

WHAT YOU NEED TO KNOW ABOUT SUBMITTING DATA TO THE FDA



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Objectives

- Share Merck's experience with FDA requirements and plan ahead to ensure that submitted electronic data are compliant with FDA regulations and review expectations
- Share lessons learned and differences while preparing tabulations, analysis and site selection (BIMO) packages
- Review requirement of the data standards start date
- Review waivers request for clinical data standards
- Examine FDA's enforcement of the technical rejection



Scope: Guidances related to clinical study data

Out of Scope: Study Data Standardization Plan (SDSP) and clinical study reports

Agenda

1. Overview of the electronic submission packages
2. Data standards requirement
3. Waivers request
4. Technical rejection
5. Differences between CBER and CDER
6. Conclusion



Overview of the Electronic Submission Packages

Tabulation/ SDTM

- ❖ **SDTM data in SAS Transport file format (.xpt)**
 - ts.xpt, dm.xpt etc.
- ❖ **define.xml version 2.0**
 - Make sure all links are working
 - Derivation rules are correctly document in plain English
- ❖ **define.pdf**
- ❖ **acrf.pdf**
 - Annotated with SDTM domains and variables
 - If two domains are used on the same page use different font and background color
 - SUPQUAL variables are annotated with QNAM
 - Use TESTCD for --ORRES values
- ❖ **csdrg.pdf**

Analysis/ ADaM

- ❖ **ADaM data in SAS Transport file format (.xpt)**
 - adsl.xpt etc.
- ❖ **define.xml version 2.0**
 - Make sure all links are working
 - Derivation rules are correctly document in plain English
- ❖ **define.pdf**
- ❖ **adrg.pdf**
- ❖ **analysis-results-metadata.pdf or part of the define.xml**
 - Key safety and efficacy
- ❖ **Programs in ASCII Text format (.txt)**

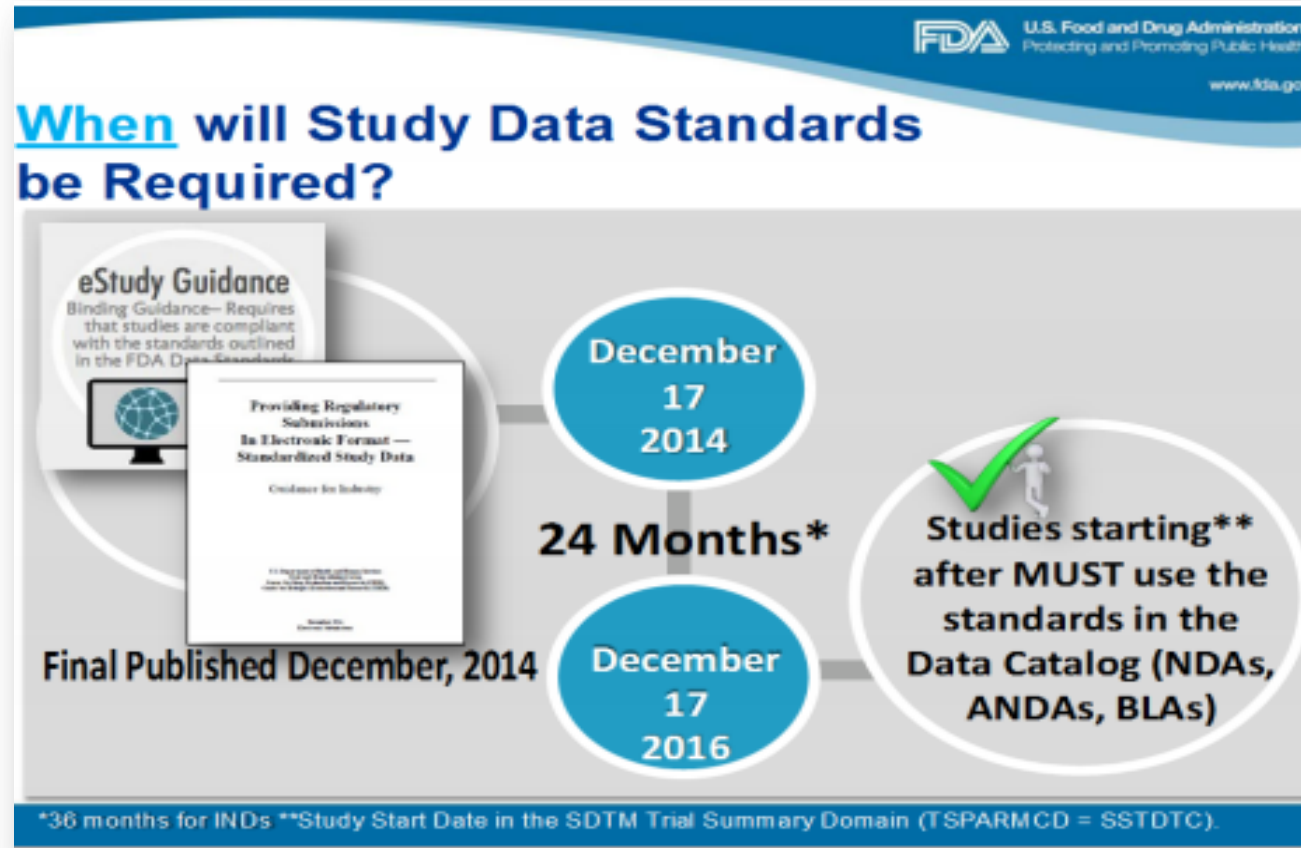
Bioresearch Monitoring (BIMO)

