Paper DS02

What You Need to Know About Submitting Data to the FDA

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ABSTRACT

Sponsors need to stay current with FDA requirements and plan to ensure that submitted electronic data are compliant with FDA regulations and review expectations.

The focus of this paper is to share lessons learned while preparing clinical tabulations, analysis and site selection packages for Module 5 submission and to address key differences between CBER and CDER. Careful attention must be given to the requirement start dates as these can have significant impact on SDTM and ADaM implementation. FDA guidance continues to change which affects submission throughout the product development lifecycle. Regulatory communication such as waiver requests for data standards and meetings are outlets for sponsors to capitalize on the agreements prior to submission. The lack of data standards awareness may result in delays especially in times where FDA is enforcing technical rejection. How much do you know about submitting data to FDA?

INTRODUCTION

The scope of this paper is to share Merck's experience aligned with FDA requirements and to ensure that the submitted electronic data is compliant with FDA regulations and reviewer's expectations. First, the paper will include lessons learned and differences while preparing tabulations, analysis and site selection (BIMO) packages. Next, the paper will highlight the review requirement of the data standards start date and review a request for a waiver for clinical data standard. Lastly, the paper will examine FDA's enforcement of the technical rejection.

OVERVIEW OF THE ELECTRONIC SUBMISSION PACKAGES

For clinical studies, sponsors should include the source data that was used to generate the CSR reports. This data should be submitted in CDISC Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) standards to ensure traceability.

Tabulation Package

Collected data should be mapped in accordance to a valid SDTM version. Valid version can be located on FDA Data Standard Catalog: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources. This clinical package is submitted under the Module 5 of the eCTD (m5/tabulations/datasets/sdtm).

Deliverables	Comments

SDTM datasets	• The SAS Transport Format (XPORT) Version 5 is the file format for the submission of all electronic datasets (e.g. ts.xpt, dm.xpt, etc.)
	• Datasets greater than 5 GB should be split into smaller datasets
	  ○ Sponsors should submit these smaller datasets, in addition to the larger non-split datasets
	  ○ The split datasets should be placed in a separate sub-directory labeled *split*

define.xml	• Version 2.0 and accompanying style sheet • Ensure all links are working • Derivation rules are correctly documented in plain English
define.pdf	As needed

acrf.pdf	• Annotate
	  ○ SDTM domain and variables
	  ○ QNAM for SUPPQUAL variables
	  ○ TEST
	• Apply different font and background color when two domains are used on the same page
	• When data is recorded on the Case Report Form (CRF) but is not submitted, the CRF should indicate *NOT SUBMITTED*. There should be an explanation in the cSDRG stating the reason data was not been submitted.

csdrg.pdf	This document facilitates FDA review by describing the standards used in the study; any special considerations; and conformance issues that may help a reviewer to understand the relationship between the study report and the tabulation data.

Analysis Package

These datasets are usually generated using the SDTM data. This package is submitted under the Module 5 of the eCTD (m5/analysis/datasets/adam).

Deliverables	Comments

ADaM datasets	• The SAS Transport Format (XPORT) Version 5 is the file format for the submission of all electronic datasets (e.g. adsl.xpt, adae.xpt, etc.)
	• Datasets greater than 5 GB should be split into smaller datasets
	  ○ Sponsors should submit these smaller datasets, in addition to the larger non-split datasets
	  ○ The split datasets should be placed in a separate sub-directory labeled *split*

define.xml	• Version 2.0 and accompanying style sheet • Ensure all links are working • Derivation rules are correctly document in plain English
define.pdf	As needed
adrg.pdf	• This document provides FDA reviewers with context for analysis datasets, terminology, and summary of ADaM conformance findings. Submission of an ADRG does not eliminate the requirement to submit a complete and informative define.xml file corresponding to the analysis datasets.
analysis-results-metadata.pdf	• The analysis results metadata (ARM) is an extension of the define.xml. An alternative approach is to implement the ARM as a separate document and link it to the define.xml. While FDA does not require the ARM, it can be a helpful addition to reviewers • Identifies tables, listings, and figures that support the primary and key secondary analysis and provides a link to the analysis datasets and programs.
Programs in ASCII format	• The main purpose of requesting the submission of these programs is to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms and results. • At minimum submit the programs that create all ADaM datasets and those that generate tables and figures associated with primary and secondary efficacy analyses. • File format as .txt file

Bioresearch Monitoring (BIMO)
This package supports site inspection and should be provided for all pivotal studies in CDER submissions. This package is submitted under the Module 5 of the eCTD (m5/datasets/bimo/site-level).

