

Ready, Set, Go: Planning and Preparing a CDISC Submission

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Proactive

Serving to prepare for, intervene in, or control an expected occurrence or situation, especially a negative or difficult one; anticipatory



Best Practices for CDISC Submissions

1. **Educate yourself on regulatory requirements**
2. Points to consider for data deliverables
3. Include all tasks in resource and timeline plans
4. Seek agreement with Regulatory Agencies early
5. Build in quality from the beginning

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Educate Yourself on Regulatory Requirements

FDA Must Read Documents

- [FDA Data Standards Catalog](#)
- [FDA Study Data Technical Conformance Guide](#)
- [FDA Business Rules](#) & [FDA Validator Rules](#)
- [FDA Technical Rejection Criteria](#)
- [eCTD Guidance](#)
- All available at [FDA Study Data Standards Resources Website](#)

PMDA Must Read Documents

- [Basic Principles on Electronic Submission of Study Data for New Drug Applications](#)
- [Notification on Practical Operations of Electronic Study Data Submissions](#)
- [Data Standards Catalog \(2017-03-03\)](#)
- [Technical Conformance Guide on Electronic Study Data Submissions](#)
- All available at [PMDA Information for CDISC Data Submissions](#)

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Electronic Common Technical Document



**U.S. FOOD & DRUG
ADMINISTRATION**



eCTD SUBMISSION REQUIREMENTS: WHAT YOU NEED TO KNOW

eCTD

The **Electronic Common Technical Document (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).

An eCTD submission has five modules: region-specific information, summary documents, quality-related information, nonclinical study reports, and clinical study reports.

When materials are submitted electronically, it is easier for FDA to review data, approve new drugs, and monitor drugs after they go on the market. Using eCTD also simplifies the process for submitters, because it is the same format used by drug regulatory agencies in other countries.

Starting in 2017, eCTD will be required for submissions to CDER and CBER. After the dates listed below, submissions that are not in eCTD format will not be filed or received unless exempted from the requirement.

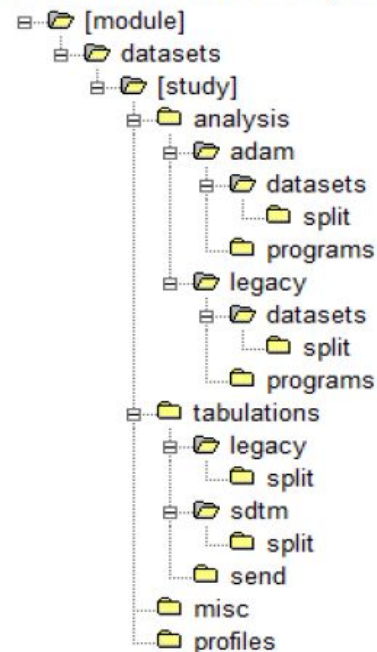
Study Data Delivered in Case Report Tabulations (CRTs)

- Stored in Module 5 of eCTD
 - Folders for ADaM and SDTM data
 - Folders for Legacy data
 - Split datasets (for datasets > 5gb) go into Split folders

[Link to eCTD Table of Contents](#)

[Link to FDA eCTD Info](#)

Figure 1: Folder Structure for Study Datasets



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FDA Data Standards Requirements

FDA Data Standards Catalog

- Specifies the data standards and versions that FDA requires and supports
- Separate tabs for Data Exchange standards and Terminology standards

FDA Data Standards Catalog v5.0 (04-20-2018) - 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)	Date Requirement Ends	Statutory, Regulatory, or Guidance Authority
Clinical study datasets	Study Data Tabulation Model (SDTM)	XPT	Clinical Data Interchange Standards Consortium (CDISC)	1.1	3.1.1	CDER, CBER	Ongoing	01/28/2015			Standardized Study Data
											Study Data Technical Conformance Guide
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]		Standardized Study Data
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]		Standardized Study Data
Clinical study datasets	SDTM	XPT	CDISC	1.3	3.1.3	CDER, CBER	12/01/2012		12/17/2016 [1] 12/17/2017 [2]		Standardized Study Data
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

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FDA Technical Conformance Requirements

STUDY DATA TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following
Guidance Document(s):

**Guidance for Industry Providing Regulatory Submissions in Electronic
Format – Standardized Study Data**

For questions regarding this technical specifications document, contact CDER at
cdcr-edata@fda.hhs.gov or CBER at cber.cdisc@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

