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Submission of Software Programs to Regulatory Agencies

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Submission of Software Programs to Regulatory Agencies

Introduction

Some things that are harder than they initially appear

- Pinterest Holiday recipes
- Home renovation / repair projects
- Parenting
- Skiing
- Submitting software programs to regulatory agencies



Submission of Software Programs to Regulatory Agencies

Agenda

Goal

Provide information to help programmers and statisticians fulfil the requirements for submission of software programs for data analysis to regulatory agencies

Scope

Software programs for data analysis



THE
POWER
TO KNOW.



Agenda

1. **Regulatory Requirements** for software programs for data analysis
2. **Frequently Asked Questions**
3. **Best Practices** for preparing and submitting software programs

IBM SPSS





Regulatory Requirements

Software Programs for Data Analysis

Submission of Software Programs to Regulatory Agencies

FDA General Guidance for Software Packages

Guidance	Take Home Message
Guidance for Industry E9 Statistical Principles for Clinical Trials (1998)	“Computer software used for data management and statistical analysis should be reliable, and documentation of appropriate testing procedures should be available.”
Guidance for Industry - Computerized Systems Used in Clinical Investigations (2007)	Applies to computerized systems in clinical investigations. Describes requirements such as: • Design of computerized systems • Security safeguards • Audit trails & date/time stamps • Recommended SOPs • Controls for system changes • Training of personnel

Submission of Software Programs to Regulatory Agencies

FDA General Guidance for Software Packages

Guidance	Take Home Message
FDA General Principles of Software Validation; Final Guidance for Industry and FDA Staff (2002)	Describes general validation principles for validation of medical device software, but also applies to computer systems used for electronic records and can be applied to any software.
FDA Position Statement - Statistical Software Clarifying Statement	Clarifies that the FDA “ does not require use of any specific software for statistical analyses ”. “Sponsors are encouraged to consult with FDA review teams and especially with FDA statisticians regarding the choice and suitability of statistical software packages at an early stage in the product development process.”

Submission of Software Programs to Regulatory Agencies

Submission of Software Programs to FDA

FDA Study Data Technical Conformance Guide

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.cdsc@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)

FDA Specifications for File Format Types Using eCTD Specifications

Specifications for File Format Types Using eCTD Specifications

This document provides specifications for submitting file format types using eCTD specifications. It is a list of accepted file types and the eCTD locations in which those file types should be provided.

I. General Information

Documents should be provided in PDF searchable format. Images and other document types should be rendered into PDF format and retain searchable text whenever possible. Additional information related to PDF documents is available in the FDA technical specification FDA Portable Document Format (PDF) Specifications.

II. Acceptable File Formats for Use in eCTD

In most cases, files submitted in formats below should also be provided in PDF format for archival purposes, please reference the “Archive Format Copy” column to see if an alternative version of the document should also be provided.

Submission of Software Programs to Regulatory Agencies

FDA Study Data Technical Conformance Guide

4.1.2.10 Software Programs

- ☐ Submit software programs used to:
 - Create ADaM datasets
 - Generate tables and figures for primary and secondary efficacy analyses
 - To generate prescribing information presented in product labels.
- ☐ Specify specific software utilized in Analysis Data Reviewers Guide (ADRG)
- ☐ Main purpose of requesting programs is to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms and results
- ☐ Submit software programs in ASCII text format
- ☐ Executable file extensions should not be used