Pivotal studies submitted to CDER only

- ❖ **Listings**
 - By Site Subject data listings organized by site for each study (PDF)
 - 10 Listings per site
- ❖ **clinsite.xpt**
 - Site-Level dataset
 - One dataset for all pivotal studies(.xpt)
- ❖ **define.pdf**
- ❖ **bimo-reviewer-guide.pdf (optional)**

Data Standards Requirement

FDA announced that for any study start date on or **after** December 17, 2016, sponsors are required to submit data in a valid SDTM version indicated in the FDA Data Standards Catalog



FDA Data Standards Catalog

These are binding regulatory requirements

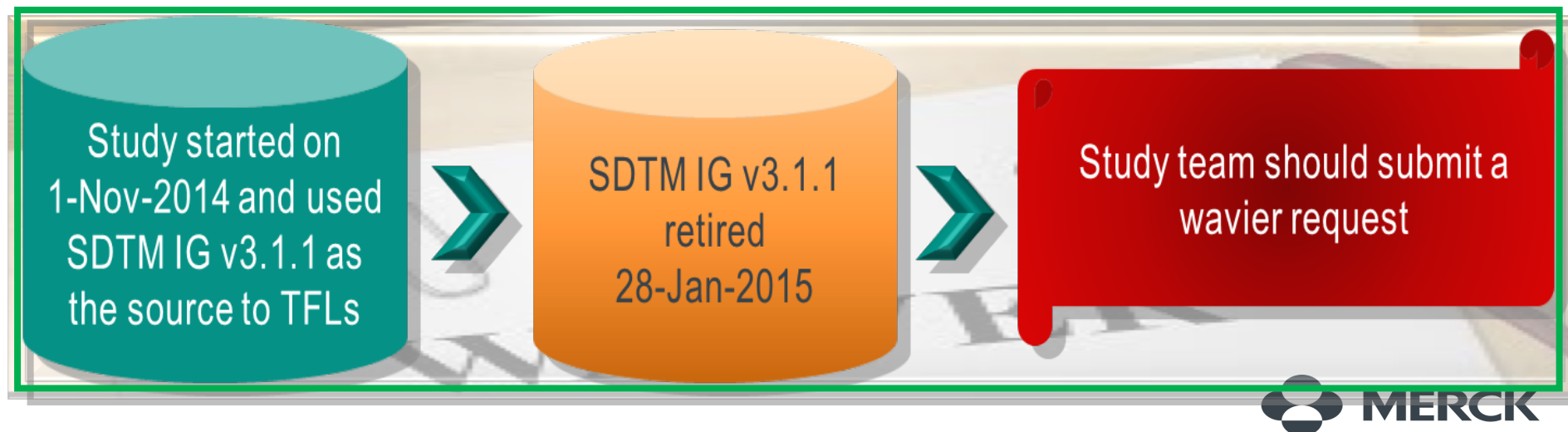
FDA Data Standards Catalog v6.0 (07-19-2019) - Supported and Required Standards									
For full description of column headings, see Instr & Column Descriptions tab									
Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Supported Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends
Study Data Tabulation Model (SDTM)	XPT	Clinical Data Interchange Standards Consortium (CDISC)	1.1	3.1.1	CDER, CBER	Ongoing	01/28/2015		
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]
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]
SDTM	XPT	CDISC	1.3	3.1.3	CDER, CBER	12/01/2012		12/17/2016 [1] 12/17/2017 [2]	
SDTM	XPT	CDISC	1.4	3.2	CDER, CBER	08/17/2015		03/15/2018 [1] 03/15/2019 [2]	
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]
ADaM	XPT	CDISC	2.1	1.1	CDER, CBER	03/15/2018		03/15/2019 [1] 03/15/2020 [2]	
Standard for Exchange of									

Standard & Version FDA expects for a submission

FDA Support and Requirement Start/End dates

Waivers Request

- To apply for a waiver, an email request must be sent to the FDA technical staff when planning to submit study data that is no longer supported in the FDA Data Standards Catalog.
 - For CDER submissions, requests should be addressed to: cder-edata@fda.hhs.gov
 - For CBER submissions, requests should be addressed to: cber.cdisc@fda.hhs.gov
- FDA encourages the sponsors to submit the waiver request to the FDA technical staff as early as possible during product development.
- FDA intends to notify the requestor within 30 days from the date the waiver request is received.
- FDA will notify the sponsor or applicant in a written email as to whether the waiver request is denied or granted.



