U.S. FOOD & DRUG ADMINISTRATION

eCTD

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The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Poll

How would you characterize your ability to submit your NDA/BLA in proper eCTD format?

- ❑ I'm an experienced expert
- ❑ I'm pretty good at it
- ❑ Somebody else in my company handles the eCTD
- ❑ I am a beginner
- ❑ Wait. What is eCTD?

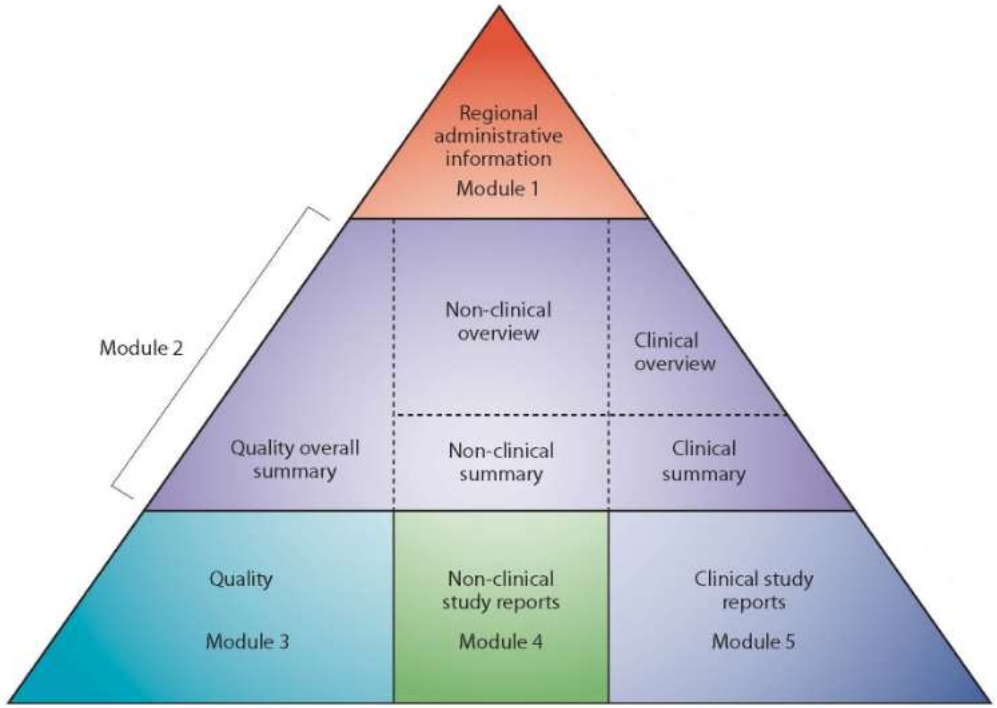
Topics Covered

- eCTD Background, Guidance, and Metrics
- Preparing to Submit Electronically and Points to Consider
- Electronic Submission Processing

eCTD Background

eCTD is the electronic version of the Common Technical Document (CTD). The eCTD contains an electronic table of contents, also referred to as a “backbone”, that manages all the metadata for an application.