Submission of Software Programs to Regulatory Agencies



FDA Study Data Technical Conformance Guide

7.1 eCTD Specifications

Figure 1: Folder Structure for Study Datasets

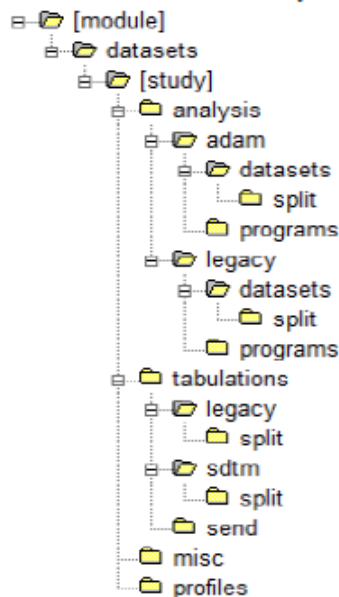


Table 2: Study Dataset and File Folder Structure and Description

Folder Name	Folder Level	Description/Contents
[module]	1	Refers to the eCTD module in which study data are being submitted. Name this folder m4 for nonclinical data and m5 for clinical data. Do not place files at this level.
datasets	2	Resides within the module folder as the top-level folder for study data (nonclinical or clinical) being submitted for the specified module (m4 or m5). Do not place files at this level.
[study]	3	Name this folder with the study identifier or analysis type performed (e.g., study123, iss, ise). Do not place files at this level.
analysis	4	Contains folders for analysis datasets and software programs; arrange in designated level 6 subfolders. Do not place files at this level.
adam	5	Contains subfolders for ADaM datasets and corresponding software programs. Do not place files at this level.
datasets	6	Place ADaM datasets in this subfolder.
split	7	Place any split ADaM datasets in this subfolder.
programs	6	Place software programs for ADaM datasets, tables and figures in this subfolder.

Submission of Software Programs to Regulatory Agencies



FDA Specifications for File Format Types Using eCTD Specifications

II. Acceptable File Formats for Use in eCTD

Modelling and Simulation Reporting					
	.lua	SimCYP PD script	M5		CDER Only
	.sas	SAS Script file	M3-M5		
	.r	R Script file	M3 – M5		CDER Only
	.ctl	NONMEM model control stream	M5		CDER Only

Submission of Software Programs to Regulatory Agencies

Submission of Software Programs to PMDA

PMDA Revision of Technical Conformance Guide on Electronic Study Data Submissions

- Provides information on programs to be submitted and file format of the programs

PMDA Basic Principles on Electronic Submission of Study Data for New Drug Applications

- States requirement that program for the primary endpoint in a confirmatory study should be submitted and “additional programs may be required to be submitted even after an application if further evaluation is judged necessary during the process of review.”

PMDA Notification on Practical Operations of Electronic Study Data Submissions

- Contains requirements for software programs for PK population analysis, including simulations:
 - “submit the programs of models that were important in the model building process, such as base model and final model, and files with the output of major results. If simulation was performed, submission of the program used for the simulation and program procedures is desirable. If it is difficult to submit the program itself, submission of specifications that demonstrate the analysis algorithm would be sufficient.”

Submission of Software Programs to Regulatory Agencies

PMDA Technical Conformance Guide on Electronic Study Data Submissions

4.1.6.1 Programs to be submitted

- ❑ Programs used to create the ADaM datasets and programs used for analyses must be submitted
- ❑ Main purpose of requesting programs is to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms.
- ❑ Not necessary to submit the programs in a format or content that allows the PMDA to directly run the program under its given environment.
- ❑ Programs to be submitted are not limited to specific software or versions
- ❑ Information on the environment in which the programs were created or run (operation system and software used and their versions) must be provided together in the data guide
- ❑ Macro programs should preferably be submitted together. However, if submission of the macro program is difficult or submission of the program itself is difficult because the creation of the dataset or program was outsourced, the submission of specifications that show the analysis algorithm would be sufficient.

Submission of Software Programs to Regulatory Agencies

PMDA Technical Conformance Guide on Electronic Study Data Submissions

3.5 Folder structure

- ❑ Specifies the location in the eCTD folder structure for storing programs

4.1.6.2 File format of the programs

- ❑ File name should include the extension attached by the analysis program

4.2.3 Specific content of programs to be submitted

- ❑ Provides information on submission of programs for pharmacokinetic analyses and for PK population analyses



Frequently Asked Questions

Submission of Software Programs to Regulatory Agencies

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

Examples of FDA Technical Conformance Requirements

Can sponsors submit SAS programs with .sas extensions?

FDA: Recommend changing .sas to .txt, but .sas should pass eCTD checks

- Sources:
 - Study Data Technical Conformance Guide
 - Specifications for File Format Types Using eCTD Specifications
 - Communications with CDER eDATA Team
- Confirm with FDA review team for your submission

PMDA: Submit SAS pgms with .sas extension

- Source:
 - PMDA Technical Conformance Guide on Electronic Study Data Submissions

Submission of Software Programs to Regulatory Agencies

Frequently Asked Questions

Are sponsors required to submit executable programs?