Version 1.3 finalized December 2017

FDA Business Rule ID

FDA Business Rule

Clinical and Nonclinical

FDAB005	Age or age range should be provided for all subjects, except for Screen Failures.
FDAB008	All exposure records should occur between First and Last Study Treatment dates.
FDAB009	All paired variables should have a one-to-one relationship. Examples include Short Name and Name of Test; Parameter Name and Parameter Code or Number; Variable Name and Variable Label, etc.
FDAB011	All Trial Design data should be submitted as specified in the Technical Conformance Guide (TCG).
FDAB012	Assessment results should include units whenever a unit of measure is available.
FDAB013	Baseline flags for Laboratory results, Vital Signs, ECG, Pharmacokinetic Concentrations, and Microbiology results should be submitted if the data was collected or can be derived.
FDAB015	Character values should not have leading spaces or only have a period character.
FDAB016	Collection Study Day should be populated when Date/Time of Collection is available.
FDAB017	Controlled terms should use the exact same case used by the terminology maintenance organizations (e.g., MedDRA, CDISC controlled terminology).
FDAB018	A variable's length across a study should be no longer than the maximum length of the actual data (except for SUPPLEMENT).

These and other FDA guidances available at [FDA Study Data Standards Resources Website](#)

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Examples of FDA Technical Conformance Requirements

Trial Summary domain must be submitted for all studies

- For non-CDISC studies, TS must contain at least one record with study start date, where Study Start Date = Earliest informed consent date for all subjects in study

EPOCH should be included for clinical subject-level observations

- e.g., adverse events, laboratory, concomitant medications, exposure, and vital signs

Definition of datasets, variables, and codelists in define.xml should reflect the actual study data

- Subset codelists to actual values that are possible in the study

Split datasets greater than 5 gigabytes

- Submit both split and non-split datasets. Place split datasets in separate sub-directory labeled "split"
- Explain splitting method in relevant data reviewer's guide
- Split LB using LBCAT and if necessary LBSCAT

Optimise length of variables

- A variable's length across a study should be no longer than the maximum length of the actual data (except for SUPPQUAL)

And More

- See FDA Technical Conformance Guide and FDA Business Rules

FDA Validation of Study Data

“Validation activities occur at different times during submission and review of study data, including submission receipt and at the beginning of the regulatory review” – from *FDA Study Data Technical Conformance Guide V4.1*

Upon receipt of a submission

- **Technical Rejection Criteria***
 - TS domain must be submitted for all studies
 - Correct STF file-tags must be used
 - DM dataset and define.xml must be submitted
 - No more than one dataset of the same name should be submitted as new

During review of a submission

- CDISC Conformance checks
- [FDA Business Rules](#)
- [FDA Validator Rules](#)

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Educate Yourself on Components of CDISC Submissions

Submission Deliverables	
For Each Submission	• Study Data Standardization Plan • PopPK Package (if needed)
For Each Study	• SDTM Case Report Tabulation • ADaM Case Report Tabulation • Software Programs • Clinical Site Data for CDER's Inspection Planning
For Integrated Data Analyses (ISS and/or ISE)	• SDTM Case Report Tabulation • ADaM Case Report Tabulation • Software Programs

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Educate Yourself on Components of CDISC Submissions

Study Data Standardization Plan	Document describing the data standardization approach for studies in a submission, PhUSE Template
Software Programs	For FDA, submit software programs used: ○ To create ADaM datasets ○ To generate tables and figures for primary and secondary efficacy analyses ○ To generate prescribing information presented in product labels ○ Submit programs in ASCII format with non-executable file extension (.txt)
Clinical Site Data for CDER's Inspection Planning	FDA has requested that pharmaceutical companies voluntarily submit clinical data organized at site level. The FDA uses this data to plan their site inspections. ○ Listings of clinical data by site (i.e. BIMO listings) ○ A summary level clinical site dataset in a standardized electronic format with a DEFINE file

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Points to Consider for Data Deliverables



Non-CRF Data

- Include all data in CRTs
- Plan format of non-CRF data:
 - SDTM
 - ADaM Other
 - XPT in Misc Folder



ISS/ISE CRTs

- Integrated analyses must have single version of CDISC, controlled terminology, and dictionaries
- Integrate at SDTM or ADaM – that is the question