CTD Triangle



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

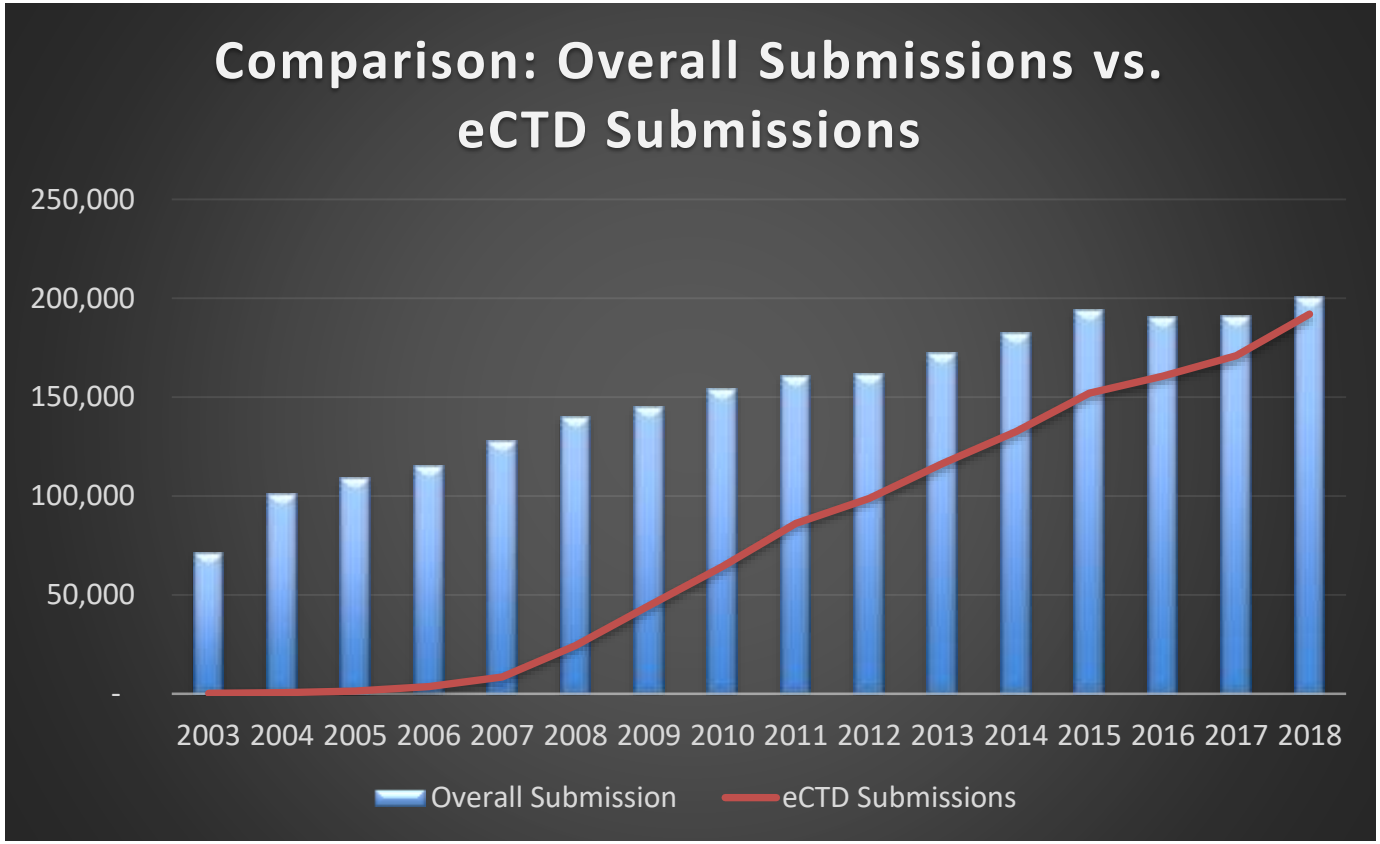
Guidance – eCTD Required

- **NDAs, BLAs, DMFs*, ANDAs** and **Commercial INDs** must be in eCTD format
- Paper and/or non-eCTD submissions are no longer accepted for above application types
- Study information in modules 4 or 5 must include the Study Tagging File (STF)
- Please see the eCTD web page www.fda.gov/ectd for further information and guidance

*Type III DMFs deadline extended to May 5, 2020

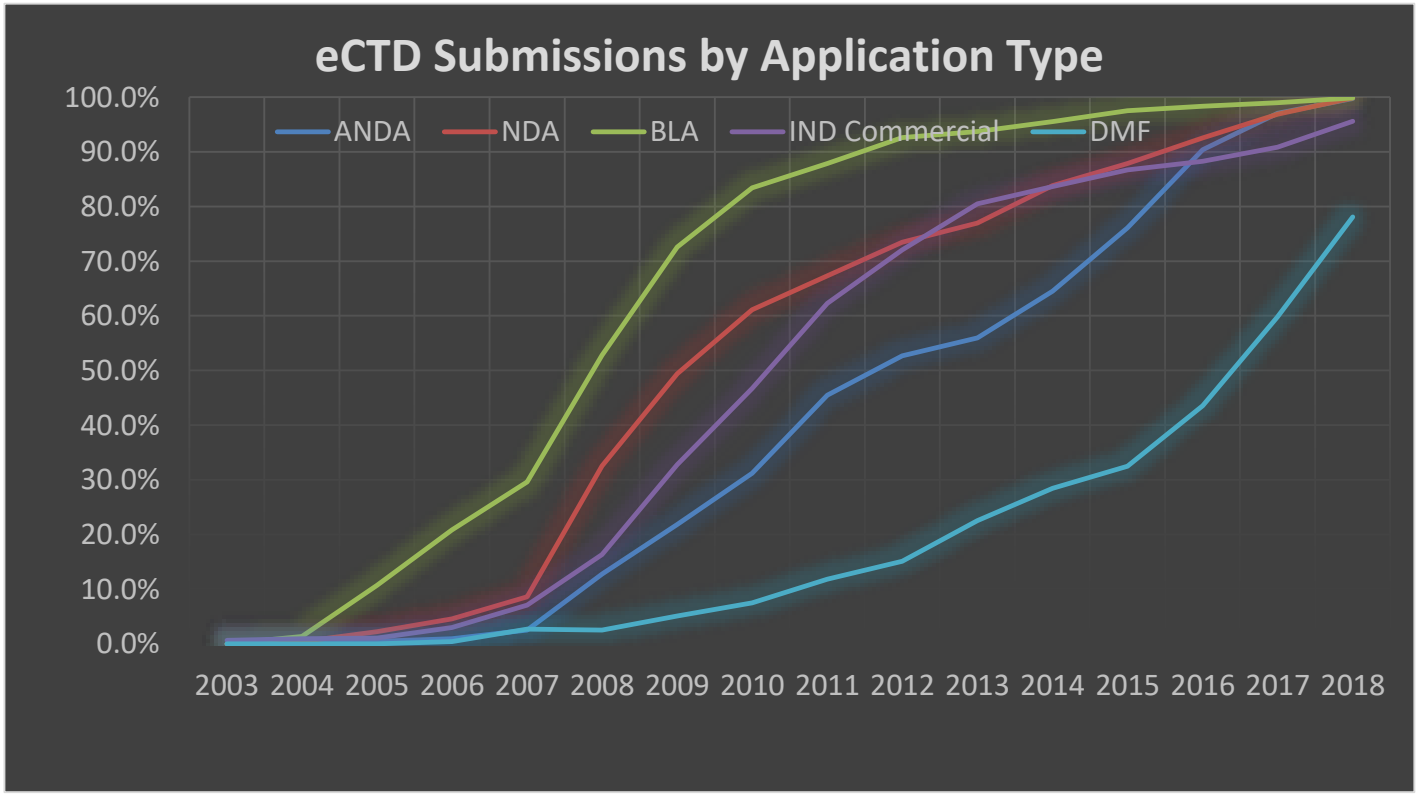
eCTD Submission Metrics

CDER receives approximately 200,000 electronic submissions via ESG annually. Nearly 192,000 were in eCTD in FY 2018.



