

SA03: ADaM Submission - How to Work with the Inconsistencies Between the FDA and PMDA requirements

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- Marianne has over 20 years experience in the industry.
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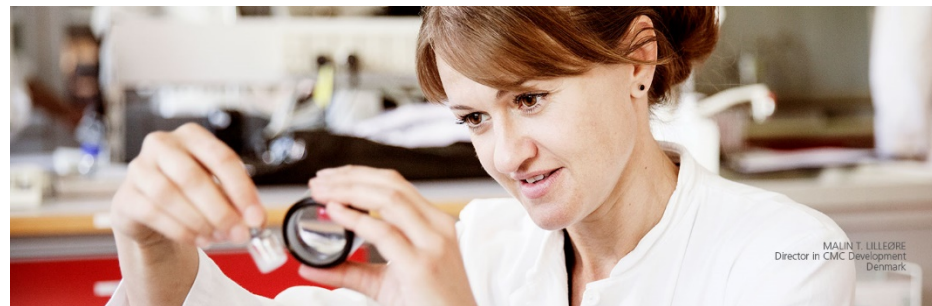
ADaM Submission – How to Work with the Inconsistencies Between the FDA and PMDA requirements



By Marianne Carames
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Agenda

- Sources for requirements
- Deliverables of an ADaM submission
- Storage of datasets
- Software programs
- Datasets
- Conformance checks
- Recommendations



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Different sources for requirements for ADAM Submissions

CDISC:

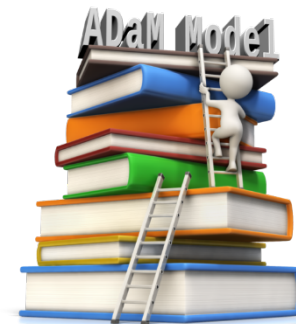
- ADaM v.2.1
- ADaMIG v.1.1
- Analysis Results Metadata Specification v1.0 for Define-XML v2.0

FDA:

- Data Standards Catalogue v.6.1 (09-Sep-2019)
- Study Data Technical Conformance Guide v. 4.4 (Oct-2019)
- Technical Rejection Criteria for Study Data (Revised 22-Jan-2019)

PMDA:

- Data Standards Catalogue (03-Mar-2017)
- Revision of Technical Conformance Guide on Electronic Study Data Submissions (published on 24-Jan-2019)
- Study Data Validation Rules (18-Nov-2015)
- FAQs on Electronic Study Data Submission (Excerpt) (Apr-2019)



What is included in the ADaM submission?

FDA requires:

- xpt files¹
- Programs and macros¹
- define.xml v2.0 and/or pdf files¹
- Style sheet (define-2-0-0.xsl)¹
- ADRG (filename: adrg.pdf) ¹
- ARM data are not required

PMDA requires:

- Basically the same as FDA
- Both define.xml v1.0 and v2.0 are accepted²
- Requirement for filename for ADRG softened **as long as the contents is identifiable**³
- ARM is required to support **main results of efficacy and safety that provide rationales for setting of the dosage and administration**³

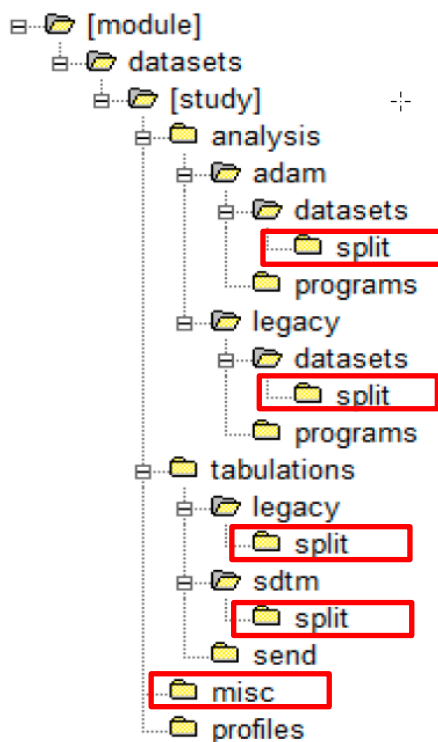
1: FDA Study Data Technical Conformance Guide

