

Optimizing Development and Regulatory Submission of eSUB Package for Exposure-Response and PK/PD Analysis

Saumil Tripathi

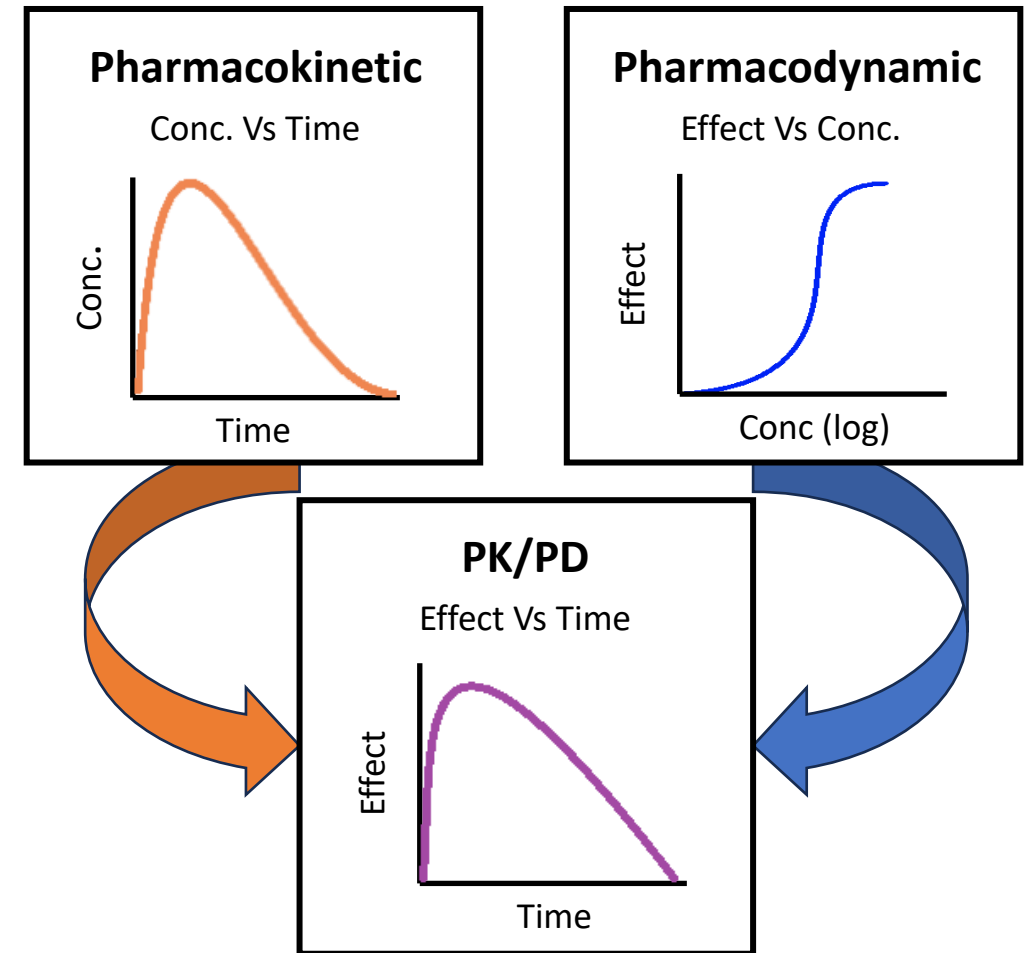
Associate Director – Biostatistics & Programming
Ephicity Lifescience Analytics, India.

Agenda

- Background of PK/PD and E-R Analysis
- Analysis Roadmap
- Role of PKPD Programmer and Pharmacometrician
- Details on ADPPK Dataset
- Regulatory Guidance for PK/PD and E-R Analysis
- Content and Folder Structure for eSUB package
- Q & A

Background of PK/PD Analysis

- **Pharmacokinetic (PK) :**
What Body Does to the Drug
- **Pharmacodynamic (PD) :**
What Drug Does to the Body
- **PK/PD Analysis :**
 - Links the drug exposure to its effects to optimize dosing and therapeutic response.
 - Helps to determine optimal dosing regimens.
 - Improves drug efficacy & minimizes side effects.
 - Enables modeling & simulation to predict drug behavior.
 - Supports regulatory approvals and drug development.



Background of E-R Analysis

- Exposure-Response Analysis defines the relationship between
 - **Exposure (PK) :**
Drug concentration in the body (e.g., C_{max}, AUC).
 - **Response (Clinical Outcome) :**
 - Efficacy → Therapeutic effect, biomarker changes, symptoms improvement.
 - Safety → Adverse events, toxicity levels.
- E-R Modeling uses Statistical & Pharmacometric methods (e.g., NONMEM, Phoenix NLME) to analyze this relationship.