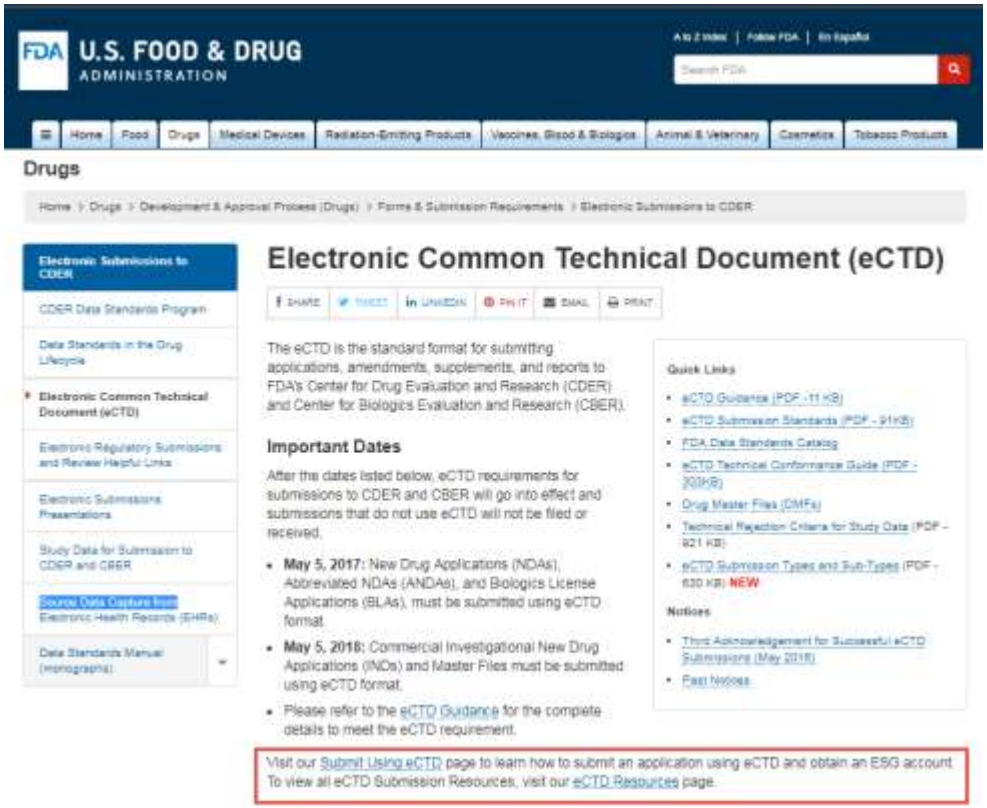
eCTD Submission Metrics

In FY 2018, nearly 100% of the regulatory submissions for NDA, BLA, and ANDA were in eCTD. For Commercial IND and DMF, 96% and 78% (Type II, IV, V).



Preparing to Submit Electronically and Points to Consider

Become familiar with the eCTD website



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Drugs

Home > Drugs > Development & Approval Process (Drugs) > Forms & Submission Requirements > Electronic Submissions to CDER

Electronic Submissions to CDER

- CDER Data Standards Program
- Data Standards in the Drug Lifecycle
- Electronic Common Technical Document (eCTD)
- Electronic Regulatory Submissions and Review Helpful Links
- Electronic Submissions Presentations
- Study Data for Submission to CDER and CBER
- Source Data Capture from Electronic Health Records (EHRs)
- Data Standards Manual (monographs)

Electronic Common Technical Document (eCTD)

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

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

Important Dates

After the dates listed below, eCTD requirements for submissions to CDER and CBER will go into effect and submissions that do not use eCTD will not be filed or received.

- **May 5, 2017:** New Drug Applications (NDAs), Abbreviated NDAs (ANDAs), and Biologics License Applications (BLAs), must be submitted using eCTD format.
- **May 5, 2018:** Commercial Investigational New Drug Applications (INDs) and Master Files must be submitted using eCTD format.
- Please refer to the eCTD Guidance for the complete details to meet the eCTD requirement.

Quick Links

- eCTD Guidance (PDF -11 KB)
- eCTD Submission Standards (PDF - 91KB)
- FDA Data Standards Catalog
- eCTD Technical Conformance Guide (PDF - [illegible]KB)
- Drug Master Files (DMFs)
- Technical Rejection Criteria for Study Data (PDF - 921 KB)
- eCTD Submission Types and Sub-Types (PDF - 630 KB) NEW

Notices

- Third Acknowledgement for Successful eCTD Submissions (May 2016)
- Past Notices

Visit our Submit Using eCTD page to learn how to submit an application using eCTD and obtain an ESG account. To view all eCTD Submission Resources, visit our eCTD Resources page.

Important Dates

Quick Links

- eCTD Guidance (PDF -11 KB)
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Visit our Submit Using eCTD page to learn how to submit an application using eCTD and obtain an ESG account.

Submission Hierarchy

"Where should I place my documents?"

- Organize content to follow Common Technical Document (CTD) structure

- Resources
  - The Comprehensive Table of Contents Headings and Hierarchy
  - M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use Guidance for Industry

The Comprehensive Table of Contents Headings and Hierarchy

Module 1 Administrative information
- ***1.1 Forms***
  - Form [form-type]
- ***1.2 Cover letters***
- ***1.3 Administrative information***
  - 1.3.1 Contact/sponsor/applicant information
    - **1.3.1.1 Change of address or corporate name**
    - **1.3.1.2 Change in contact/agent**
    - **1.3.1.3 Change in sponsor**
    - **1.3.1.4 Transfer of obligation**
    - **1.3.1.5 Change in ownership of an application or reissuance of license**
  - 1.3.2 Field copy certification
  - 1.3.3 Debarment certification
  - 1.3.4 Financial certification and disclosure
  - 1.3.5 Patent and exclusivity
    - **1.3.5.1 Patent information**
    - **1.3.5.2 Patent certification**
    - **1.3.5.3 Exclusivity claim**
  - 1.3.6 Tropical disease priority review voucher

File Format and PDF Specifications

- When creating content, follow the Specifications for File Format Types Using eCTD Specifications for guidance on file formats FDA expects under the different CTD headings

- Follow FDA's PDF Specifications and communicate to vendors the need to follow these specifications

Study Data

Learn about FDA requirements for submission of study data at the Study Data for Submission to CDER and CBER website.

