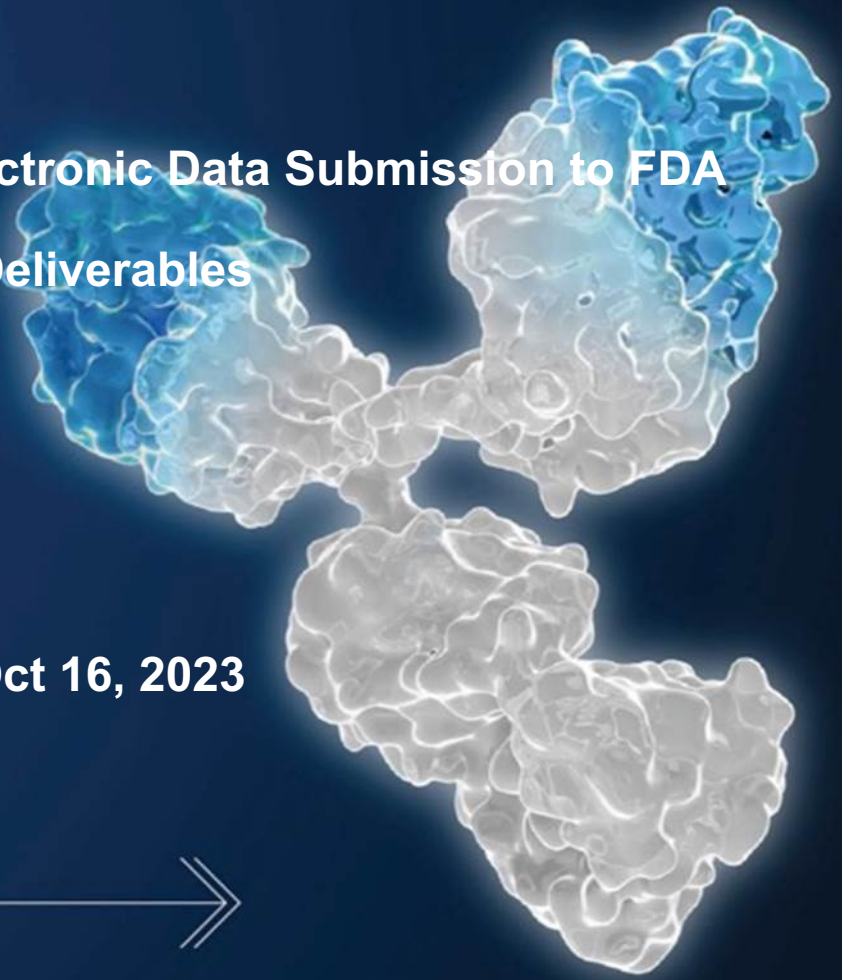
Regulatory Requirements and Electronic Data Submission to FDA and PMDA for Pharmacometrics Deliverables



Hong Yan, Oct 16, 2023

REGENERON

Outlines

- **Pharmacometrics deliverables** support BLA/NDA and subsequent submissions to these types of applications.

- **Overview** of Electronic Submission Regulatory Guidelines and Electronic Data Submission Requirements
  - General
    - FDA
    - PMDA
  - Pharmacometrics deliverables
    - FDA
    - PMDA

- **Experience** in electronic data packages planning/submission and address FDA and PMDA requests for Pharmacometrics deliverables.

Abbreviations, Acronyms

Term	Description
ADaM	Analysis Data Model
ADaMIG	ADaM Implementation Guide
ANDA	Abbreviated New Drug Applications
ARM	Analysis Results Metadata
BLA	Biologics License Applications
CDISC	Clinical Data Interchange Standard Consortium
eCTD	Electronic Common Technical Document
E-R	Exposure Response Analysis
eSUB	Electronic Submission
NCA	Non Compartment Analysis
NDA	New Drug Applications

Term	Description
PBPK	Physiology Based Pharmacokinetic Analysis
PD	Pharmacodynamics
PK	Pharmacokinetics
PopPK	Population Pharmacokinetics
QSP	Quantitative System Physiology Modeling
RG	Reviewer's Guide
SCP	Summary of clinical pharmacology
SDSP	Study Data Standardization Plan
SDTM	Standard Data Tabulation Model
SDTMIG	SDTM Implementation Guide
SDSP	Study Data Standardization Plan

