Paper SA12

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

Saumilkumar Tripathi, Ephicacy Lifescience Analytics, India

ABSTRACT

Exposure-Response (E-R) and PK/PD models and simulations are powerful tools utilized throughout the drug lifecycle, from early research and development to post-marketing surveillance. These models play an important role for dose optimization, assessing the relationship between drug exposure and therapeutic response, as well as adverse events. E-R and PKPD analysis are integral to regulatory submissions, providing critical evidence that supports the safety, efficacy and effects of various population and co-variates on drug. Creating electronic submission(eSUB) package for this analysis is slightly different from the analysis data package we prepare for CSR submission and requires meticulous planning, robust data management, strict adherence to regulatory standards and efficient collaboration between programmer and pharmacometrician. This paper outlines the regulatory requirements for eSUB package of E-R and PKPD analysis highlighting required CDISC ADaM compliant analysis datasets, documents such as define.xml and reviewer's guide, model files and folder structure to facilitate smooth regulatory review process.

INTRODUCTION

Pharmacokinetics (PK) examines how the body absorbs, distributes, metabolizes, and eliminates drugs or substances. PK is often described as what the body does to a drug. In contrast, pharmacodynamics (PD) focuses on the drug's effects on the body, including its mechanism of action, therapeutic impact, and the relationship between drug concentration at the target site and its effect. PD is commonly referred to as what a drug does to the body.

The connection between PK and PD is analyzed through PK/PD studies, which link drug concentration to its effects. Integrating pharmacokinetic and pharmacodynamic data helps predict how a drug moves through the body over time and its impact at the target site, forming the foundation for dose optimization in drug development.PK/PD modeling allows for the simulation of drug distribution across different body compartments over time. These models help estimate drug concentrations at various sites under different dosing regimens and predict the drug's overall effect.

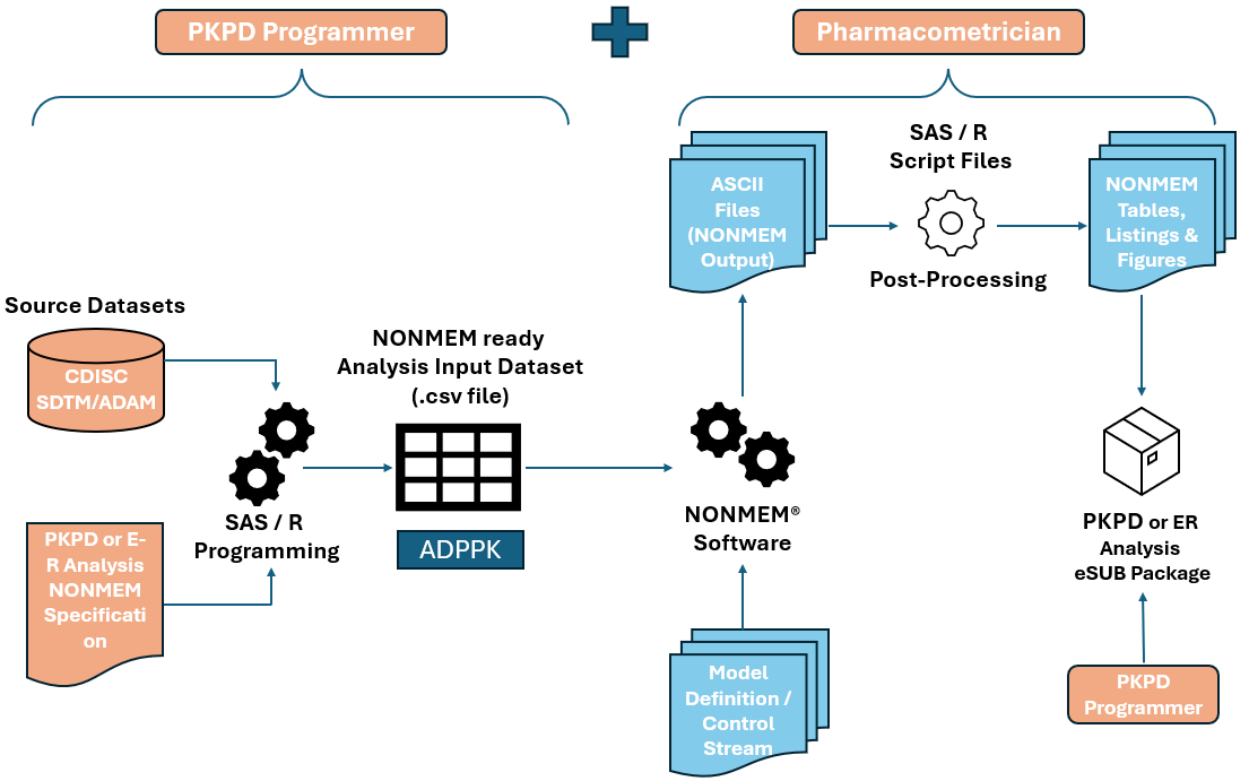
Exposure-Response (E-R) analysis is a quantitative framework utilized in clinical research to characterize the relationship between drug exposure, typically measured as plasma concentration, and its corresponding pharmacodynamic or clinical effects. This analysis is fundamental in determining the optimal dosing regimen that maximizes therapeutic efficacy while minimizing toxicity. E-R analysis plays a critical role in evaluating the safety and effectiveness of a drug, as a comprehensive understanding of the relationship between benefits and adverse effects at specific exposure levels is essential for regulatory approval and clinical decision-making. This approach aids in optimizing dose selection by identifying the exposure range associated with the desired therapeutic outcome while mitigating the risk of adverse reactions. Additionally, E-R analysis is instrumental in the design of Phase 2 and Phase 3 clinical trials by informing dose selection strategies and refining study protocols. Furthermore, it enables the assessment of inter subject variability by evaluating the effect of covariates such as age, body weight, genetics, and disease states on drug response.