- Key Study Data Resources:
  - Providing Regulatory Submissions In Electronic Format — Standardized Study Data Guidance for Industry
  - Technical Rejection Criteria for Study Data
  - Study Data Technical Conformance Guide
  - ANDA Forms and Submission Requirements Website

Have Questions? Contact eData@fda.hhs.gov

Prepare for Submission to FDA

- Request an Application Number from FDA
- Register for an Electronic Submission Gateway

Generate the eCTD for Submission to FDA

- Publish content into eCTD format via eCTD Publishing Tool or eCTD Tool Vendor
  - Utilize eCTD publishing tool to:
    - Capture administrative information
    - Map submission content to CTD section headings
    - Generate final submission in eCTD format including all required technical files/folder structure

Validate eCTD (Optional) and/or Request eSub Feedback

- (Optional) Validate via eCTD Validation Tool
- (Optional) Ask ESUB-Testing@fda.hhs.gov for technical feedback via Sample Submission Process
- eCTD Validation Criteria is posted on www.fda.gov/ectd in the eCTD Submission Standards

eCTD Submission Standards 2 / 5

Use	Standard	Exchange Format	Development Organization	Supported Version	Implementation Guide Reference	Date Support Begins (yyyy-mm-dd)	Date Support Ends (yyyy-mm-dd)	Date Requirement Begins	Date Requirements Ends	Regulatory References
This table contains a listing of the specifications and supportive files for eCTD submissions to both CDER and CBER. Last updated: 01/22/2019										
Specifications for eCTD Validation Criteria	eCTD		FDA	3.8		1/22/2019		5/5/2017 (for NDA, ANDA, BLA) 5/5/2018 (IND Commercial, MF)		Specifications for eCTD Validation Criteria Version 3.8 (PDF)
				3.8		1/22/2019				Specifications for eCTD Validation Criteria Version 3.8 (XLS)

Electronic Submission Processing: Increasing Automation

Submission Processing: 2018

All CDER regulatory submissions received are processed by Document Room

Document Room Process:

Staff reads the Cover Page of every submission (Approx. 850 per day) to categorize and route to correct Review Divisions

Submission Processing: 2019

Automate process to identify Submission Category

Process:

1. Determine Submission Category based on structured data in eCTD sequence
2. Route to Review Division based on Submission Category

Benefit:

Reviewer gets submission faster

Submission Processing Challenges

- Data submitted in eCTD backbone file (e.g. us-regional.xml) and regulatory form (e.g., Form 356h) sometimes contradict each other

eCTD Data Discrepancy Example

Can you guess the correct regulatory activity in this submission?

us-regional.xml (DTD V3.3)

```
<submission-information>
  <submission-id submission-type="fdast3" supplement-effective-date-type="fdasedt2" [redacted] </submission-id>
  <sequence-number submission-sub-type="fdasst3" [redacted] </sequence-number>
```

Indicating "CBE"

Form 356h

21. Submission (*See instructions*) ☐ Original ☐ Labeling Supplement ☑ CMC Supplement ☐ Efficacy Supplement ☐ Annual Report
☐ Product Correspondence ☐ REMS Supplement ☐ Postmarketing Requirements or Commitments ☐ Periodic Safety Report
☐ Request for Proprietary Name Review ☐ Other (*Specify*): _____

22. Submission Sub-Type ☐ Presubmission ☐ Amendment ☑ Initial Submission ☐ Resubmission

23. If a supplement, identify the appropriate category. ☐ CBE ☑ Prior Approval (PA) ☐ CBE-30

Indicating "Prior Approval"

This submission was an Initial CMC Supplement CBE.
The appropriate "**Supplement Category**" on Form 356h would have been "**CBE**"

eCTD Data Discrepancy Impact

- When data is submitted correctly in eCTD backbone files (e.g. us-regional.xml file) and regulatory form (e.g., Form 356h), submission can be efficiently routed to the assigned review division and/or reviewer(s)

- Indicating information in us-regional.xml that contradicts Form 356h could:
  - Impact FDA's ability to automate the submission process
  - Require additional effort to read the Cover Letter in order to resolve the discrepancy
  - May require Request(s) for Information that may otherwise not be necessary

Summary

- Important Guidance Requirements
  - **NDAs, BLAs, DMFs, ANDAs, and Commercial INDs must be submitted in eCTD**
  - **Study information in modules 4 or 5 must include the Study Tagging File (STF)**
- Preparing to Submit Electronically and Points to Consider
  - **Utilize FDA's eCTD Website**
  - **Align Content with CTD**
  - **Technical Rejection Criteria for Study Data**
- Confirm eCTD metadata does not contradict FDA Form
  - **eCTD Submission Type/Subtype and Supplement Category align with values on FDA Form 356h**

Thank You

Jonathan Resnick

CDER Electronic Submission Support Team

eSub@fda.hhs.gov

www.fda.gov/ectd

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. FOOD & DRUG ADMINISTRATION

Update on Technical Rejection Criteria for Study Data

Presented to: Regulatory Education for Industry (REdI)
Spring Event, Boston

Ethan Chen
Director, Division of Data Management Services and Solutions
Office of Business Informatics, CDER, FDA

May 29, 2019

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

Study Data Conformance from Previous Analysis

- **Study Data was assessed for:**
  - NDA, BLA, and ANDA Submissions received from 12/18/2016 to 3/31/2018
  - Commercial IND Submissions received from 12/18/2017 to 3/31/2018
  - No duplicates

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

Reference: FDA Study Data Technical Rejection Criteria (Revised May 2018)

Overall Conformance Statistics from Previous Analysis

Error	Description
1734	Trial Summary (TS) dataset must be present for each study in eCTD section 4.2 and 5.3
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

	NDA	ANDA	BLA	Comm. IND	All
Total Number of Submissions with Study Data	1,126	1,446	473	176	3,221
Total Number Submissions with Critical Errors	302	551	138	41	1,032
Error 1734	290	506	137	35	968
Error 1736	14	63	1	6	84
Failure Rate (% among submissions with Study Data)	26.8%	38.1%	29.2%	23.3%	32.0%