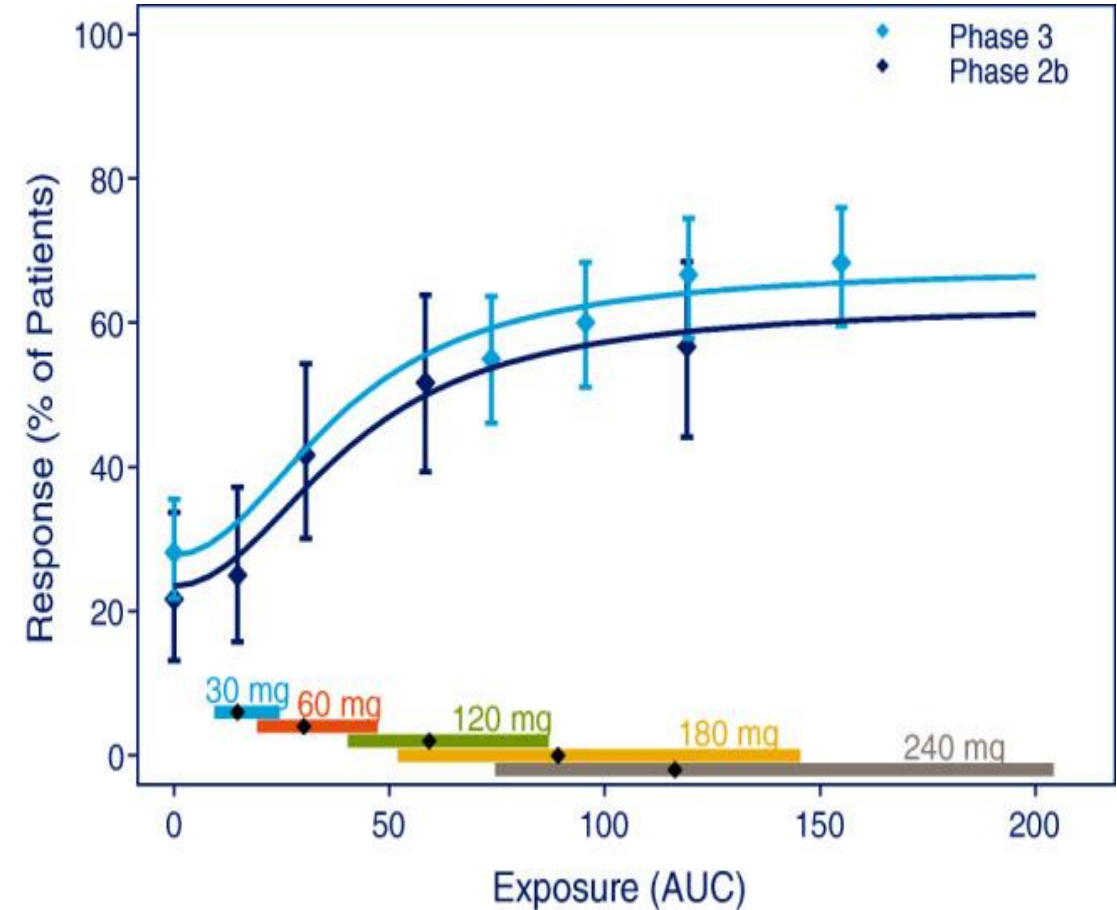
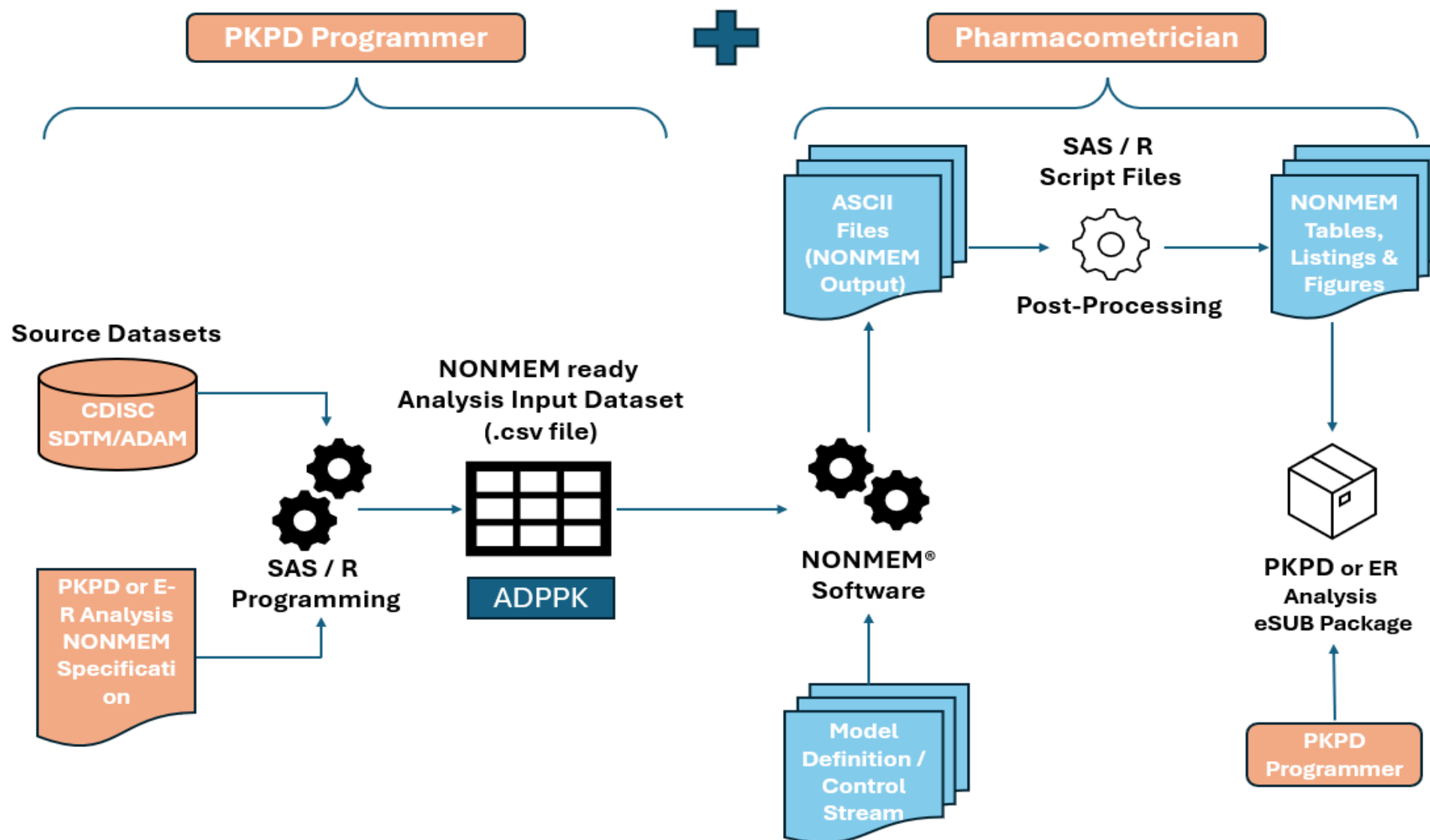