What does “executable” mean?

- **Definition:** Software programs that can execute on the FDA’s or PMDA’s computer systems without any modification

Challenges

- Software programs written to execute on sponsor or CRO system
- Challenging to execute programs on a different computer system
 - LIBNAME statements expect a specific directory structure
 - Input datasets expected in specific folders
 - Programs may need to be executed in a specific order to execute correctly
 - Some SAS statements may function differently in different environments

Submission of Software Programs to Regulatory Agencies

Frequently Asked Questions

Are sponsors required to submit executable programs? (continued)

Both FDA and PMDA are clear that they do not expect sponsors to provide programs that will execute on their systems without modification.

- Sources:
 - FDA Study Data Technical Conformance Guide
 - Communications from CDER eData Team
 - PMDA Technical Conformance Guide on Electronic Study Data Submissions

Submission of Software Programs to Regulatory Agencies

Frequently Asked Questions

Are sponsors required to submit executable programs? (continued)

Caveat: Some FDA review teams have requested executable programs in the past

To provide executable programs:

- Be aware that providing executable programs will take much more effort and time
- Recommend writing a Program Guide giving very detailed instructions on how to set up programming environment on the FDA's computer system
 - How to create the directory structure the programs expect
 - Specify which XPT files must be converted to SAS datasets and then loaded into expected folders
 - Correct order for executing the programs
 - Instructions for modifying any statements that will execute differently on different systems, E.g. PC-SAS versus Linux SAS

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

Frequently Asked Questions

Should sponsors submit standard macros?

FDA: No specific requirements

- Use judgement – submit macros that will help FDA understand analyses
- ADaM macros helpful
- Utility macros may not be helpful

PMDA: Prefers that macros are submitted

- PMDA Technical Conformance Guide on Electronic Study Data Submissions
- “If programs with macros have been used, the macro programs should preferably be submitted together. However, if submission of the macro program is difficult ..., the submission of specifications that show the analysis algorithm would be sufficient.

Submission of Software Programs to Regulatory Agencies

Frequently Asked Questions

What documentation should be included with programs?

- ❑ Programs should have headers and inline comments
 - Follow Good Programming Practices Guidance on PhUSE Wiki
- ❑ Section 7 Submission of Programs in Analysis Data Reviewers Guide (ADRG)
 - Description of programs being submitted
 - Software version and environment
 - Table of Contents (optional but helpful) – could be in Section 7 or in a stand-alone document
 - Example of completed Section 7 of ADRG available on PhUSE Wiki
- ❑ Analysis Results Metadata (ARM)
 - Technically not program documentation, but useful for understanding analyses

Submission of Software Programs to Regulatory Agencies

Frequently Asked Questions

Example of Table of Contents for Software Programs

- Just an example, this format is not required

Type Program	Program	Output	Inputs	Macros Used	Description
ADAM	adsl.sas	ADSL	DM, EX, PD, etc.	%ru_ittpop.sas	Create ADSL from input SDTM datasets
Table	t_aesumm.sas	Table 8.3	ADAE, ADSL	None	Create Summary of AEs
Utility	t_addperiod.sas			None	This macro will derive ADaM period variables. It will create new variables on the output dataset: • APERIOD / APERIODC when EVENTTYPE=PL (planned, e.g. for laboratory data) • TPERIOD / TPERIODC when EVENTTYPE=SP (spontaneous, e.g. for adverse events)

Submission of Software Programs to Regulatory Agencies

Frequently Asked Questions

Are requirements & process different for non-SAS languages?

- FDA and PMDA do not require any specific software for statistical analyses
 - But sponsors should consult with them to confirm their choice of software
- Regulatory requirements for software programs apply to all languages and software packages
 - e.g. Should convert .r and .py extensions to .txt for submissions to FDA but do not change extensions for PMDA