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, and ANDA submissions received by CDER between 12/18/2016 and 3/31/2018, and commercial IND submissions received by CDER between 12/18/2017 and 3/31/2018

(3) Validation of error 1736 of a study is not performed if a study has Error 1734

(4) A submission with multiple studies can report both Errors 1734 and 1736. In this instance, the submission is counted only once at the submission level when calculating failure rate

Reference: FDA Study Data Technical Rejection Criteria (Revised May 2018)

CY2018 Conformance Analysis for Validation Errors 1734 & 1736

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

** Refer to the latest Technical Rejection Criteria for Study Data*

	NDA	ANDA	BLA	Comm. IND	All
Total Number of Submissions with Study Data	877	1078	291	649	2895
Total Number Submissions with Critical Errors	195	266	50	113	624
Error 1734	185	186	48	96	515
Error 1736	16	88	2	18	124
Failure Rate (% among submissions with Study Data)	22.2%	24.7%	17.2%	17.4%	21.6%

Notes:

(1) Analysis includes NDA, BLA, ANDA and Commercial IND submissions received by CDER between 1/1/2018 and 12/31/2018

(2) Validation of error 1736 is not performed if a study has Error 1734

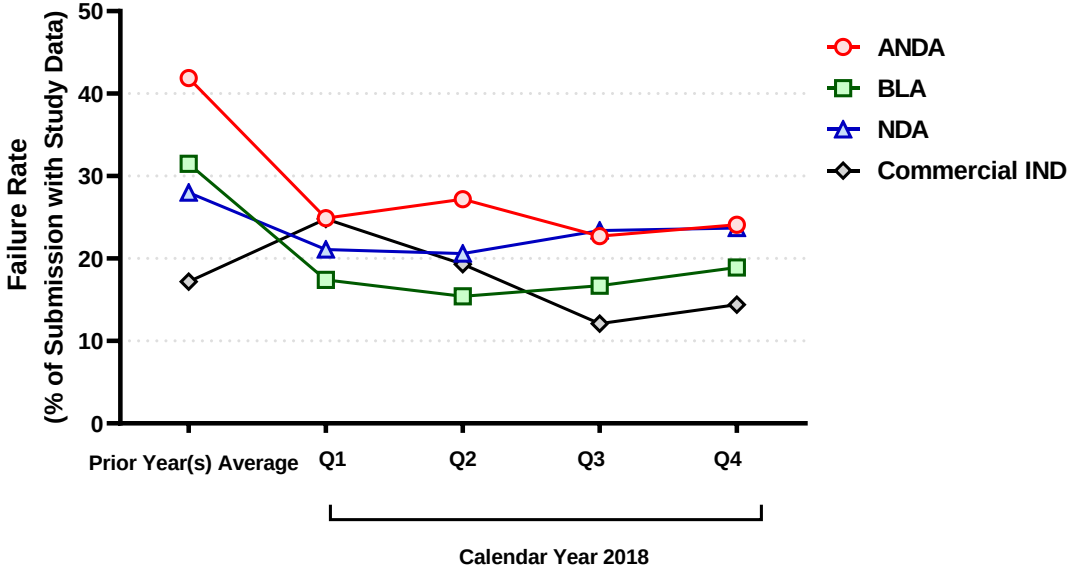
(3) A submission with multiple studies can report both Errors 1734 and 1736. In this instance, the submission is counted only once at the submission level when calculating failure rate

(4) Analysis is conducted according to the revised TRC (Revised Jan. 2019)

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

Overall Conformance Trend for Validation Errors 1734 & 1736

- Submissions with study data received during CY2018 showed overall decreases in failure rate of Validation Errors 1734 and 1736 compared to prior years' average failure rate



Notes:

(1) Prior year(s) average uses data from the previous analysis, but excludes any submissions received in 2018

(2) CY2018 analysis is conducted according to the revised TRC (Revised Jan. 2019)

Summary of 1734 and 1736 Conformance Trend

- The failure rate for Errors 1734 and 1736 for all application types received in CY2018 is 21.6%
- Overall conformance for Errors 1734 and 1736 improved compared to the previous analysis (previous years' average of 68.0% vs. CY2018's average of 78.4%)
- FDA has identified the need to provide additional clarifications on TRC to help Industry meet study data requirements and continue to improve the conformance trend over time
  - **Revision to TRC**
    - Details on 1734 and 1736
    - Emphasis on Error 1735
    - Inclusion of Error 1789
    - Inclusion of **Table 1** eCTD Technical Rejection Criteria for Study Data Expectation
    - Inclusion of **Appendix 1** Examples of Validation Findings in Study Data
    - Inclusion of **Appendix 2** Examples of ts.xpt datasets
  - **Additional Tools**: Self-Check Worksheet and Instructions for Study Data

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.

Reference:
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 (Reference to FDA Study Data Technical Rejection Criteria May 2018 version)	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 (Reference to FDA Study Data Technical Rejection Criteria Jan. 2019 version)	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**	STF Files must be submitted for required study sections*	**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*

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

CY2018 Conformance Analysis of IND, NDS and BLA Submission Studies: Errors 1734, 1735 & 1736