Technical Rejection Criteria for Clinical Study Data

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

- Correct STF file-tags must be used for all datasets and define.xml files
- **SDTM package:**
 - dm.xpt, ts.xpt and define.xml must be present
 - For **legacy package** simplified ts.xpt must be provide with Study Start Date (SSTDTC) populated
 - For **SDTM package** full ts.xpt file must be provide with Study Start Date (SSTDTC) populated in addition to CDISC Standard and FDA Study Data Technical Conformance Guide (TCG)
- **ADaM package:**
 - adsl.xpt and define.xml must be present



To assist sponsors when submitting study data,

FDA has created the [Technical Rejection Criteria Self-Check Worksheet \(PDF\)](#) and [Worksheet Instructions \(PDF\)](#).

Sample Self Check Work



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 intended to help you prepare newly submitted study data to FDA, i.e. studies for which no files have been submitted.

***Required Field**

Section 1: Application & Submission Information

1a. FDA Center*	1b. Application Type*	1c. Application Type
☒ CDER ☐ CBER	☒ NDA ☐ BLA ☐ ANDA ☐ Commercial IND	
1d. eCTD Sequence Number	1e. eCTD Submission Type	1f. eCTD Submission

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 documents 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.

Section 3: STF File Information

3a. Are Files Included in a Study Section? (Not Applicable to Studies for which no files have been submitted)

☐ Yes ☐ No

If you answered "No" in Field 3a, and no files are included in the submission, Validation Rules 1734, 1735, 1736, and 1789 do not apply. Do not proceed.

3b. Is STF File Included?*

☐ Yes ☐ No

3c. Does STF File Reference Study ID Exist?*

☐ Yes ☐ No

If you answered "No" in Fields 3b or 3c, Validation Rule 1788 applies. Do not proceed.

3d. Study ID (study-id) in STF File*

If you answered "No" in Field 3e, ensure the study ID is consistent across all documents being submitted for the same study, i.e. STF File, ts.xpt, dm.xpt, etc.)

3f. Are XPT Datasets (other than the ts.xpt file) Included?*

☐ Yes ☐ No

3g. If the Study ID in the XPT Dataset is the Same as the Study ID in the STF File?

☐ Yes ☐ No

Section 4: TS File Information

4a. If the Study is for a Commercial IND Application, Is the Study Start Date Prior to or on 17-Dec-2017?

☐ Prior to or on 17-Dec-2017 ☐ After 17-Dec-2017

4b. If the Study is for an NDA, BLA, or ANDA Application, Is the Study Start Date Prior to or on 17-Dec-2016?

☒ Prior to or on 17-Dec-2016 ☐ After 17-Dec-2016

Study Start Date	Application Type	Data Type
Prior to or on 17-Dec-2016	NDA, BLA, or ANDA	Nonclinical
Prior to or on 17-Dec-2016	NDA, BLA, or ANDA	Clinical
Prior to or on 17-Dec-2017	Commercial IND	Nonclinical
Prior to or on 17-Dec-2017	Commercial IND	Clinical
After 17-Dec-2016	NDA, BLA, or ANDA	Nonclinical
After 17-Dec-2016	NDA, BLA, or ANDA	Clinical
After 17-Dec-2017	Commercial IND	Nonclinical
After 17-Dec-2017	Commercial IND	Clinical

**See the Study Data Technical Conformance Guide for more information.

4c. Is TS File Required?*

☐ Yes ☐ No

Refer to guidelines in chart above. If you answered "No" in Field 4c, and no TS file is required, then Validation Rules 1734, 1735, and 1736 do not apply. Do not proceed.

4d. If TS File is Required, Is it Included?*

☐ Yes ☐ No

If you answered "No" in Field 4d, Validation Rule 1734 FAILS. Do not proceed.

4e. If TS File is Required, Is it Included?*

☐ Full TS ☒ Simplified TS

Refer to guidelines in chart above. If you answered "Simplified TS" in Field 4e, Validation Rules 1734, 1735, and 1736 do not apply. Do not proceed.