In pharmacokinetic-pharmacodynamic (PKPD) and exposure-response (E-R) analyses, PKPD programmers play a critical role in data extraction, processing, and preparation. They curate data from various sources, including CDISC SDTM/ADaM datasets or raw clinical trial data, using programming platforms such as SAS, R, or Python. Their primary responsibility is to generate structured input datasets suitable for PKPD or E-R analysis performed by pharmacometricians. Additionally, the programming team contributes to regulatory submissions by generating standardized PKPD outputs, Define.xml files, and Reviewer's Guides.

Once the input dataset is available, pharmacometricians apply nonlinear mixed-effects (NLME) models for population PK/PD modeling and E-R analysis using specialized software such as NONMEM or Phoenix NLME. These tools facilitate population modeling, dose optimization, and clinical trial simulations, enabling data-driven decision-making in drug development. The integration of PK, PD, and clinical outcomes through model-informed drug development (MIDD) enhances the efficiency of dose selection, improves therapeutic strategies, and supports regulatory decision-making, ultimately contributing to the advancement of model-based drug development (MBDD).

Population PK datasets are Crucial components in NDA/BLA submissions. More than 85% of regulatory submissions include Population PK analysis report. This paper discusses the content and regulatory requirements for developing eSUB package of E-R and PKPD analysis and optimizing same with use of CDISC ADaM compliant Population PK analysis datasets (ADPPK) and relevant documents such as define.xml and reviewer's guide.

ROADMAP OF PK/PD or E-R ANALYSIS AND SUBMISSION



Most of the organizations follow different approaches for performing PKPD or E-R analysis and have their own internal standards to follow for preparing NONMEM ready analysis input dataset. The above flowchart highlights the recommended steps right from creating the analysis input dataset to preparing final eSUB package for regulatory submissions. This process also utilizes recently published CDISC standards for creating and submitting Population PK analysis dataset (ADPPK).

There are two important team members, PKPD Programmer and Pharmacometrician who play vital roles in this whole process along with other team members such as clinical data manager and study statistician.