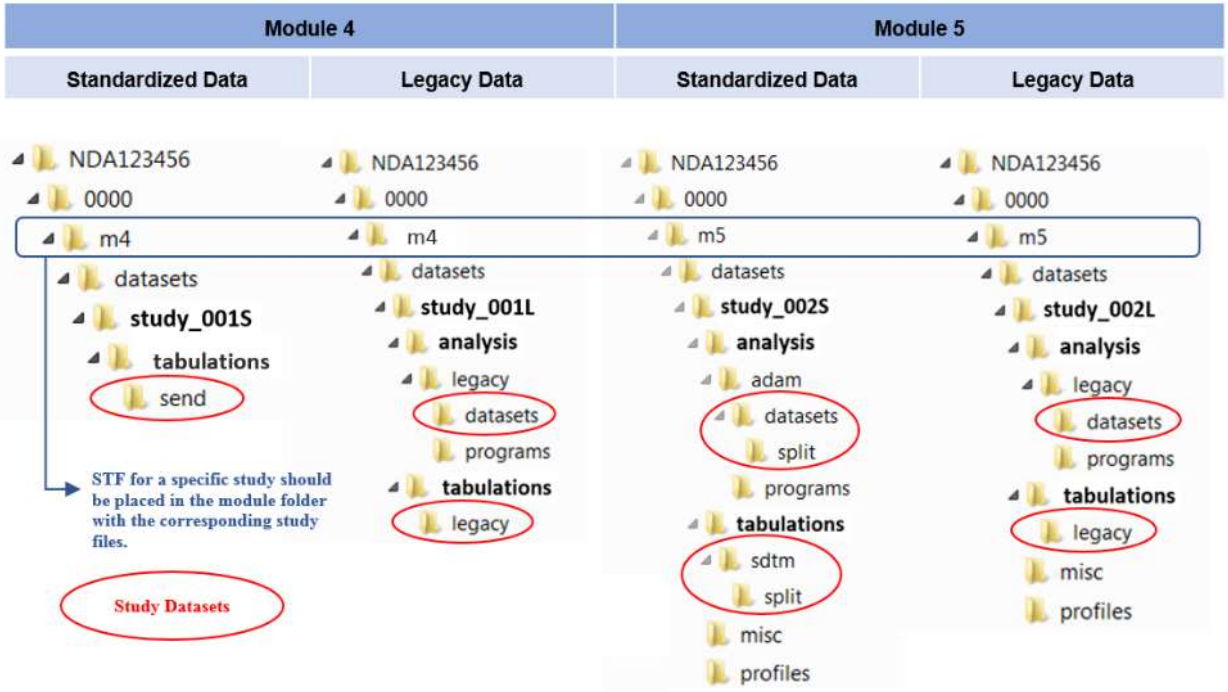
Error	Description
1734	Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections*
1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*
1736	For SEND data, a DM dataset and define 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*

** Refer to the latest Technical Rejection Criteria for Study Data*

	IND		NDA		BLA	
	Nonclin (m4)	Clin (m5)	Nonclin (m4)	Clin (m5)	Nonclin (m4)	Clin (m5)
Total Number of Studies	883	288	403	1810	12	206
Total Number Studies with Critical Errors	105	98	38	390	3	51
Error 1734	65	85	33	321	2	46
Error 1735	36	2	6	53	0	5
Error 1736	11	13	1	35	1	1
Error Rate (% among Total Number of Studies)	11.9%	34.0%	9.7%	21.6%	25.0%	24.8%

Folder Structure for Module 4 and Module 5

❖ STF files and their associated datasets should be organized into a specific file directory structure and a specific headings and hierarchy structure



References:
FDA Study Data Technical Conformance Guide (Appendix E; Version 4.2, October 2018)
ICH M2 EWG: The eCTD Backbone File Specification for Study Tagging Files

Additional Details for Error 1734

❖ **Full ts.xpt**

Sponsors should submit a dataset named 'ts.xpt' following published CDISC Standard and FDA Study Data Technical Conformance Guide

❖ **Simplified ts.xpt**

Sponsors should submit a dataset named 'ts.xpt' with four variables: STUDYID, TSPARMCD, TSVAL, AND TSVALNF)

Example of ts.xpt Datasets

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	• Left blank when study start date is provided in TSVAL • Exception code as specified in the ISO 21090 Standard when study start date is not available

References:
FDA Study Data Technical Conformance Guide (Appendices F & G; Version 4.2, October 2018)
FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

Additional Details for Error 1734

❖ **STUDYID in STF.xml and ts.xpt should match**

Based on the FDA Study Data TCG and the ICH STF Specification the Study ID uniquely and unambiguously identifies a particular study

ICH M2 EWG: The eCTD Backbone File Specification for Study Tagging Files (June 2008)

II. STUDY-IDENTIFIER ELEMENT

Information describing the study is contained in the *study-identifier* element of the STF. There are three elements contained in the *study-identifier* element: *title*, *study-id*, and *category*.

A. Title Element

The *title* element provides the full title of the study, not the title of each individual document.

B. study-id Element

The *study-id* is the internal alphanumeric code used by the sponsor to unambiguously identify this study.

CDISC Submission Metadata Model

The following variables are considered core selection variables for use in all CDISC domain models. These variable roles may also be defined with other roles (such as Key), and roles may differ from dataset to dataset.

Variable Name	Variable Label	Comments	Included in:
STUDYID	Study ID	Uniquely identifies a study within a particular submission.	All files
SITEID	Site ID	Some sponsors may use INVID instead of or in addition to a SITEID.	At least one of these variables must be included in all files
INVID	Investigator ID		
USUBJID	Unique Subject ID	Must be unique subject identifier within a submission (previously defined as PID; should be consistent with PID references used elsewhere in the submission)	All files

References:

- ICH M2 EWG: The eCTD Backbone File Specification for Study Tagging Files (June 2008) (http://estri.ich.org/STF/STFV2-6-1.pdf)
- CDISC Submission Metadata Model (https://www.cdisc.org/system/files/all/reference_material_category/application/pdf/submissionmetadatamodelv2.pdf)

Study Data Requirements for Submissions

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	

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

Emphasis on Errors 1735 and Inclusion of 1789

- Each submission typically contains many studies, an STF file is necessary to process study files into their corresponding studies; Accepting a submission where CDER cannot process the study tagging file will result in the reviewer seeing a list of files for which they do no not know the study they belong to

- If a study data file (e.g. define.xml) is not properly tagged in the STF file, it cannot be identified and located, resulting in Error 1736 being reported

Error	Description	Severity Level
1789	STF Files must be submitted in a study section. STF s are not required 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**