Regulatory Divergence

- Different agencies have different requirements and preferences (e.g. FDA & PMDA)
- Need careful planning to use same CRT packages for both FDA and PMDA



Test Submissions

- Can submit a sample eCTD for FDA validation
- Will only yield info on compliance to standard FDA checks
- FDA reviewers do not review test submissions

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Include All Tasks in Resource and Timeline Plans

Submission Project Management Plan

Be sure to include:

- Study Data Standardization Plan
- Integration of data: Allow adequate time after reporting of individual studies
- Clinical Site Data for CDER's Inspection Planning
- Preparing SAS programs for delivery
- SDTM and ADaM Reviewers Guides
 - Legacy Data Conversion Plan and Report
- Creating Trial Summary datasets for non-CDISC studies
- Time to incorporate comments from test submissions (if applicable)
- Review of submission documents by someone outside of submission team
- Review of eCTD to ensure correct files loaded

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Seek Agreement with Regulatory Agencies Early

Pre-NDA / Pre-BLA Communication & Agreements

- Different agencies have different requirements & preferences
- Different review teams may have different preferences

Critical to consult with regulatory agencies prior to submissions to confirm exact requirements



For data deliverables, seek agreement on:

- Acceptance of legacy formats for studies that started before December 17, 2016
- Legacy Data Conversion Plan & Report
- ISS/ISE integration at SDTM or ADaM level
- Confirm details of CLINSITE dataset for Clinical Site Data for FDA's Site Inspection Planning
- Confirm which software programs to submit
- Any data standard or eCRT question

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Build in Quality from the Beginning

- Finalize ADaM Metadata Specifications prior to programming ADaM datasets
 - Specs are basis for DEFINE file
- Run Pinnacle 21 checks on SDTM and ADaM datasets prior to release of CSR analyses
- Write Reviewer's Guide instream
- Write clear documentation for reviewers (DEFINE, Reviewer's Guides)
 - Avoid company-specific jargon
 - Ask someone outside your team to review
- Follow Good Programming Practices for programs
 - Comment code during development
 - Write readable code
 - Software programs are a deliverable to regulatory agencies!!
 - [Good Programming Practice Guidance on PhUSE Wiki](#)



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Resources for More Information

PhUSE SDTM/ADaM FAQ Project

Standard Implementation nuances exist across the multiple available versions of SDTM and ADaM and the remit of this project is to establish a framework for the collection, compilation, assessment, responding to, and the publishing of common implementation challenges/nuances. This is a joint project between PhUSE and CDISC.

This project is split into 5 sub-teams:

[SDTM ADaM IG Nuances](#)

[Validation / Conformance Rules](#)

[Data Submissions \(SDTM & ADaM\)](#)

[Legacy SDTM Mapping](#)

[Trial Design Domains](#)

This [link](#) takes you to the main project page

This [link](#) takes you to the questions received and already answered by the project team

This [link](#) take you to the form for submitting a question

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Resources for More Information

FDA CDER eData Team

Send questions to edata@fda.hhs.gov

PhUSE Papers on PMDA Submissions

[Japanese Electronic Study Data Submission in CDISC Formats](#)

By Yuichi Nakajima, Takashi Kitahara, and Ryan Hara

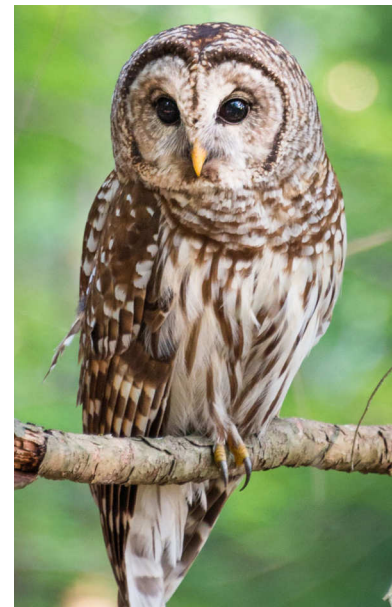
[Drug Development and e-Submission for PMDA Filing](#) by Fan Zhang

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Summary

- Be proactive
- Start planning early
- Educate yourself on components and regulations for CDISC submissions
- Proactively seek early agreement with regulatory agencies
- Create a robust project management plan that includes all tasks
- Build in quality from the beginning





Backup Slides

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Types of Submission Requirements

1. Compliance with Electronic Common Technical Document (eCTD) Standards
2. Compliance with Data Standards
 - CDISC, LOINC, dictionary requirements, etc.
3. Technical Conformance