Pharmacometrics Deliverables for NDAs/BLAs/sBLA

Pharmacometrics is the science of using quantitative analysis and modelling and simulation approaches to inform and enhance drug development and regulatory review. It also encompasses quantitative system pharmacology and model-informed drug development (MIDD) approaches. The population pharmacometrics/pharmacodynamics analysis has become a valuable analytical approach in the evaluation and quantify the impact of intrinsic and extrinsic patient factors on the exposure of a drug. In conjunction with supporting exposure-response data, population PK data can be used to identify patient factors that result in a clinically significant change in drug exposure and inform the proper use of drugs. The most important strength of such analyses is its ability to integrate knowledge across the development program and compounds, and biology.

Common applications:

- aid efficient drug development and /or regulatory decisions
- characterize pharmacokinetic and exposure-response profiles
- extrapolate efficacy to special populations, e.g.: pediatrics
- Support drug product labeling for all patients

Pharmacometrics Deliverables at Regeneron

A dedicate pharmacometrics programming group in pharmacometrics department handles all deliverables in close collaboration with pharmacologist (CP), pharmacometrician (QP) and BDM team.

- Clinical pharmacology report for study: SDTM and ADaM datasets for study drug concentration (PC, ADPC); immunogenicity (IS, ADIS); ADNCA for NCA analysis to generate PK parameters; PK parameters (PP, ADPP); concentration-response (ADPCRSP); table/figures/listing for clinical pharmacology analysis.
- Highly complex analysis datasets for:
  - population PK analysis (PopPK)
  - population PK and PD analysis (PopPKPD)
  - Exposure response analysis (exposure metrics and safety, efficacy, biomarkers and other PD)
  - Quantitative System Physiology Modeling (QSP)
- Pooled analysis across studies supporting M 2.7.2 Summary of clinical pharmacology.

FDA Electronic Submission Guidance

- Sponsors whose studies start after Dec. 17, 2016, must submit data in the data formats that the Agency can process, review and archive, as specified FDA Data Standards Catalog. This applies to New Drug Applications and Biologics License Applications, Abbreviated New Drug Applications, and subsequent submissions to these types of applications.
- For clinical and nonclinical studies, sponsors should include a Study Data Standardization Plan (SDSP). SDSP can be discussed in FDA-sponsor meetings (e.g.: preNDA/preBLA, end of phase 2), a example template at https://www.phuse.eu/css-deliverablesExternal Link Disclaimer.
- FDA issued the guidance revision in June 2021 (Guidance for Industry, Providing Regulatory Submissions in Electronic Format — Standardized Study Data (PDF - 131 KB). This binding guidance describes the requirements for an electronic submission of standardized clinical and nonclinical study data under section 745A(a) of the FD&C Act.
- Study Data Technical Conformance Guide in June 2023 Study Data Technical Conformance Guide_v4.9_March 2022 (fda.gov)*.
- The final guidance for Population Pharmacokinetics | FDA in Feb., 2022.

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FDA Study Data Standards, Procedures for Updating Standards

Currently supported study data standards:

- CDISC **Standard for Exchange of Nonclinical Data (SEND)** for nonclinical data
- CDISC **SDTM** for clinical data
- CDISC **ADaM** for analysis of clinical data
- CDISC **Case Report Tabulation Data Definition Specification (Define-XML)** for the metadata that accompany SEND, SDTM, and ADaM datasets
- CDISC controlled terminology, NDF, MedDRA

FDA procedures for updating standards:

- FDA will periodically publish its intent to begin supporting new standards and new versions of current standards
- FDA will give at least one year's notice before a new version of a standard is required
- For entirely new standards, the notice will be at least two years
- FDA is supporting efforts to develop clinical terminology standards for particular therapeutic areas within the SDTM. The SDTM will be updated periodically to include new and revised standards for specific therapeutic areas