Simplified TS File Information

4l. Study ID (STUDY ID) in TS File*

4m. Does Study ID Exist in TS File?*

☒ Yes ☐ No

If you answered "No" in Field 4m, Validation Rule 1734 FAILS. Do not proceed.

4n. Is there a Value in the TS File for the Study ID?*

☐ Yes ☐ No

If you answered "No" in Field 4n, Validation Rule 1734 FAILS. Do not proceed.

4o. Is the Value in the TS File for the Study ID the Same as the Study ID in the STF File?*

☐ Yes ☐ No

If you answered "Yes" in Field 4o, Validation Rule 1734 FAILS. Do not proceed.

4p. Study Start Date in TS File:

The Study Start Date (SSD) should follow the ISO 8601 standard that provides, at a minimum, the year, month, and date for the study start date (yyyy-mm-dd).

4q. If Study Start Date Exists, Is it in Valid Format (yyyy-mm-dd)?

☐ Yes ☐ No

If you answered "No" in Field 4q, Validation Rule 1734 FAILS. Do not proceed.

Section 5: Standardized Datasets (SEND, SDTM, ADaM)

5a. Are Standardized Datasets Required?*

☐ Yes ☐ No

Study Start Date	Application Type	Standardized Datasets Required?
Prior to or on 17-Dec-16	NDA, BLA, or ANDA	Not Required
After 17-Dec-16	NDA, BLA, or ANDA	Required
Prior to or on 17-Dec-17	Commercial IND	Not Required
After 17-Dec-17	Commercial IND	Required

If you answered "No" in Field 3f and "Yes" in Field 3g, standardized datasets are not required in this submission and Validation Rules 1735 and 1736 do not apply. Do not proceed.

If you answered "No" in Field 5a, standardized datasets are not required and Validation Rules 1735 and 1736 do not apply. Do not proceed.

Fields 5b-5e are applicable to nonclinical tabulation datasets (SEND), Fields 5f-5i are applicable to clinical tabulation datasets (SDTM), and Fields 5j-5m are applicable to clinical analysis datasets (ADaM).

Note: For clinical data in Commercial INDs standardized datasets are required if the study start date is after the date stated, however, study data technical rejection criteria will not be applicable until further notice.

Selecting the button will add another set of Sections 2-5 to the fillable form.

Add an Additional Study 2-5

[Referenced Validation Error Number 1734](#)



Differences between CBER and CDER

The *FDA Industry Guidance Providing Regulatory Submissions In Electronic Format — Standardized Study Data* applies to both CBER and CDER; however, there are additional technical specifications published by individual Offices that contain specific details for submitting data.

CDER	CBER
BIMO package required for all pivotal studies	No BIMO package, but CBER uses the tabulations/SDTM data such as DM, DV, IE etc.
N/A	Recommends Vaccines Technical Specification Guidance for Office of Vaccine Research and Review (OVRR)
Submitting Select Clinical Trial Data Sets for Drugs Intended to Treat Human Immunodeficiency Virus (HIV) -1 Infection	N/A
Submitting Clinical Trial Datasets for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Drugs	N/A
Technical Specifications—Comparative Clinical Endpoint Bioequivalence Study Analysis Datasets for Abbreviated New Drug Applications	N/A

Conclusion

The **study start date** has a significant impact on SDTM and ADaM implementation.

The version of the study data standards that should be used for a study's data is dependent on the study start date and regulatory agency requirements.

To help ensure that the correct version of study data standards is supported, sponsors can use the FDA Study Data Standards Catalog.

Additional guidelines to help ensure compliance with FDA submission requirements include:

- The FDA Technical Rejection Criteria Self-Check Worksheet
- The latest Study Data Technical Conformance Guide
- OVRG Guidelines etc.

If study data is not aligned to the study data standards supported in the FDA technical specifications, then regulatory communication, such as a waiver request, is required.

Reference Links

Guidelines for Requesting Waiver to Current Supported Study Data Standard Versions: <https://www.fda.gov/drugs/forms-submission-requirements/guidelines-requesting-waiver-current-supported-study-data-standard-versions>

FDA Data Standard Catalog: <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>

Study Data Technical Conformance Guide: <https://www.fda.gov/media/122913/download>

Technical Rejection Rules: <https://www.fda.gov/media/100743/download>

Therapeutic Area Information & Specifications

- **FDA Guidance for Industry: Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review (OVRR):**
<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM605147.pdf>
- **Human Immunodeficiency Virus:** <https://www.fda.gov/media/112667/download>

Summary Level Clinical Site Data for CDER's Inspection Planning:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>

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**Thank You for
Your Attention**