Submission of Software Programs to Regulatory Agencies

Frequently Asked Questions

R Programs

- Open-source programming language, Often used for graphics and simulations
- Submitting R programs to FDA and PMDA:
 - R programs should be submitted in ASCII text format with “.txt” file extensions to the FDA and with “.R” file extensions to the PMDA.
 - R programs do not need to be directly executable on the FDA or PMDA computer systems.
 - R packages should be provided, if they will help the reviewers understand the analyses.
 - Documentation should be provided for R programs, including Section 7 of ADRG and program comments
 - [Good Programming Practices](#) should be followed when writing R programs.
- Larger question is whether R meets regulatory requirements for validation
 - See “R: Regulatory Compliance and Validation Issues, A Guidance Document for the Use of R in Regulated Clinical Trial Environments by the R Foundation for Statistical Computing



Best Practices

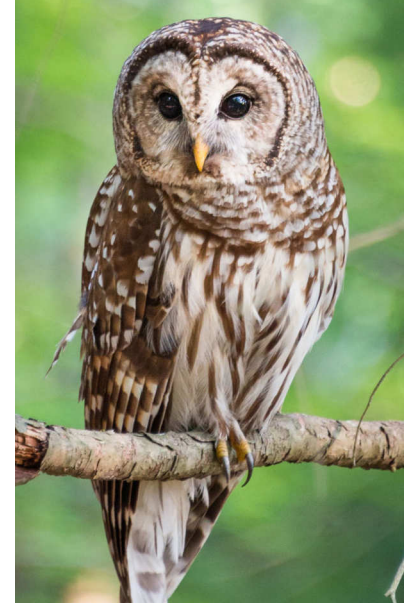
Submission of Software Programs to Regulatory Agencies

Submission of Software Programs to Regulatory Agencies

Educate yourself on Regulatory Requirements

Guidance Documents

- FDA Study Data Technical Conformance Guide
- FDA Specifications for File Format Types Using eCTD Specifications
- PMDA Revision of Technical Conformance Guide on Electronic Study Data Submissions
- PMDA Basic Principles on Electronic Submission of Study Data for New Drug Applications
- PMDA Notification on Practical Operations of Electronic Study Data Submissions



Submission of Software Programs to Regulatory Agencies

Seek Agreement with Regulatory Agencies Early

Pre-NDA / Pre-BLA Communication & Agreements

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



For software programs, seek agreement on:

- Use of non-typical software packages, if applicable
- Confirm in general which software programs to submit
- Clarify whether the review team wants executable programs
- FDA: Confirm file extension for SAS programs

Submission of Software Programs to Regulatory Agencies

Build in Quality from the Beginning



Paul Schuette (OB-IO) and Weiya Zhang (DBIII)

FDA Study Data Technical Conformance Guide Updates for Software Program Submissions

Center for Drug Evaluation and Research, Office of Translational Sciences, Office of Biostatistics

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Recommendations

Observe Good Programming Practices:

1. Write all programs and documentation in grammatically correct English.
2. Include detailed headers at the beginning of each program. (see below).
3. Comment liberally (endeavor to make code self-documenting).
4. Practice version control.
5. Document all dependencies such as macros and packages. Use readme files. Flowcharts can be helpful.
6. Specify language, version and build.
7. Specify Operating System and hardware configuration.
8. Document any configuration file changes, document changes to the BLAS (Basic Linear Algebra System) if appropriate.
9. Use standard naming conventions for variables (CDISC) and follow a style guide (e.g. The tidyverse style guide, <http://style.tidyverse.org/>).
10. Do not submit code that contains errors. Avoid spaghetti code.

Submission of Software Programs to Regulatory Agencies

Build in Quality from the Beginning

Follow Good Programming Practices for programs

- Program headers
- Comment code during development
- Write readable code
- Software programs are a deliverable to regulatory agencies!!
- [Good Programming Practice Guidance on PhUSE Wiki](#)



Submission of Software Programs to Regulatory Agencies

Plan Which Software Programs Will Be Submitted

Programs for Product Label Information

- “Furthermore, sponsors should submit software programs used to generate additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information” – FDA Study Data Technical Conformance Guide
- Drug labels may contain AE summaries, PK analyses, and other analyses dependent on therapeutic area, indication, and drug.
- Make sure you plan to submit these programs

Standard Macros

- Decide which standard macros would add value to a regulatory reviewer and plan to submit these

Submission of Software Programs to Regulatory Agencies

Summary

Submitting Software Programs to Regulatory Agencies

Not as easy as it initially appears, but manageable with proper planning & preparation