FDA Electronic Data Submission Requirements

- Extensible mark-up language (xml): use case is CDISC's define.xml, should not be compressed.
- Portable document format (pdf): use case is aCRF/blank CRF, cSDRG, ADRG etc. with *.pdf file extension.
- File transport format: V5 transport format (XPORT) is the format for all eData submission, one dataset per transport file, note: SAS CPORT processed xport file can not be reviewed.
- Data size: dataset > 5 GB should be split into < 5 GB.
- Variable names, as well as variable and dataset labels should include American Standard Code for Information Interchange (ASCII) text codes only, also the variable value should be restricted to ASCII text codes, UTF-8 is not recommended.
- Ensure that LBSTRESC and controlled terminology extensions in LBTEST do not contain byte values 160-191.
- Do not include unbalanced apostrophe, ‘, “, “(“, “{“, “[“ in variable and dataset labels.
- Adjudication data should be clearly identified to allow reviewer distinguish the adjudicated results from original collected data.
- Updated datasets should “replace” the old datasets.

FDA Electronic Data Submission Requirements continue

- SDTM datasets: all required, expected, and permissible variables that were collected, plus any variables that are used to compute derivations, should be submitted following SDTMIG.
- ADaM datasets should be derived from SDTM datasets with traceability.To ensure traceability, all SDTM variables utilized for variable derivations in ADaM should be included following ADaMIG.
- Data definition file should be submitted in *.xml format, if define.xml is not printable, a printable define.pdf should be provided.
- Common dictionaries (MedDRA or WHODrug) should be used across all clinical studies and throughout the submission for each of the following: adverse events, concomitant medications, procedures, indications, study drug names, and medical history.
- Regardless of the specific versions used for individual studies, pooled analyses (e.g., for ISS) should be conducted using a single version of a dictionary/terminology. The current version should be used at the time that data across studies are pooled.
- When updated datasets are submitted, updated and complete define.xml and RG covering all datasets should be submitted using the “replace” lifecycle operator to update the original file.

FDA Electronic Data Submission Requirements continue

- Data traceability: An important component of a regulatory review is an understanding of the provenance of the data (e.g., traceability of the sponsor's results back to the CRF data). Traceability permits an understanding of the relationships between the analysis results (tables, listings and figures), analysis datasets, tabulation datasets, and source data.
- Legacy study data (a non-standardized format): not supported by FDA. Sponsors should use processes for legacy data conversion that account for traceability.
- Prepare and submit a legacy data conversion plan and report in SDRG:
  - describe the legacy data and the process intended for the conversion.
  - present the results of the conversions, issues encountered and resolved, and outstanding issues.
  - Provide SDRG, an aCRF which maps the legacy data elements, aCRF based on the converted data (i.e., SDTM) when legacy datasets are submitted. The legacy CRF tabulation data should include all versions and all forms used in the study.
  - Record significant data issues, clarifications, explanations of traceability, and adjudications
  - Legacy data (i.e., legacy aCRF, legacy tabulation data, and legacy analysis data) may be needed in addition to the converted data.

FDA eSUB Requirements for Pharmacometrics Deliverables

- FDA released the general expectations for submitting pharmacometrics data and models (population pharmacokinetic, physiologically based pharmacokinetic, exposure-response, and other pharmacometrics analyses for eCTD submissions) in August 2021 (Model | Data Format | FDA).
- Pharmacometrics analysis reports for NDAs/BLAs can be submitted in Module 5.3.3.5.
- All datasets used for model development, validation, and simulations can be submitted as SAS transport (*.xpt) or comma delimited (*.csv) files.
- Data definition file can be provided in a define file (*.xml or *.pdf)
- A RG file can be provided and includes:
  - listing and description of all submitted analysis scripts, software, version, and package dependencies needed to run the analysis scripts
  - specific order for execution
  - flowchart and/or table depicting input and output files for each analysis script
- Model codes or control streams and outputs can be provided for all major model building steps (e.g., base structural model, covariates models, final model, validation model).

FDA eSUB Requirements for Pharmacometrics Deliverables continue

- Files for generating key tables and figures in the report and relevant simulations can be included as ASCII text files. It is not necessary to rename ASCII files ending in different extensions (e.g., .R, .sas, .ctl) to a file with a *.txt extension for submission. In addition, project files (e.g., .rmd, .phxproj) can also be included with a submission.
- if exposure metrics from population PK analyses are included in datasets for E-R analyses, the sponsor should ensure the traceability between the population PK model output and any postprocessing steps involved in the construction of the dataset. This can be accomplished by providing definition files, reviewer guides, and/or codes utilized for dataset assembly.
- All conclusions drawn from the population PK analysis should be reproducible by the Agency with the available codes and data.
- Unique subject identifier (USUBJID) should be kept in the population PK dataset to trace participant to the individual clinical study datasets. This information is vital if data integration is required between the individual-level outputs (e.g., individual, post hoc estimates for clearance or volume of distribution generated from the population PK model) and the efficacy or safety datasets from the individual clinical study.