** Refer to the latest Technical Rejection Criteria for Study Data*

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

Tools for Industry

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

www.fda.gov

Sponsor reviews Study Data Standard Resources:

- **Revised Study Data Technical Rejection Criteria with eCTD Validation Table**
- **Study Data Self-Check Worksheet & Instruction**

Sponsor submits a eCTD and/or Standardized Data Sample to the FDA for validation

After review, FDA will provide with feedback, highlighting the errors found during the processing of the sample submission

Gateway

Sponsor submits an application with study data

1. Revised Study Data Technical Rejection Criteria (Revised Jan. 2019)

Purpose: To clarify the requirements for eCTD Validation of submissions with study data and to provided examples (**Appendix 1 and 2**) to illustrate the requirements

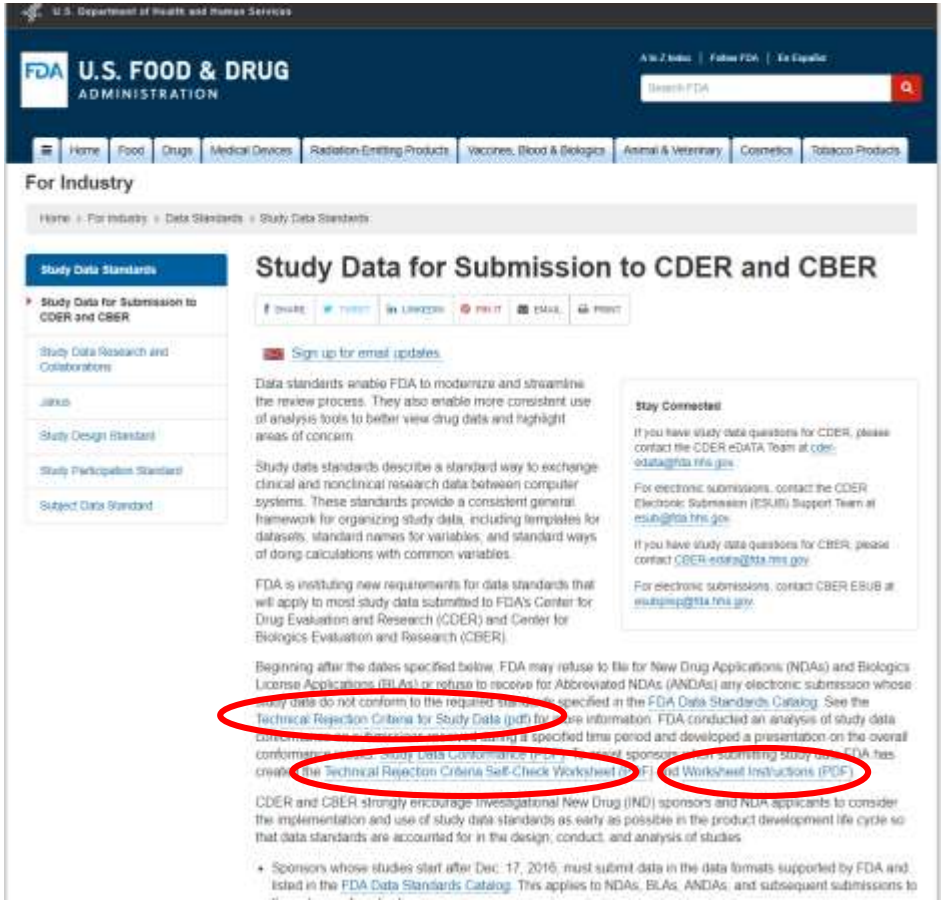
2. TRC Self-Check Worksheet & Instruction

Purpose: To help sponsors understand criteria for submissions with study data to pass the updated TRC

3. eCTD and/or Standardized Data Sample Validation

Purpose: To help sponsors validate their sample submissions and receive feedback with identified errors

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



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For Industry

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Study Data Standards

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

Study Data for Submission to CDER and CBER

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

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

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

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 esubpiep@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 in electronic submissions received during a specified time period and developed a presentation on the overall conformance issues. 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).

CDER and CBER strongly encourage Investigational New Drug (IND) sponsors and NDA applicants to consider the implementation and use of study data standards as early as possible in the product development life cycle so that data standards are accounted for in the design, conduct, and analysis of studies.

- Sponsors whose studies start after Dec. 17, 2016, must submit data in the data formats supported by FDA and listed in the FDA Data Standards Catalog. This applies to NDAs, BLAs, ANDAs, and subsequent submissions to

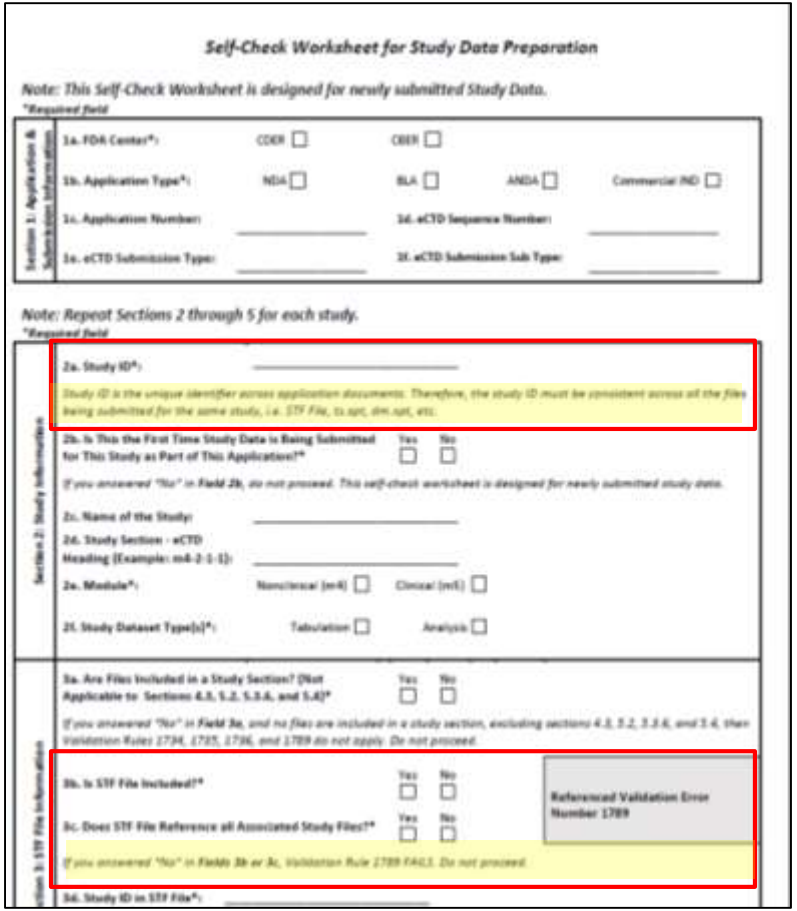
"Technical Rejection Criteria for Study Data"
https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm630740.pdf"