2: PMDA Data Standards Catalogue

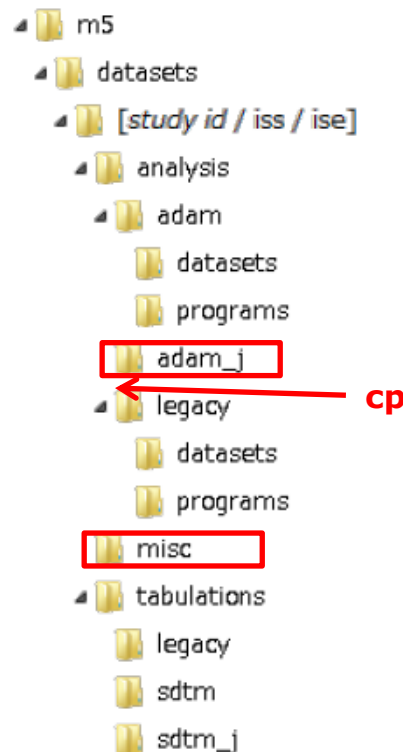
3: PMDA Revision of Technical Conformance Guide on Electronic Study Data Submissions

eCTD backbone

FDA



PMDA



Storage of datasets

CDISC ADaMIG v1.1:

Analysis Datasets within the eCTD Folder Structure

The specification for organizing datasets and their associated files in folders within a submission is summarized in the following figure, as noted in the FDA TCG v2.3. For ease of use with the define file and in the eCTD (electronic Common Technical Document) folder structure, all analysis datasets should be kept in one folder. If a set of analysis datasets includes an ADaM-compliant ADSL dataset (as required for a CDISC-conformant submission), then the whole set of analysis datasets should be placed into the **adam** folder. If not, the whole set of analysis datasets should be placed into the **legacy** folder.

Software programs

FDA requires:

- Programs and macros to create:
 - ADaM datasets
 - Intermediate datasets
 - Output (tables/figures) for **primary and key secondary endpoints**¹

PMDA requires:

- Programs and macros to create:
 - ADaM datasets
 - Analyses performed to obtain the **important results on efficacy and safety and clinical study results that provide rationales for setting the dosage and administration**²
 - 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

1: FDA Study Data Technical Conformance Guide

2: PMDA Revision of Technical Conformance Guide on Electronic Study Data Submissions

Software programs

FDA requires:

- Additional programs: programs used for additional information included in section 14 in CLINICAL STUDIES of the **Prescribing Information**¹
- Location: submitted as **legacy/programs** or **adam/programs**
- Filetype: **.sas** files^{1,2}

PMDA requires:

- Additional programs: **pooled drug related AE summary tables for the medical package insert** to be prepared for all indication of the same compound
- Location: submitted as **legacy/programs** or **adam/programs**
- Filetype: **.sas** files³

1: FDA Study Data Technical Conformance Guide

2: FDA Data Standards Catalogue

3: PMDA Revision of Technical Conformance Guide on Electronic Study Data Submissions

Datasets

FDA requires:

- Datasets submitted as **SAS Transport files in V5 format**¹
- Dataset names¹:
 - **Max 8 characters**
 - Only contain **lowercase letters and numbers**
 - **Start with a letter**
 - **'_'** (underscore) is permitted for legacy studies

PMDA requires:

- Datasets submitted as **SAS Transport files in V5 format**²
- Dataset names²:
 - **Max 32 characters**
 - Only contain **lowercase letters and numbers**
 - **'_'** (underscore) and hyphen **'-'** is permitted

Notice the PMDA Gateway throws errors for xpt files with hyphens

1: FDA Study Data Technical Conformance Guide

2: PMDA Revision of Technical Conformance Guide on Electronic Study Data Submissions

Dataset size

FDA requires:

- Dataset **> 5 GB to be split** in a split folder¹
- Both split datasets and non-split datasets must be submitted¹
- The define.xml must link to the non-split datasets (can be used both for legacy and ADaM datasets)¹

PMDA requires:

- **to be consulted** if sponsors have datasets ≥ 5 GB²
- No requirement to split datasets



1: FDA Study Data Technical Conformance Guide

2: PMDA Revision of Technical Conformance Guide on Electronic Study Data Submissions

Conformance checks

FDA requires:

- Checks to apply:
 - CDISC rules
 - FDA eCTD Technical Rejections Criteria
 - FDA Business and Validator rules (SDTM and SEND)
Notice no ADaM checks
- Versions of checks to use:
 - No requirements

PMDA requires:

- Checks to apply:
 - PMDA Validation Rules (SDTM, ADaM and define.xml)
- Versions of checks to use:
 - PMDA uses **Pinnacle 21 Enterprise**
 - If sponsors are using the Pinnacle 21 **Community version**, then **the version must be compatible with the Enterprise version**, meaning that Community version 2.1.3 had to be used when PMDA used Enterprise version 3.0.