PMDA Electronic Submission Guidance

- Pharmaceuticals and Medical Devices Agency (PMDA) since October 2016 with 3.5 years transitional period and mandatory from April 2020) Released “Notification on Handling of Submission of Electronic Study Data for New Drug Applications” in June 2022, which consolidates the notification of basic principles (June 2014) and the notification on practical operations (April 2015) 000247154.pdf (pmda.go.jp)
- Question and Answer Guide Regarding “Notification on Handling of Submission of Electronic Study Data for New Drug Applications” (000247155.pdf (pmda.go.jp), Apr 1, 2022)
- FAQs on electronic data submission (000251897.pdf (pmda.go.jp), Apr 3, 2023)
- New Drug Applications Using the Gateway System (000247156.pdf (pmda.go.jp), Apr 1, 2022)
- Technical Conformance guide on electronic data submission (000247157.pdf (pmda.go.jp), Apr 1, 2022)
- Applicants must outline the contents of electronic study data that will be submitted at time of pre-NDA consultation using the “Explanation of Electronic Study Data (Form A)” on the PMDA’s website 000247169.pdf (pmda.go.jp). The explanation on exemption of submission e-data should be attached to the item of pre-NDA consultation. Using "Explanation of Electronic Study Data (Form B)” on PMDA’s website 000247164.pdf (pmda.go.jp)

PMDA Electronic Data Submission Requirements

- PMDA electronic data submission requirements are similar as FDA (slide 18, 19).
- PMDA performs data conformity validation using Pinnacle 21 enterprise 5.1.2 and engine PMDA 2211.0 currently. Data acceptability is informed 5 business days usually from submission of electronic study data
- Data written in Japanese text: Japanese dataset and a dataset comprising letter sets specified by ASCII such as alphanumeric characters should be created and submitted in separate folders, described in RGs.
- ARM is strongly recommended and includes:
  - Figure or table numbers and titles in CSR
  - Purpose and reasons for the analysis
  - Analysis program name, parameter name and code to be used
  - Dataset to be used, variables subject to analysis, selection criteria for the records subject to analysis
  - Corresponding description in the statistical analysis plan, and summary of the analytical methods
  - Extract of the analysis program corresponding to the analysis method
- Resubmit the datasets (correction, new data etc.) should be conformed using the same version data standard as previous submitted, or submit the new sets of data using the new version.

PMDA Electronic Data Submission Requirements continue

- Refer to the PMDA's website (http://www.pmda.go.jp/) for versions of the CDISC standards, controlled terminologies, and dictionaries that are accepted by the PMDA.
- It is acceptable to use different versions within the same application, but the same version must be used within the same clinical study.
- 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.
- The programs for ADaM datasets and analysis must be submitted.
- Consultation with PMDA is required, a series of consultation through the submission preparation:
  - Data to be submitted, whether part of or whole of electronic study data can be exempted, and format
  - PMDA final confirmation on the contention and timing at Pre-NDA meeting, submit the Form A, Form B if needed
- Any changes after consultation, submit the revised Form A an day before submission, PMDA will review the contents of the submitted data based on the final version Form A.
- Final Form A can be submitted separately or included in RG.

PMDA eSUB Requirements for Pharmacometrics Deliverables

PMDA use the “Explanation of electronic study data package on clinical pharmacology” to review the data submitted for Clinical pharmacology analyses.

- The PK or PK/PD analysis datasets should contain doses, actual elapsed time from sampling time to 1st dose, derived values for the analysis such as AUC used as a PK index, the change in a PD marker from baseline, and flags to extract records for analysis.
- All datasets on clinical pharmacology must be submitted regardless of the format of data to be submitted
- The datasets on clinical pharmacological analyses may be acceptable for submission according to standards other than the CDISC standards. Ensure to include the flag on the data that were excluded from the analysis for reasons other than those specified in the analysis plan (e.g., excluded data because they were determined to be outliers at the time of analysis) and reason for it.
- When the datasets used for the PK analysis are in a format other than ADaM and are converted to ADaM datasets for the application, the original datasets used for the analysis can be submitted only if these are useful for traceability between datasets or contents of analysis.