Image Reference : https://www.researchgate.net/figure/E-R-relationship-obtained-from-phase-II-and-phase-III-trials-Data-points-are-mean_fig1_280915064

Analysis Roadmap



Role of PK/PD Programmer

- **Source Data Identification :**
Use CDISC SDTM/ADaM datasets for exposure, PK/PD concentrations, lab findings, and subject-level data
- **Specification Development:**
Pharmacometricians and PKPD programmers collaborate on developing NONMEM input dataset specifications
- **Analysis Dataset Creation:**
PKPD programmers use SAS/R programming to create Analysis input dataset (ADPPK) for NONMEM in alignment with CDISC ADaM PopPK standards.
- **eSUB Contribution:**
After the analysis is done by Pharmacometrician, PKPD programmers contribute in creating the eSUB package for regulatory submission.



Role of Pharmacometrician

- **Data Analysis:** Pharmacometricians analyze ADPPK dataset (.csv) using NONMEM or Phoenix NLME.
- **Output Generation:** NONMEM produces several output files (.lst, .cov, .ext) containing parameter estimates and model results which are saved in ASCII format for regulatory submission.
- **Results Processing:** Model outputs and ADPPK are used to create Tables, Listings, and Figures (TLFs) using SAS/R programming.
- **eSUB Compilation:** Pharmacometrician helps PKPD programmers to assemble datasets, programs, model codes and outputs & report for regulatory submission.