Conformance checks – technical rejection criteria

FDA will not accept an electronic submission that does not have study data in compliance with the required standards specified in the FDA Data Standards Catalog.⁴

The standards apply to the following types of submissions to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER):

- New drug applications (NDAs), abbreviated new drug applications (ANDAs), certain biologics license applications (BLAs), and all subsequent submissions to these types of applications, including amendments, supplements, and reports, even if the original submission was filed before the requirements went into effect
- Commercial investigational new drug applications (INDs) (for products that are intended to be distributed commercially)

Deadlines: Sponsors whose studies started after **December 17, 2016**, must use the data standards listed in the FDA Data Standards Catalog for NDAs, BLAs and ANDAs. For Commercial INDs, the requirement applies to studies started after **December 17, 2017**.

FDA requires:

- Technical Rejection Criteria for studies starting after December 17, 2016:
 - **SDTM ts must be included** (also for studies starting before December 17, 2016)
 - Use correct **file tags** for xpt files
 - For each study the following must be included:
 - SDTM: **dm and define.xml**
 - ADaM: **adsl and define.xml**
 - Only 1 dataset with the **same name** must be submitted as new

Conformance checks – severity and actions

FDA requires:

- Conformance checks with severity **'ERROR', 'WARNING' and 'NOTE'**
- Discrepancies between study data and standard/business rules **should be corrected or explained in the Reviewer's Guide**



PMDA requires:

- Conformance checks with severity **'REJECT', 'ERROR' and 'WARNING'**
- **'REJECT': the review will be suspended until corrections have been made**
- **'ERROR': without any prior explanations, the review will be suspended until corrections have been made**
- **'ERRORs' need to be brought to e-data consultations and discussed**

Recommendations – requirements and storage

- If inconsistencies between requirements exist the following ranking can be used:
 - Data model requirements (CDISC model and IG)
 - Binding requirements
 - Non-binding requirements
 - Most strict requirements between FDA and PMDA
 - If in doubt, consult your reviewer(s)
- Storage of datasets:
 - Use available folders
 - Metadata helps the reviewer(s) understand the data/programs and enhance transparency, so they should be submitted in misc folder

Recommendations - deliverables

- Deliverables:
 - **adrg.pdf** can be submitted for both agencies
 - **define.xml v.2.0** can be submitted for both agencies
 - **ARM data for key analyses** can be included for both agencies
 - Programs and macros can be submitted as **.sas files** for both agencies
 - Additional programs should be submitted
 - Prescribing Information (FDA)
 - Pooled drug related AE summary tables for the medical package insert (PMDA)

Recommendations – datasets

- Datasets:
 - FDA has the most strict requirements for dataset names, so they should be followed
 - Dataset names of max 8 characters
 - Avoid underscore and hyphen
 - Datasets can be split and submitted in split folder for FDA. For PMDA you need to contact the agency.



Recommendations – data conformance



- Data conformance:
 - Run **both FDA and PMDA checks** during study conduct
 - Run the **latest checks** except when using the Pinnacle 21 Community version for PMDA – here you need to select the version compatible with the Enterprise checks
 - Remember also to **execute integration checks and checks for define.xml**
 - Always aim of solving the discrepancies to the extend possible
 - Handling of discrepancies:

FDA:

- Technical Rejection Criteria must be corrected
- Explain un-correctable errors in Reviewer's Guide

PMDA:

- REJECT errors must be corrected
- Explain un-correctable errors in Appendix 8 and Reviewer's Guide and discuss at e-data consultations

Acknowledgements

- I want to thank N. Bauer from Boehringer Ingelheim for inspiration from his analysis of 'FDA and PMDA eSubmission Requirements Differences with Focus on Analysis Essentials'
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Thank you for your attention !



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