PMDA Electronic Submission Guidance for Pharmacometrics Deliverables

continue

- Analysis type should be STS for standard PK analysis (i.e. NCA or statistical analysis to generate PK , PD parameters), POP for PopPK, PopPKPD datasets, PBPK for PBPK datasets and OTHER for analysis type not mentioned (e.g.: study SDTM, ADaM Datasets for clinical pharmacology)
- Standard PK analysis: SAS XPORT format (*.xpt), ASCII Format Data Files, Phoenix Projects (*.phxproj) and WinNonlin Files (*.pmo, *.pwo), analysis specifications (BLQ, data exclusion etc.), data definition in *.pdf
- ARM is not required for NCA to calculate PK or PD parameters but recommend for statistical evaluation of PK and PD parameters
- POP including simulation: datasets in *.xpt, files of model control stream, model output, script for tables, figures in ASCII text format
- PBPK including simulation:
  - Files that contain model structure used for the analysis, the set values of drug and physiological parameters, analysis results, and sensitivity analyses should be submitted, the file format is optional
  - Clinical study datasets If the datasets were created or modified to be used using a specific software for PBPK model analysis, the files of the created or modified datasets should be submitted in the format for the specific software [Simcyp PE Data Files (xml format), etc.].
  - If the datasets were not created or modified for a specific software for PBPK model analysis, the datasets can be submitted in an optional file format

FDA and PMDA: eSUB Requirements Comparison on Key Elements

	FDA	PMDA
NDA, ANDA, BLA: all data adhere to CDISC standards	Study started after December 17 2016*, FDA data standards catalog	NDA from April 1 2020, irrespective to study start date*, PMDA data standards catalog
Study data standard planning	Study data standardization plan (SDSP)	Form A, From B
SDTM, ADaM data packages, reviewer's guide	FDA Study Data Technical Conformance Guide, June 2023	Technical Conformance guide on electronic data submission, June 2022
File/Data size	5GB per data	10GB per file, 100GB all files
Data submission folder structure for clinical study data	eCTD M5 (4.0), updated datasets should "replace" the old dataset.	eCTD M5 (4.0)
CT, Dictionaries and Unit	CDISC CT, MedDRA for events (current version from Mar 15, 2019), WhoDrug Global for drugs, SNOMED CT for TS.TSVAL when TSPARM=TDIGRP etc., LOINC for LB.LBLOINC	CDISC CT latest version, MedDRA for events (v 8 or later), WHoDrug for drugs, values in SI units
Data exchange standards	CDAR, CBER: SDTM 1.4/IG 3.2 from Aug 17, 2015 (required Mar 15, 2019); SDTM 1.7/IG 3.3 from Mar 15, 2021 (required 4/15/2023); , ADaM 2.1/IG 1.0 ends from Mar 15, 2019 and ADaM 2.1/IG 1.1 from Mar 15, 2019; Define.xml 2.1 from Mar 15, 2023, 2.0 still supported, but 1.0 ended Mar 15, 2018	NDA: SDTM 1.4/IG 3.2, ADaM 2.1/IG 1.0 and define.xml 1.0* and 2.0 since Oct 1, 2016; SDTM 1.7/IG 3.3 and ADaM 2.1/IG 1.1 since Apr 1, 2023

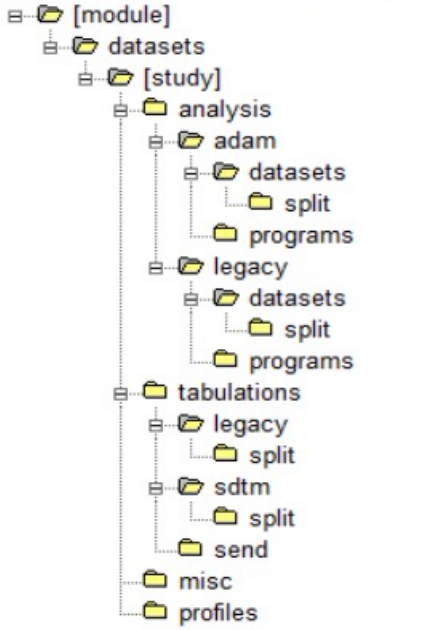
FDA and PMDA: eSUB Requirements Comparison on Key Elements continue