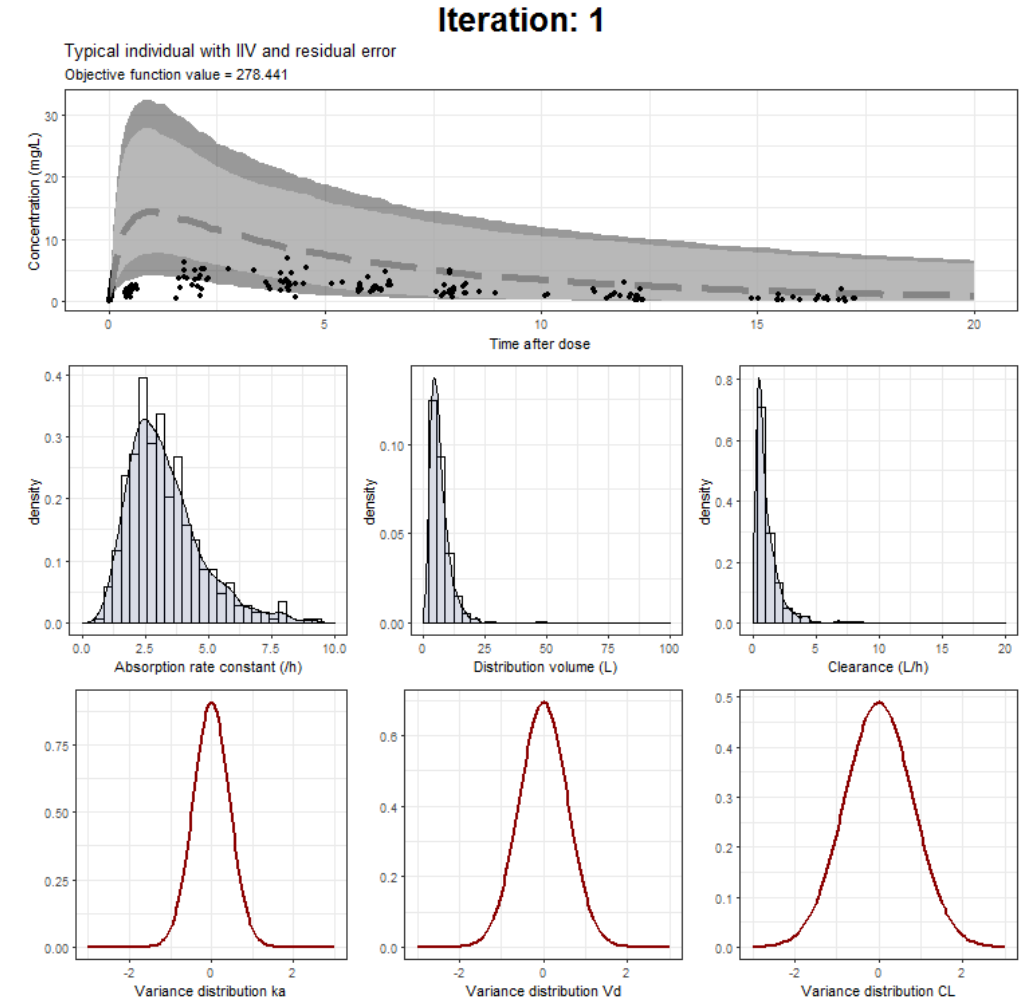


Image Reference : <https://www.pmxsolutions.com/2018/08/06/nonmem-model-fitting-as-a-gif-in-r-with-code/>

Details on ADPPK Dataset

Data Structure Name	Data Structure Description	Class of Dataset	Subclass of Dataset	CDISC Notes
ADPPK	Basic Data Structure Population Pharmacokinetic Analysis	BASIC DATA STRUCTURE	POPULATION PHARMACOKINETIC ANALYSIS	Dataset designed to support PPK. Sourced from SDTM (e.g., PC, DM, EX, LB) and ADaM (e.g., ADSL and ADEX datasets)

Current Challenges in PK/PD or E-R Analysis Dataset Creation

- Organizations using different approaches and source for creating NONMEM analysis input datasets.
 - **Raw eCRF data** with external PK/lab data.
 - **CDISC SDTM/ADaM datasets.**
- **Inconsistencies in variable names and metadata.**
- **Complex data transformations.**
 - Derivations, exclusions, and record flagging.
- **Non-standard dataset structures** can delay regulatory review and decisions.
- **Lack of traceability** makes it harder to track data sources and transformations.

