Paper SA03

Making an ADaM Submission – how to work with the inconsistencies between FDA and PMDA requirements

Marianne Caramés, Novo Nordisk A/S, Soeborg, Denmark

ABSTRACT

Several sources with requirements exist both from CDISC, FDA and PMDA for preparing an ADaM submission. Some of the requirements are binding and some are not. Some of them are very specific and detailed and sometimes not aligned.

This presentation/paper will present the details of some of the not-aligned requirements and how we have dealt with them at Novo Nordisk A/S.

INTRODUCTION

This presentation will focus on ADaM requirements and provide some examples of differences. Requirements are issued from:

- CDISC: ADaM model and Implementation Guide (IG)
- FDA: Technical Conformance Guide (TCG), rejection criteria
- PMDA: TCG, validation checks, FAQ

Requirements are updated frequently, so sponsors need to be on top of changes and differences between versions.

ECTD BACKBONE AND STORAGE OF DATASETS

Familiarity with the eCTD backbone structure is essential for knowing where to place ADaM datasets and documentation for a submission. The CDISC ADaM IG states that all analyses datasets must be submitted in the same folder. If an ADaM compliant ADSL dataset exists, then all datasets must be submitted in the adam folder, otherwise in the legacy folder.

The eCTD backbone structure for FDA and PMDA are very similar, but some differences exist.

Requirement	FDA	PMDA
Location of split datasets	Split subfolder	No requirements about splitting or location, but states that datasets larger than 5GB must be discussed at an e-data consultation
Additional folders in structure	None	adam_j: can be used for storing the Japanese datasets that corresponds to the ADaM datasets • cp: can be used for clinical pharmacology datasets in a non-CDISC format
misc folder	Folder to contain non-SDTM datasets used in the ADaM creation, e.g. look-up tables, metadata datasets	Same as FDA, but the misc folder can be used for interim analyses and input to imputation of missing data

Novo Nordisk A/S uses the available folders except for the adam_j folder as we are not submitting in Japanese. Some Novo Nordisk submissions have supplied the metadata used for creating the ADaM datasets to provide full transparency for the agency reviewer.

WHAT IS INCLUDED IN THE E-SUBMISSION?
The requirements from the two agencies are similar for many of the deliverables.

Deliverable	FDA requirement	PMDA requirement
Datasets as ixpt files	Yes	Yes
Programs and macros for generation of ADaM and output	Yes	Yes
Analysis Data Reviewer's Guide	Yes, named adrg.pdf	Yes, filename of ADRG is preferably analysis-data-reviewers-guide.pdf, but PMDA has loosened up the naming requirement
Stylesheet for define.xml	Yes, define-2-0-0.xsl	Yes, both define-1-0-0.xsl and define-2-0-0.xsl are supported
Define file	Yes, v2.0 as part of xml; if intermediate datasets are submitted, they must be included in the define file	Yes, both v1.0 and v2.0 are supported
Analysis Results Metadata (ARM)	No, not required yet	Yes, for main results of efficacy and safety that provides rationales for setting of the dosage and administration

Novo Nordisk A/S follows the naming convention defined by FDA and submits define.xml v.2.0 including ARM data for key analyses.

SOFTWARE PROGRAMS
The requirements for submitted software programs also differ slightly between the two agencies.

Requirement	FDA	PMDA
Programs and macros for creation of ADaM datasets	Yes	Yes
Programs and macros for creation of intermediate datasets	Yes	No
Programs and macros for creation of output	Yes, for primary and key secondary endpoints	Yes, for analyses performed to obtain the important results on efficacy and safety and clinical study results that provide rationales for setting the dosage and administration • primary efficacy analyses • secondary efficacy analyses • primary safety analyses • basic analyses of AEs • analyses to investigate the effect of major factors on efficacy and safety
Programs used for Prescriptive Information	Yes	No
Where to submit programs	Legacy trials: under legacy/programs CDISC trials: under adam/programs	Requirement applies only to CDISC trials: under adam/programs
File types to submit	ASCII text format without executable file extension. .sas is fine	ASCII text format without executable file extension. .sas is fine

Requirement	FDA	PMDA
If the programs cannot be submitted	Sponsors must communicate to the FDA and show the analysis algorithms instead	Sponsors must show analysis algorithms for all datasets and output

Novo Nordisk A/S submits the programs and macros for creation of ADaM datasets and output of primary and important secondary endpoints. Initially, we submitted the programs as .txt for FDA and .sas for PMDA, but recent submissions for FDA sent .sas files.