	FDA	PMDA
Dataset name, length, label	Name must start with letter, lower case letters and number, <= 8 in length, "_" only permissible for legacy studies on/before 17 December 2016; label <= 40 in length.	Identical but allow to use "_"
Variable name, length, label	Name must start with letter, use ASCII text codes, upper case letters and number, <= 8 in length, use ASCII text codes, "_" only permissible for legacy studies on/before 17 December 2016, label <= 40 in length.	Identical but allow to use "_", use ASCII alphanumeric text codes
Submission of programs, macros	All programs, macros for ADaM datasets, tables and figures for primary and secondary efficacy in ASCII text format, not expect executable unless specifically requested by agency. All file name should be lower case, contains only letters, numbers or hyphens, no underscore or spaces	All programs, macros for ADaM datasets, tables and figures for primary and secondary efficacy, primary safety, basic analysis of AE, clinical pharmacology analysis. Text format or with software extension files are acceptable, not expect executable. Similar requirement for file name but allow to use "_"
Analysis results metadata (ARM)	optional	Strongly recommend
Datasets and codes support pharmacology analysis, standard PK analysis to calculate PK/PD parameters	same as other SDTM and ADaM datasets, Phoenix projects is not required.	Phoenix projects and WinNonlin files, or codes of statistical analysis are required in addition to PC, ADPC, ADNCA, PP, ADPP
Datasets support ISS/ISE	ADaM data packages are required	Same for ADaM, may request SDTM datasets if these were used for analysis.

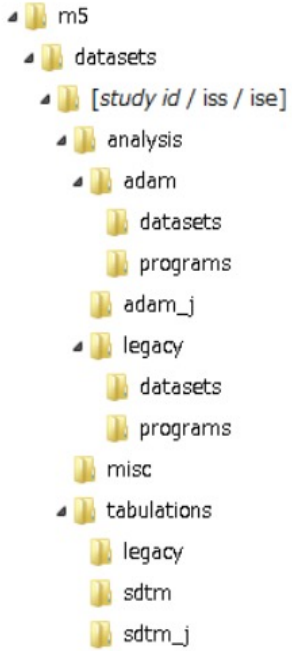
FDA and PMDA: eCTD Study Data and File Structure, Location

FDA: M 5.3

Figure 1: Folder Structure for Study Datasets



PMDA: M 5.3



Our Experiences: Planning Electronic Data Submission

- Proactive planning the electronic data submission is one of key factors for successful filing.
- The plans should integrate SDSP into the life cycle of regulatory IND to NDA/BLA within a development program.
- SDSP should be drafted well before the preBLA/preNDA meeting if not before IND: to facilitate internal discussions and agreement on the data standards approach of ongoing studies, on the rationale for legacy data conversion strategies that support data pooling and on roles and responsibilities.
- Ensure the study data standards are defined as early as possible.
- Communication to agencies early, adjust the plan accordingly.
- Get agency confirmation on the electronic data submission plan before submission.
- CDISC conformity check of SDTM, ADaM dataset should be done using agreed CT, dictionary version before database lock, address all findings.
- Separate data packages should be prepared for FDA, PMDA.
- Ensure SDRG, ADRG in sync with final SDSP.

Our Experiences: Planning Electronic Data Submission

- SDSP for FDA

Study Data Standardization Plan

Contents

4.3 Pooled Studies

Data Pool Identifier	Data Pool (List of Studies)	Pool Status	Pool Description	Exchange Standards	Terminology Standards
ISS	RXXXX-HM-NNNN RXXX-ONC-NNNN	PLANNED	ISS for indications of X and Y	ADaM v2.1/ ADaM IG 1.1 ADaM Define.xml 2.0	MedDRA (Adverse Events, Medical History) Version 25.1 WHO-DD (Medications) WHODrug-Global-B3 202209
2.7.2 Summary of Clinical Pharmacology	RXXXX-HM-NNNN RXXX-ONC-NNNN	PLANNED	Cross study comparison for indications X and Y	ADaM v2.1/ ADaM IG 1.1 ADaM Define.xml 2.0	MedDRA (Adverse Events, Medical History) Version 25.1 WHO-DD (Medications) WHODrug-Global-B3 202209