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CDISC and Data Package Requirements by Country/Region

Country/ Region	CDISC Data Package Requirement
US	• Data Packages required • CDISC required for studies <u>starting</u> after 2016-12-17 • Trial Summary required for all studies (even legacy)
EU	Under review
Japan	• Data packages currently not required • CDISC data packages required for submissions on/after 2020-04-01 • Currently in transitional period
China	• Data packages currently not required, Has endorsed CDISC • Has requested CDISC data packages for some submissions
Canada	• Data packages currently not required, No CDISC requirement yet • Has requested CDISC data packages for some submissions

For all submissions, consult with the regulatory agency prior to submission to confirm requirements

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Educate Yourself on Components of CDISC Submissions

Components	
SDTM Case Report Tabulation	• XPT datasets (Required) • Annotated Case Report Form • DEFINE.xml and style sheets (Required) • DEFINE.pdf (Recommended) • SDTM Reviewers Guide (Required)
ADaM Case Report Tabulation	• XPT datasets (Required) • DEFINE.xml and style sheets (Required) • DEFINE.pdf (Recommended) • ADaM Reviewers Guide (Required) • Analysis Results Metadata (Optional but recommended for key analyses)

Submission Requirements from Regulatory Agencies



FDA Submission Requirements

Software Programs

- **FDA Study Data Technical Conformance Guide V4.1** states:
4.1.2.10 Sponsors should provide the software programs used to create all ADaM datasets and generate tables and figures associated with primary and secondary efficacy analyses. Furthermore, sponsors should submit software programs used to generate additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information (PI)²⁶ if applicable. The specific software utilized should be specified in the ADRG. 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. Sponsors should submit software programs in ASCII text format; however, executable file extensions should not be used.

- The FDA Study Data Technical Conformance states: “Regardless of the specific versions used for individual studies, pooled analyses of coded terms across multiple studies (e.g., for an integrated summary of safety) should be conducted using a single version of a terminology. This will ensure a consistent and coherent comparison of clinical and scientific concepts across multiple studies.”
- The PMDA Technical Conformance Guide on Electronic Study Data Submissions states “Datasets of integrated analyses of multiple clinical studies should be created using the same version, even if the version used to create the dataset of each clinical study was different.” Thus, both agencies require that integrated data packages be harmonized to a single version of a data standard. CDISC has stated that they will address CDISC standards for integrated data from multiple studies in future releases of the ADaM Implementation Guide.

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Key Differences between FDA and PMDA Submission Requirements

Requirement	FDA	PMDA
Studies in Scope of Data Standards Requirements	All studies in submission	Studies which provide the major evidence for efficacy, safety, & dosage/administration i.e. all Phase II & III & some Phase I studies
Data standards versions	Version on the FDA Standards Catalog at the time of study start. Individual studies in submission may have different data standards versions.	Version on the PMDA Standards Catalog at time of submission. Individual studies in submission may have different data standards versions.
Integrated analyses	Prefers that data be integrated at SDTM level, but must provide at least ADaM, with terminology aligned to a single version.	May be asked to provide ADaM (no specific requirements articulated about terminology)
Study Data Standardisation Plan	Initial: expected at IND Updated: at least 1) no later than EOP2 & 2) at pre-NDA, Final: required with NDA	“Form 8” document Draft: well in advance of submission preferred Final: required with NDA Consultation meeting 1 year before submission

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Key Differences between FDA and PMDA Submission Requirements

Requirement	FDA	PMDA
Pinnacle21 checks	Categorizes severity as Error and Warning	PMDA-specific versions of some checks Categorizes severity as Reject, Error, & Warning
SI Unit	Does not require SI units for all parameters	Requires SI units in SDTM. ADaM should include unit used for analysis.
Submission of Software Programs	• Programs to create ADaM datasets, tables, and figures for primary and secondary efficacy analyses • Programs used to create analyses included in the drug label	Requires submission of programs used to create the ADaM datasets and programs used for analyses
Analysis Results Metadata	No stated preference for Analysis Results Metadata.	Strong preference for Analysis Results Metadata
Reviewer's Guides	SDRG file name (clinical data): csdrg.pdf ADRG file name (clinical data): adrg.pdf	SDRG file name: study-data-reviewers-guide.pdf ADRG file name: analysis-data-reviewers-guide.pdf