Deliverables	Comments
Subject-Level Data Line Listings	• For each pivotal study, prepare the subject data listings (PDF) organized by site. • Expect to provide 10 (criteria a-j) multiplied by the number of sites
SUMMARY-LEVEL CLINICAL SITE DATASET	• A single summary-level clinical site dataset (clinsite.xpt) that contains the pivotal studies used to support primary safety and/or efficacy endpoints
define.pdf	• Required to submit for BIMO review
define.xml	• XML format is optional • Version 2.0 with a style sheet • Make sure all links are working • Derivation rules are correctly documented in plain English
bimo-reviewer-guide.pdf	• This document is optional but can be beneficial for inclusion • This document provides FDA reviewers with context to the clinsite.xpt dataset, terminology, and summary of BIMO package. Submission of this document does not eliminate the need to provide a define.pdf file.

DATA STANDARDS REQUIREMENT
For any studies starting on or after December 17, 2016, FDA requires sponsors to submit data in a valid SDTM version as indicated in the binding FDA Data Standards Catalog. If a study does not adhere to a valid data standard, then sponsors need to submit a waiver request.

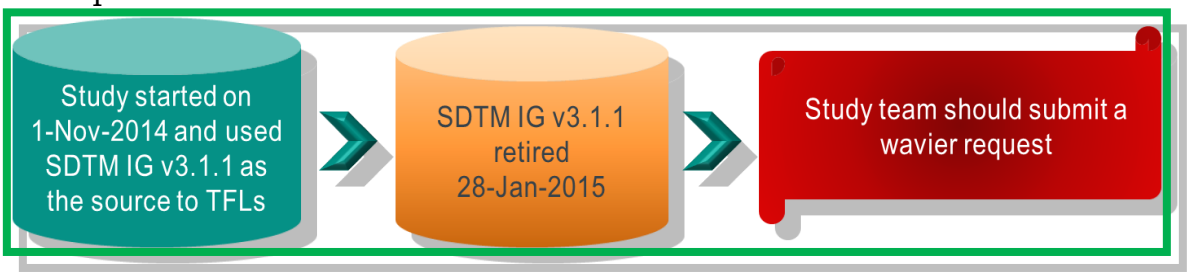
WAIVER REQUEST
A waiver request applies to studies using a version of study data standards that are no longer supported in the FDA Data Standards Catalog. To apply for a waiver, sponsors must e-mail the FDA technical staff when planning to submit study data that is no longer supported in the FDA Data 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 sponsor to submit the waiver request to the FDA technical staff as early as possible during product development. They intend 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.

Example:



TECHNICAL REJECTION CRITERIA FOR CLINICAL STUDY DATA

FDA developed tools to help sponsors meet updated study data standard requirements. To provide more transparency on the validation process, FDA is checking for the following:

- Correct study tagging file (STF) 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: a simplified ts.xpt must be provide with the Study Start Date (SSTDTC) populated
  - For SDTM package: a full ts.xpt file must be provided with the Study Start Date (SSTDTC) populated, including the parameters defined in the FDA Study Data Technical Conformance Guide (TCG) Appendix.
- 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).

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. As regulatory agency requirements are updated, sponsors should assess their planned submission package and determine whether deliverables are compliant with expected standards.

To help ensure that the correct version of study data standards is supported, sponsors can use the FDA Study Data Standards Catalog. Additional tools to help ensure compliance with FDA submission requirements include the FDA Technical Rejection Criteria Self-Check Worksheet and the latest Study Data Technical Conformance Guide.

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.

REFERENCES

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

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

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

CONTACT INFORMATION

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