Our Experiences: Planning Electronic Data Submission

Form A for PMDA

4.3.1. R8888-HV-1214

a. Information about clinical study

Type of clinical studies

- ☐ Phase I studies for oncology drugs
- ☐ Phase I studies conducted on both the Japanese and Non-Japanese subjects (in case of a development utilizing multi-regional clinical studies or bridging studies)
- ☐ QT/QTc studies based on the ICH E14 guideline
- ☐ Phase I and Phase II studies of antibacterial agents and so on, where the results on pharmacokinetics or pharmacokinetics/pharmacodynamics provide major evidence for the dosage and administration
- ☐ Clinical pharmacology studies for children
- ☐ Clinical pharmacology studies for geriatric subjects or subjects with hepatic or renal impairment
- ☐ Drug interactions studies
- ☐ Studies investigating the effect of food
- ☐ Studies investigating the effect of foodBioequivalence studies
- ☐ Studies investigating the comparability with reference biologic products
- ☒ Other (as stated below)

Phase 1 study in healthy volunteers

b. Information about the electronic data

Analysis dataset planned to be submitted in clinical pharmacology area
※For the column "Dataset", please fill with ADaM dataset name if submitted data format is ADaM format, otherwise please leave blank.

Dataset	Contents of the dataset	File format
ADPP		
ADPC		

c. Analysis information

Analysis related to the calculation of pharmacokinetic/pharmacology parameter

Software used in the analysis: Phoenix WinNonlin, Certara LP
Software used in the analysisSoftware name (version): 6.3
Software execution environment (operating system, version): Virtual Windows Server 2016

Submission of analysis specification or corresponding information related to non-compartmental analysis

- ☐ Analysis specification (PDF format)
- ☒ Information corresponding to analysis specification (R8888-HV-1214_IV_CoreOutput and R1500-HV-1214_SC_CoreOutput file format: .txt)
- ☒ Text Output of Phoenix Projects (*.phxproj)
- ☐ Other ( )

Submission of analysis program related to the calculation of parameter other than non-compartmental analysis

- ☐ Submit
  - ☐ Submit with marco code
  - ☐ Not submit with marco code, but submit the specification including the analysis algorithm (The reason:)
  - ☐ Not submit, but submit the specification including the analysis algorithm (The reason:)
  - ☐ Other ( )
- ☒ Not submit

Analysis related to statistical examination used in pharmacokinetic/pharmacology parameter

Software used in the analysis
Software name (version): SAS 9.4
Software execution environment (operating system, version): Red Hat Enterprise Linux, version 3.10.0-514.6.1.el7.x86_64

Submission of analysis program

- ☐ Submit with macro code
- ☐ Not submit with macro code, but submit the specification including the analysis algorithm (The reason:)
- ☐ Not submit, but submit the specification including the analysis algorithm (The reason:)
- ☒ Other (Not submit, no statistical analyses were performed, descriptive summaries were provided only)

d. Information on dataset

Submission of dataset definition file

- ☐ Submit
  - ☐ Define-XML
  - ☐ PDF format (File name :)
  - ☐ Other ( )
- ☒ Submit with analysis report (File name : R8888-HV-1214)

Our Experiences in eData Submission for Pharmacometrics Deliverables to FDA

- Individual study:
  - CDISC's conformity check using Pinnacle 21 engine, address all findings
  - PC, IS, PP and their SUPP domains are included in study SDTM data package,
  - ADPC, ADIS, ADNCA, ADPP, ADPCRSP etc. datasets are included in study ADaM data packages
  - ADRG (.pdf), data definition file (define.xml, define.pdf and style sheet)
  - Programs (ASCII text format) for all ADaM datasets, tables/figures for primary and secondary efficacy, pharmacology analysis upon the request. The program reviewer guide is included in ADRG
  - Data packages are placed in 5.3.5.1 for controlled clinical study and 5.3.5.2 for uncontrolled clinical study
- Pooled ADaM datasets support 2.7.2
  - ADaM dataset packages (*.xpt)
  - data definition file (define.xml, define.pdf and style sheet), ADRG (.pdf), programs (ASCII text format) for all ADaM datasets, for tables/figures upon the request
  - Data packages are placed in M 5.3.5.3
- Population PK, PK/PD, ER, QSP analysis: one data package
  - nm, poppkpd, nm_qsp, er datasets in SAS V5 XPORT format (.xpt)
  - model control files, output files and R scripts (ASCII text format), reviewer's guide or readme (.pdf)
  - Data definition files (define.pdf) using R tool (define.rnw)
  - Data packages are placed in M5.3.3.5