Details on ADPPK Dataset

Advantages of CDISC ADaM ADPPK Dataset

- Standardized data structure from CDISC.
- Traceability, consistency, and regulatory compliance.
- Follows CDISC ADaM Basic Data Structure.
- SDTM/ADaM datasets as Source.
 - SDTM.PC / ADAM.ADPC (PK concentration data).
 - SDTM.EX / ADAM.ADEX (Dosing data)
 - ADAM.ADSL (Demographic & Baseline Characteristic)
- Integrates key variables for modeling tools (NONMEM).
- Includes **subject-level, dosing, and concentration data**
- Derived variables such as Nominal & actual sampling times, dose amounts, and exclusion flags.
- Enhances data integrity and regulatory submissions



Basic Data Structure for ADaM PopPK Implementation Guide

Version 1.0

Prepared by the CDISC ADaM Population Pharmacokinetic Standards Development Team

Notes to Readers

- This is the final Version 1.0 of the Basic Data Structure for ADaM PopPK Implementation Guide.
- This implementation guide corresponds to the Analysis Data Model Implementation Guides (ADaMIG) v1.1 and higher.

Revision History

Date	Version
2023-10-06	1.0 Final

Details on ADPPK Dataset

- **NONMEM** is considered Gold Standard software to perform PKPD or E-R analysis.
- Includes Tool specific ADPPK Variables such as **DV, EVID, CMT, RATE, AMT** etc.
- **Character Variables to be dropped** by PK Modeler while importing datafile.
- **Time variables use suffix – RLT** to represent relative time as suffix – TM will cause errors with common P21 compliance checks.
- Contains Standard BDS variables such as **PARAM, PARAMCD, AVISIT, ATPT, AVAL**.
- Implementation guide to follow for imputing missing data
- Specific variables for identifying exclusion and imputation records
 - **EXCLF, EXCLFCOM, FLGREAS, FLGREASC**
- Included datetime variable for traceability - **UDTCs**

Details on ADPPK Dataset

Sample ADPPK Dataset

USUBJID	TRTA	ADT	ATM	APERIOD	ADY	NFRLT	AFRLT	AMT	DOSE	FORM	COHORT	AGE	SEX	RACE	WTBL	BMIBL	DV	MDV	EVID
10011712	POPPK1712_50_mg_BID	5/3/2023	7:28	1	1	0	0	0	50	TABLET	1	32	1	2	69.8	22.6	0	0	0
10011712	POPPK1712_50_mg_BID	5/3/2023	8:05	1	1	0	0	50	50	TABLET	1	32	1	2	69.8	22.6	-999	1	1
10011712	POPPK1712_50_mg_BID	5/3/2023	8:35	1	1	0.5	0.5	0	50	TABLET	1	32	1	2	69.8	22.6	457	0	0
10011712	POPPK1712_50_mg_BID	5/3/2023	9:05	1	1	1	1	0	50	TABLET	1	32	1	2	69.8	22.6	541	0	0
10011712	POPPK1712_50_mg_BID	5/3/2023	9:35	1	1	1.5	1.5	0	50	TABLET	1	32	1	2	69.8	22.6	1050	0	0
10011712	POPPK1712_50_mg_BID	5/3/2023	10:05	1	1	2	2	0	50	TABLET	1	32	1	2	69.8	22.6	1920	0	0
10011712	POPPK1712_50_mg_BID	5/3/2023	11:05	1	1	3	3	0	50	TABLET	1	32	1	2	69.8	22.6	2390	0	0
10011712	POPPK1712_50_mg_BID	5/3/2023	12:05	1	1	4	4	0	50	TABLET	1	32	1	2	69.8	22.6	1490	0	0
10011712	POPPK1712_50_mg_BID	5/3/2023	14:05	1	1	6	6	0	50	TABLET	1	32	1	2	69.8	22.6	1180	0	0
10011712	POPPK1712_50_mg_BID	5/3/2023	18:05	1	1	10	10	0	50	TABLET	1	32	1	2	69.8	22.6	350	0	0
10011712	POPPK1712_50_mg_BID	5/3/2023	20:00	1	1	12	11.92	0	50	TABLET	1	32	1	2	69.8	22.6	252	0	0
10011712	POPPK1712_50_mg_BID	5/3/2023	20:05	1	1	0	12	50	50	TABLET	1	32	1	2	69.8	22.6	-999	1	1
10011712	POPPK1712_50_mg_BID	5/4/2023	7:26	1	1	24	23.35	0	50	TABLET	1	32	1	2	69.8	22.6	524	0	0
10011712	POPPK1712_50_mg_BID	5/9/2023	7:27	1	7	0	143.37	0	50	TABLET	1	32	1	2	69.8	22.6	696	0	0
10011712	POPPK1712_50_mg_BID	5/9/2023	8:05	1	7	0	144	50	50	TABLET	1	32	1	2	69.8	22.6	-999	1	1
10011712	POPPK1712_50_mg_BID	5/9/2023	8:38	1	7	0.5	144.55	0	50	TABLET	1	32	1	2	69.8	22.6	1170	0	0
10011712	POPPK1712_50_mg_BID	5/9/2023	9:10	1	7	1	145.08	0	50	TABLET	1	32	1	2	69.8	22.6	1430	0	0
10011712	POPPK1712_50_mg_BID	5/9/2023	9:35	1	7	1.5	145.5	0	50	TABLET	1	32	1	2	69.8	22.6	1580	0	0
10011712	POPPK1712_50_mg_BID	5/9/2023	10:05	1	7	2	146	0	50	TABLET	1	32	1	2	69.8	22.6	1470	0	0
10011712	POPPK1712_50_mg_BID	5/9/2023	11:05	1	7	3	147	0	50	TABLET	1	32	1	2	69.8	22.6	1730	0	0
10011712	POPPK1712_50_mg_BID	5/9/2023	12:06	1	7	4	148.02	0	50	TABLET	1	32	1	2	69.8	22.6	2070	0	0
10011712	POPPK1712_50_mg_BID	5/9/2023	14:05	1	7	6	150	0	50	TABLET	1	32	1	2	69.8	22.6	2270	0	0
10011712	POPPK1712_50_mg_BID	5/9/2023	18:05	1	7	10	154	0	50	TABLET	1	32	1	2	69.8	22.6	916	0	0
10011712	POPPK1712_50_mg_BID	5/9/2023	20:00	1	7	12	155.92	0	50	TABLET	1	32	1	2	69.8	22.6	771	0	0