"Technical Rejection Criteria Self-Check Worksheet"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630732.pdf

"Technical Rejection Criteria Self-Check Worksheet Instructions"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630733.pdf

Overview of the Self-Check Worksheet

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



Self-Check Worksheet for Study Data Preparation

Note: This Self-Check Worksheet is designed for newly submitted Study Data.

*Required field

Section 1: Application & Submission Information

1a. FDA Center*: CDER ☐ OBER ☐

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.

*Required field

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. Name 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 ☐

Section 3: STF File Information

3a. Are Files Included in a Study Section? (Not Applicable to Sections 4.3, 5.2, 5.3.6, and 5.4)* Yes ☐ No ☐

If you answered "No" in Field 3a, and no files are included in a study section, excluding sections 4.3, 5.2, 5.3.6, and 5.4, then Validation Rules 1794, 1795, 1796, and 1789 do not apply. Do not proceed.

3b. Is STF File Included?* Yes ☐ No ☐

3c. Does STF File Reference all Associated Study Files?* Yes ☐ No ☐

Referenced Validation Error Number 1789

If you answered "No" in Fields 3b or 3c, Validation Rule 1789 FAILS. Do not proceed.

3d. Study ID in STF File*: _____

Reference: "Technical Rejection Criteria Self-Check Worksheet"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630732.pdf
"Technical Rejection Criteria Self-Check Worksheet Instructions"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630733.pdf

Sections of the Study Data Self-Check Worksheet

Section	Contents	Example(s)
1	**Application & Submission Information** • Provides high level information about the application and submission	1a. FDA Center*: CDER ☐ CBER ☐
2	**Study Information** • Provides more detailed information about the specific study	2a. Study ID*: 2f. Study Dataset Type(s)*: Tabulation ☐ Analysis ☐
3	**STF File Information** (1789 Validation Error) • Provide information about STF file	3b. Is STF File Included?* Yes ☐ No ☐ 3c. Does STF File Reference all Associated Study Files?* Yes ☐ No ☐
4	**TS File Information** (1734 Validation Error) • Provide information about ts.xpt file with study start date	4c. Study ID in TS File*: _____ 4d. Does Study ID in STF & TS Files Match?* Yes ☐ No ☐
5	**Standardized Dataset Information** (1735 & 1736 Validation Error) • Provide information about SEND or STDM and/or ADaM dataset and define.xml • Provide information about STF File-tags	5f. Is DM File Included?* Yes ☐ No ☐ 5g. Is Define File Included?* Yes ☐ No ☐ 5h. Are the STF File-Tags for the SDTM Datasets "data-tabulation-dataset-sdtm"?* Yes ☐ No ☐ 5i. Is the STF File-Tag for the Define File "data-tabulation-data-definition?* Yes ☐ No ☐

Note: Sections 2 through 5 are repeated for each study.

Reference: "Technical Rejection Criteria Self-Check Worksheet"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630732.pdf
"Technical Rejection Criteria Self-Check Worksheet Instructions"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630733.pdf

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

- Per FD&C Act Section 745A(a), sponsors must conform to standards in the FDA Data Standard Catalog

NDA, BLA, ANDA studies that started after **Dec. 17th, 2016**
Commercial IND studies that started after **Dec. 17th, 2017**

FDA issued "Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry"

- FDA revised & published Technical Rejection Criteria for Study Data (Revised Jan. 2019)
- FDA published Study Data Self-Check Worksheet & Instruction
- FDA will give the industry 90 days' notice on the eCTD website prior to the criteria becoming effective

Dec. 2014 | **Dec. 2016** | **Dec. 2017** | **Jan. 2019** | **Mid to Late 2019** | **TBD**

Study Data Technical Rejection Criteria are REQUIRED but NOT IMPLEMENTED

Study Data Technical Rejection Criteria are Implemented*

FDA Monitors & Analyzes the Study Data Conformance

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

Summary

- Based on the revised TRC, about 21.6% all submissions were received with non-critical errors for 1734 and 1736
- FDA published Study Data Self-Check Worksheet to help sponsors to follow the revised TRC
- 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.

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/DOWNLOADS/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/UCM630740.PDF
- **"Study Data Technical Conformance Guide"**
  HTTPS://WWW.FDA.GOV/DOWNLOADS/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/UCM624939.PDF
- **"FDA Data Standards Catalog"**
  HTTPS://WWW.FDA.GOV/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/DEFAULT.HTM
- **"Technical Rejection Criteria Self-Check Worksheet"**
  HTTPS://WWW.FDA.GOV/DOWNLOADS/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/UCM630732.PDF

  "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" page at:**
  HTTPS://WWW.FDA.GOV/DRUGS/DEVELOPMENTAPPROVALPROCESS/FORMSSUBMISSIONREQUIREMENTS/ELECTRONICSUBMISSIONS/UCM248635.HTM
- **For the full list of Study Data standards, see the FDA "Study Data Standards Resources" page at:**
  HTTP://WWW.FDA.GOV/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS

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