Our Experiences in eData Submission for Pharmacometrics Deliverables to PMDA

Create separate distinct data packages

- Individual study:
  - CDISC's comformity check using Pinnacle 21 latest PMDA engine, address all findings
  - Update the SDTM and ADaM datasets packages for FDA accordingly
  - Programs (ASCII text format) for all ADaM datasets, tables and figures for primary and secondary efficacy, key safety and basic analysis of AE, clinical pharmacology analysis, also Phoenix projects (*.phxproj), WinNonlin files (*.pmo, *.pwo), ARM
  - Data packages are placed in 5.3.5.1 for controlled clinical study and 5.3.5.2 for uncontrolled clinical study
- Pooled ADaM datasets support 2.7.2 SCP
  - ADaM dataset packages (.xpt)
  - data definition file (define.xml, define.pdf and style sheet), ADRG (.pdf), programs (ASCII text format) for all ADaM datasets and tables/figures
  - Data packages are placed in M 5.3.5.3
- Population PK, PK/PD, ER, QSP analysis: one data package
  - nm, poppkpd, nm_qsp, er datasets in SAS V5 XPORT format (.xpt)
  - model control files, output files and R scripts (ASCII text format), reviewer's guide or readme (.pdf)
  - Data definition files (define.pdf) using R tool (define.rnw)
  - Data packages are placed in M5.3.3.5

Consultation with PMDA is very important during the submission planning, preNDA meeting and final consultation

Our Experience: Submission Data Packages

SDTM

- SDTM Datasets in *.xpt
- aCRF (SDTM annotated)
- Define.xml
- Define.pdf
- XSL Stylesheet
- CSDRG in *pdf

ADaM

- ADaM Datasets in *.xpt
- ADaM Programs in ASCII text format
- TF programs in ASCII text format
- Define.xml
- Define.pdf
- XSL Stylesheet
- ADRG in *.pdf
- program-review-guide.pdf **
- ARM (optional for FDA, strongly recommended by PMDA)
- Computation rules.pdf (if any)

Our Experience: Submission Data Packages

PopPK, PopPKPD, E-R submission data package

- nm, nmpkpd, er etc. datasets in *.xpt **
- Model files, outputs in ASCII text format
- R scripts, R packages used for TFs in the PopPK, PopPKPD, E-R reports in ASCII text format
- Data definition in define.pdf
- Reviewer's guide or readme in *.pdf
- Computation rules in *.pdf (if any)

** dataset in *.csv file upon the request

Our Experiences in Addressing FDA IR post Submission

- Each submitted SDTM dataset should have its contents described with complete metadata in the Define.xml file and within the cSDRG as appropriate. When updated datasets (e.g. ‘ae.xpt’, ‘lb.xpt’) are submitted, updated and complete Define-XML and cSDRG covering all datasets need to be submitted using the “replace” life cycle operator to update the original file.
- Each submitted ADaM dataset have its contents described with complete metadata in the Define.xml file and within the ADRG as appropriate. Unlike SDTM, where it is required to always maintain the same SDTM dataset names, ADaM datasets that are resubmitted can have new dataset names that are different from the original submission. two options regarding the Define-XML specifically
  - Each time new information is submitted, a new Define-XML is needed
  - Only the first Define-XML is considered in the submission, so anything further requested is just supplementing what is already there
- FDA accepts additional ADaM datasets without a Define-XML as an exception when stringent timeline.
- Resubmitting subsets of ADaM data, include only updated datasets in Define-XML to avoid broken links, described clearly in response letter.

Acknowledgement

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THANK YOU FOR YOUR ATTENTION

Any Questions?