DATASETS AND VARIABLES

Requirement	FDA	PMDA
Datasets as SAS Transport files in V5 format	Yes	Yes
Size of datasets	• > 5 GB, legacy and ADaM datasets must be split • The split datasets should be placed in split folder • Both split and non-split datasets must be submitted • define.xml links to the non-split datasets	• > 5 GB, the agency must be consulted • No requirement to split datasets
Names of datasets	• ASCII text • Max 8 characters • Only lowercase letters and numbers • Must start with a letter	• ASCII alphanumeric text codes and '_' (underscore)
Labels for datasets	• ASCII text codes and punctuation characters • Max 40 characters • Avoid: o unbalanced apostrophe o unbalanced single and double quotations marks o unbalanced parentheses/braces/brackets	• No requirements
Names of variables	• ASCII text • No symbols or special characters • Max 8 characters • Only uppercase letters and numbers • Must start with a letter	• ASCII alphanumeric text codes and '_' (underscore)
Labels for variables	• Same as for names of datasets	• No requirements
Length of text variables	• Must be set to maximum length for each variable	• No requirements

Novo Nordisk A/S splits the datasets > 5 GB for both FDA and PMDA and submit them in the split subfolder.

We have been struggling with file naming, since our file names often include underscores – specially the names of SAS programs and macros. In our experience underscores caused problems when submitting via the PMDA Gateway, even though PMDA allows underscores.

DATA CONFORMANCE AND P21

Requirements	FDA	PMDA
Validation rules	• CDISC rules • FDA eCTD Technical Rejections Criteria • FDA Business and Validator rules (SDTM and SEND)	• P21 SDTM, ADaM and define.xml
Technical Rejection Criteria	• Technical rejection criteria (for SDTM and ADaM). The following must be submitted: o TS domain with 'Study Start Date' o DM domain, o ADSL dataset o define.xml • If technical rejection criteria are met, the submission will be rejected	• No requirements
Severity and handling of P21 checks	• Error: try to resolve. If not possible to resolve, provide information about non-conformance in RG • Warning: if violated, provide information about non-conformance in RG • Note: for information	• Reject: if violated, the review will be suspended until corrections have been made • Error: if violated without any prior explanations, the review will be suspended until corrections have been made • Warning: if violated, an explanation is not necessarily required
P21 Enterprise or Community version	• No requirements	• No requirements, but the PSG states that PMDA checks the conformance of the data using the P21 Enterprise

At Novo Nordisk A/S we run all FDA and PMDA required validation checks during study conduct. We use the P21 Community version for datasets and the P21 GUI version for checking define.xml.

SUMMARY

The tables above summarise the different requirements and expectations from FDA and PMDA regarding ADaM datasets and deliverables. Novo Nordisk aims to adhere to the strictest requirements among the sets and at the same time make a common submission package for both agencies.

A suggested ranking of the different sources of requirements, could be:

- CDISC model and IG
- FDA and PMDA binding requirements
- FDA and PMDA non-binding requirements

The PMDA will often expect the sponsors to comply with the non-binding requirements too.

In the past year Novo Nordisk A/S has communicated some of the foreseen difficulties with contradicting requirements at conferences globally. We're pleased that the most recent versions of the regulatory guidelines indicate, that the agencies are listening.

REFERENCES

FDA: Study Data Standards Resources
https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

PMDA: Office of Advanced Evaluation with Electronic Data
https://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Marianne Caramés
Novo Nordisk A/S
Vandtaarnsvej 114
DK-2860 Soeborg
Work Phone: +45 30791211
Email: maca@novonordisk.com
Web: www.novonordisk.com