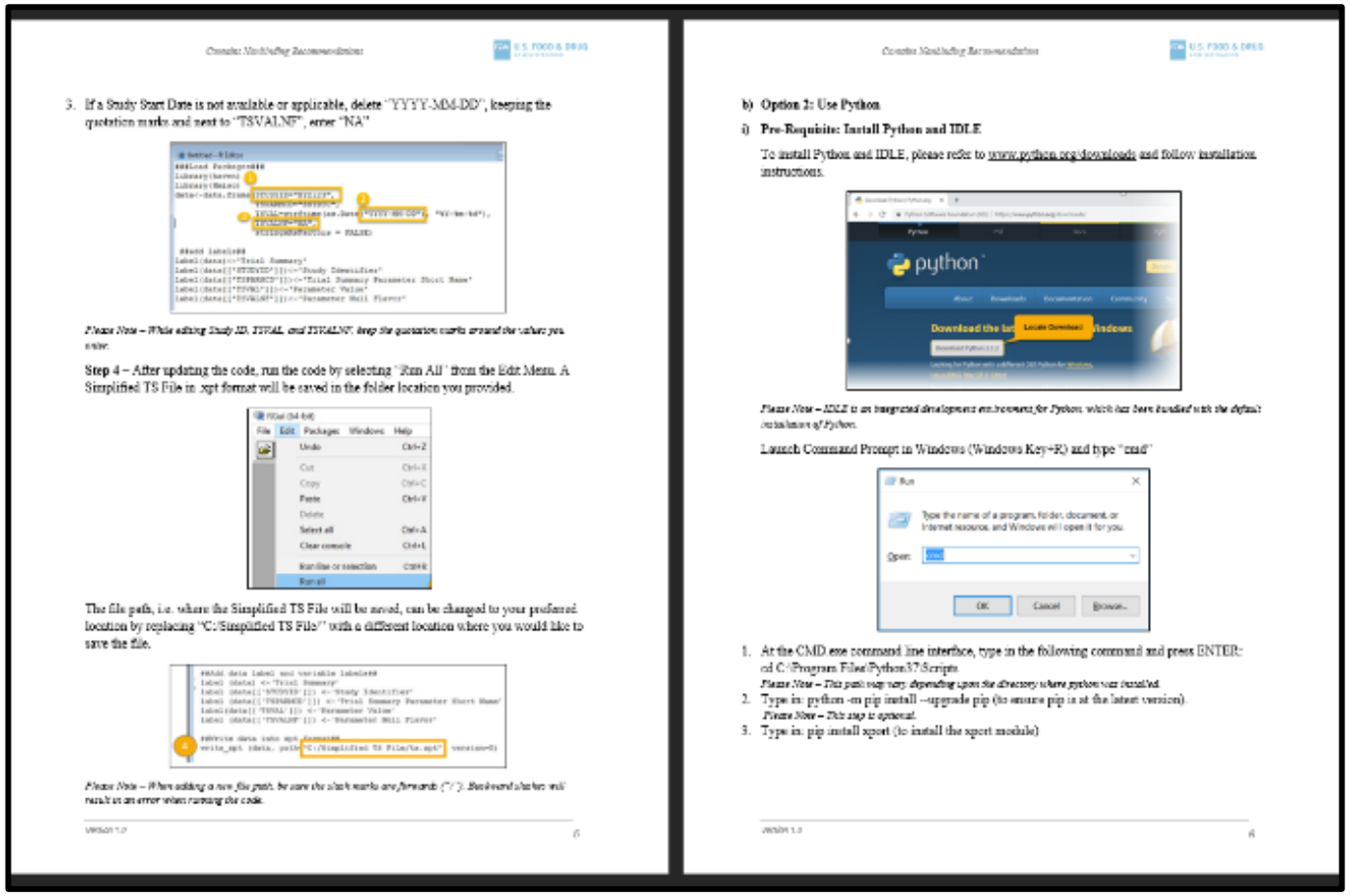
The Simplified ts.xpt Creation Guide

❖ Helps industry create simplified TS files using free and open-source software, R and Python

- Provides step by step instructions to install the necessary software
- Users can copy and paste code samples from the guide into R or Python
- Available on FDA's web page, *Study Data for Submission to CDER and CBER*
- Demonstration video also available at *Study Data for Submission to CDER and CBER*
- Additionally, a publicly available tool was developed by PHUSE:

  Simplified ts.xpt File Generator (*https://geotiger.shinyapps.io/07_genTS/*)



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]

CDER eData Mailbox: cder-edata@fda.hhs.gov
CBER eData Mailbox: cber-edata@fda.hhs.gov