Regulatory Guidance for PK/PD and E-R Analysis

- FDA, EMA and PMDA have issued guidelines to ensure consistency, reliability, and transparency in Population PK and exposure-response (E-R) analysis. These guidelines provide frameworks for study design, data analysis, model validation, and regulatory submission.

Population Pharmacokinetics Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
<https://www.fda.gov/drugs/guidance-compliance/regulatory-information/guidances/drugs>
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
<https://www.fda.gov/vaccines-blood-biologics/guidance-compliance/regulatory-information/biologics/biologics-guidances>

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)

February 2022
Clinical Pharmacology

Guidance for Industry

Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

Additional copies are available from:
Office of Training and Communications
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
<http://www.fda.gov/cder/guidance/index.htm>

or

Office of Communication, Training and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Voice Information: 800-835-4709 or 301-827-1800
<http://www.fda.gov/cber/guidelines.htm>

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)
April 2003

Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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

August 2018
Clinical Pharmacology

FDA Guidance Webpage : <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>

Regulatory Guidance for PK/PD and E-R Analysis

Accelerated Approvals

- Aligning study design, data analysis, and reporting with regulatory guidance increases approval speed and minimizes review cycles and rejection risks.

Standardized & Reproducible Data

- Guidelines ensure consistent data processing, model selection, and validation for reliable conclusions.

Optimized Dose Selection

- Regulatory-compliant PK/PD and E-R analyses help to tailor dosing for special populations (paediatrics, elderly, renal/hepatic impairment).

Advanced Modeling Approaches

- Encourages PBPK modeling, Bayesian methods, and AI to improve model-based drug development (MBDD) and reduce trial burden.

Global Regulatory Alignment

- Streamlines submissions across multiple agencies such as FDA, EMA, and PMDA.

Content for eSUB package

Sr. No.	Name of the File or Document	Description	Format
1	ADAM.ADSL	Subject level analysis dataset	.xpt
2	ADAM.ADPPK	NONMEM ready analysis input dataset used for model development, validation and simulations	.xpt or .csv
3	Define File	Description of each dataset and associated variables, Controlled Terminology, Analysis Derivations and Comments	.xml or .pdf
4	Reviewer's Guide	Listing and Description of all submitted analysis programs, software used with version details, details of all dependencies to run the required analysis, Specific order for execution, Flowchart or table highlighting input/output files for each analysis script and insights of CDISC compliance check report and issues	.pdf
5	Control Stream Output Files	Model codes and output listings can be provided for all major model building steps Base Model Covariates Model Final Model Validation Model	.mod .cov .ext .lst Submitted in ASCII format
6	SAS/R scripts	All scripts used for model evaluation, simulations and creating TLFs.	.sas .R Submitted in ASCII format (.txt)

Content for eSUB package

Model Scripts and SAS/R Programs to be included in PKPD/E-R eSUB package

File Type	Submission File Name
Control Stream (NONMEM Model Input File)	runABC1712-mod.txt
Model Output File (Standard Output)	runABC1712-lst.txt
Parameter Estimates File	runABC1712-ext.txt
Model Covariance Matrix File	runABC1712-cov.txt
Simulation Results File	runABC1712-sim.txt
Graphical Output or Diagnostic Plots	runABC1712-plot.pdf
NONMEM Table Output Files	runABC1712-tab.pdf
NONMEM Data File Program (Input Dataset)	adppk.txt
Tables, Listings and Figures Programs	t-pksum-labcov.txt
	t-pkeff-dose.txt
	g-pkcomp-eff.txt
	g-pkln-dose.txt
	

Content for eSUB package

Sample PKPD Define.xml

POPPK1712 STUDY

- Supplemental Documents
- Standards
- Analysis Results Metadata
- Datasets
- Controlled Terminology
- Methods

Expand all VLM

Collapse all VLM

Date/Time of Define-XML document generation: 2024-11-21T16:24:00
Define-XML version: 2.1.8
Define-XML Context: Submission
Stylesheet version: 2019-02-11

Study Name	POPPK1712
Study Description	Phase 2 study to evaluate Safety and Efficacy of Drug ABC1712 in subjects with COPD
Protocol Name	POPPK1712
Metadata Name	Study POPPK1712, Data Definitions
Metadata Description	Study POPPK1712, Metadata Description

Datasets

Dataset	Description	Class - SubClass	Structure	Purpose	Keys	Documentation	Location
ADSL	Subject-Level Analysis	SUBJECT LEVEL ANALYSIS DATASET	one record per subject	Analysis	STUDYID, USUBJID	Screen Failures are excluded since they are not needed for this study analysis. See referenced dataset creation program and ADRG adsl.sas Analysis Data Reviewer's Guide [Section 5.2.1]	adsl.xpt
ADPPK	Population PK Analysis Dataset	BASIC DATA STRUCTURE POPULATION PHARMACOKINETIC ANALYSIS	One record per subject per parameter (analyte) per analysis timepoint per event (dosing or observation)	Analysis	USUBJID, AFRLT (Actual Rel Time from First Dose), DVID, EVID (event ID)	See referenced dataset creation program and ADRG adppk.sas Analysis Data Reviewer's Guide [Section 5.2.2]	adppk.xpt

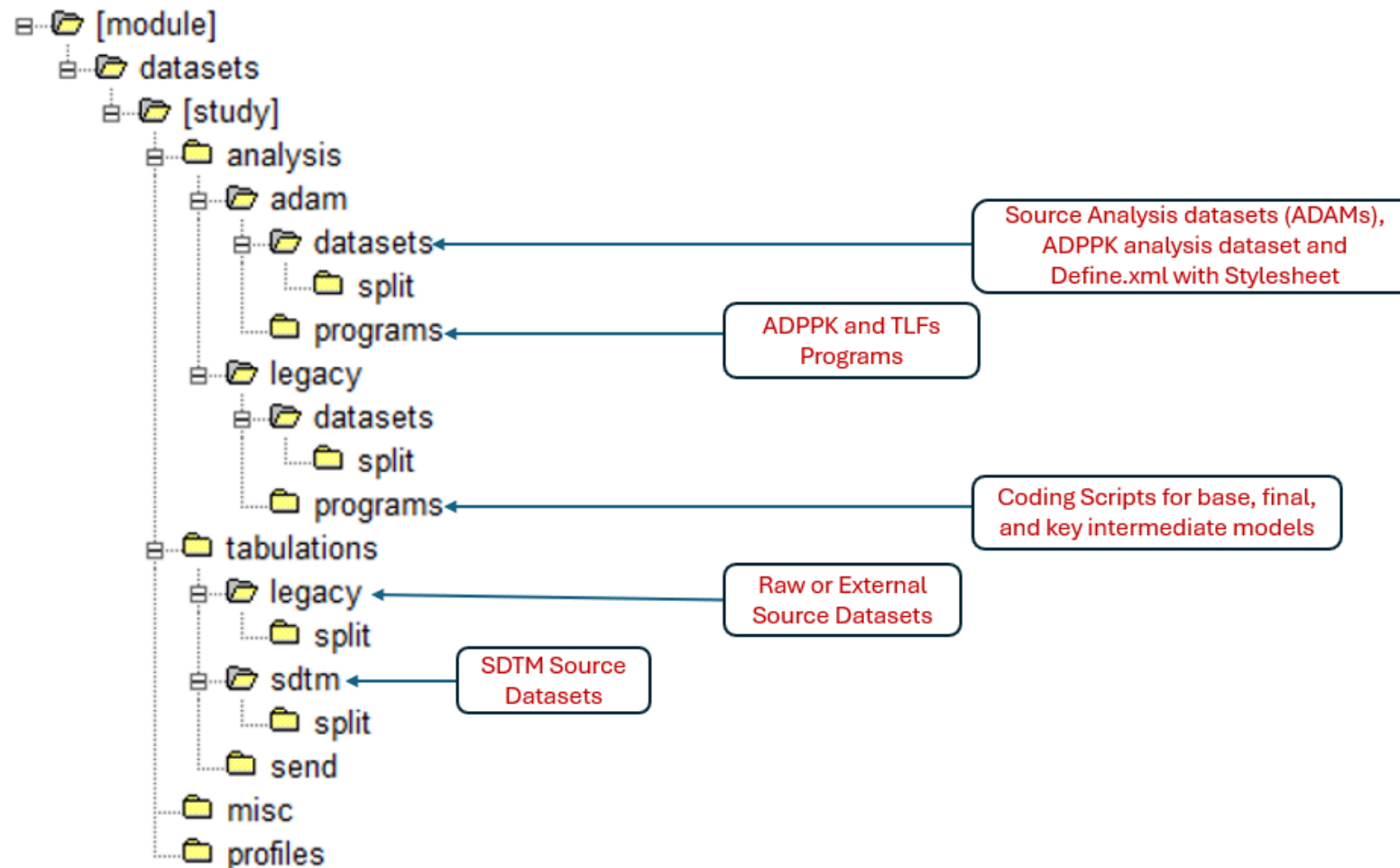
Content for eSUB package

Vital Components of ADRG



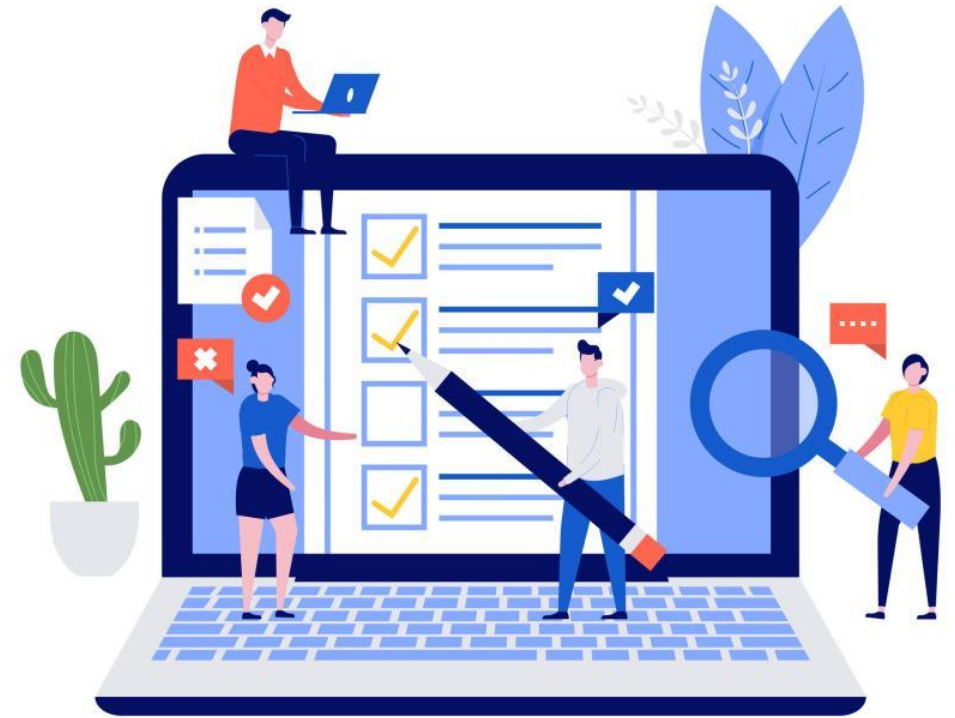
Content for eSUB package

eCTD Module 5(M5) Folder Structure



Conclusion

- Efficient regulatory submissions of the eSUB package for PK/PD and E-R analysis is crucial for,
 - Ensuring compliance and Data traceability.
 - Streamlined regulatory review.
 - Reducing the risk of delays & additional requests.
 - Expediting Drug Development Process
 - Bringing New therapies to patients faster.
- Future advancements fostering innovation in following areas will enhance regulatory submissions for Pharmacometric analysis.
 - Model-informed drug development (MIDD)
 - Real-world data integration
 - AI-driven automation





| Namaste |

Thank You !

Any Questions ?