Role of PKPD PROGRAMMER :

1. CDISC SDTM / ADAM datasets to be used as source datasets for getting the required exposure, PK concentrations, PD concentration, laboratory findings and subject level data such as age, sex, race, baseline height/weight and other co-variates.
2. Pharmacometrician work closely with PKPD programmers to prepare the NONMEM specification for PKPD or E-R analysis and draft the required variables and their mapping or derivation from source data.
3. Using this specification file and programming platforms such as SAS or R, PKPD programmer creates NONMEM analysis input dataset. This dataset structure differs from company to company. However, regulatory agencies such as FDA or PMDA recommend using available CDISC Basic Data Structure for ADaM POPPK for creating this analysis input dataset.
4. Later, once PKPD or E-R analysis is completed by Pharmacometrician using this ADPPK dataset, PKPD programmer contributes to creating eSUB package with required content which is further discussed ahead in this paper.

Role of PHARMACOMETRICIAN :

1. Using this ADPPK dataset in .csv format as input, Pharmacometrician analyzes this data using software such as NONMEM or Phoenix NLME. They create control files (.ctl) to define the PKPD model structure.

2. Once the analysis is completed, different NONMEM output files are created in ASCII format which includes parameter estimates (.lst), Covariance file (.cov), Final fixed/random effect parameter estimates (.ext).
3. Further the information obtained from this model results can be used for creating Tables, Listings or Figures using SAS / R programs.
4. Finally, PKPD programmer will assemble all required datasets, programs, model codes, NONMEM output files, define.xml, reviewer's guide, NONMEM TLFs and PKPD analysis report into eSUB package and submit it to regulatory agencies for the review.

ADPPK (NONMEM ready analysis input dataset for Population PK) :

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)

Presently, most of the companies involved in PK/PD programming use different approaches for the creation of NONMEM analysis input dataset. Some create this dataset directly using raw datasets extracted from eCRF data combined with external PK concentrations and laboratory data while others create this dataset using SDTM/ADaM datasets as source. Also, variable names and metadata are not consistent. Creating POPPK input dataset requires lot of data transformation, new derivations and flagging record or subject level exclusions. NONMEM analysis input datasets such as POPPK, PKPD and ER (Safety and Efficacy) are important parts of eSUB package for regulatory submissions. Having this dataset in non-standard structure can delay regulatory review and overall decision time. Moreover, it is difficult to establish traceability of data included in analysis.

CDISC ADaM ADPPK dataset (Analysis Data Model - Analysis Dataset for Population Pharmacokinetics) is a standardized dataset designed to support pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) analyses in clinical trials. ADPPK follows CDISC ADaM principles, ensuring traceability, consistency, and regulatory compliance. It follows Basic Data Structure and is typically derived from SDTM datasets (e.g., SDTM.PC for PK concentration data, SDTM.EX for dosing data). It integrates key variables required for NONMEM or other population PK modeling tools. ADPPK includes subject-level, dosing, and concentration information, along with derived variables such as nominal and actual sampling times, dose amounts, and exclusion flags. Standardizing PK data within ADaM ADPPK enhances data integrity, facilitates efficient PK/PD modeling, and streamlines regulatory submissions to agencies like the FDA, EMA and PMDA.

Important points for the implementation of ADPPK :

- NONMEM software which is gold standard to perform PKPD or E-R analysis requires tool specific variables available in the input dataset. ADPPK standard variables contain some of these variables such as DV, EVID, CMT, RATE, AMT, II, ADDL which are essential for software for parameter estimation.
- Character Variables included in ADPPK dataset are more like for Information and will need to be dropped by PK Modeler while importing datafile in NONMEM as this software cannot read character variables. s
- Time variables use suffix – RLT to represent relative time because using the standard suffix -TM will cause errors with common conformance rule checks.
- PARAMCD can be used with values such as "DOSE" , "PK" for EVID value of 1 and 0 respectively. While PARAM can be used to display corresponding treatment group value which can further be carried forwarded to PK or PD records.
- AVAL can be mapped with value from DV.
- Appropriate guidance to follow for imputing missing data as per implementation guide.
- Specific variables for identifying exclusion and imputation records.
  EXCLF – Record identifier for excluding record from analysis (day 1 pre-dose, BLQ record)
  EXCLFCOM – Comment for the record excluded
  FLGREAS – Primary reason for flagging the record due to data issue.
  FLGREASC – Character version of FLGREAS.
- Included datetime variable for traceability - UDTCs

Covariates play a critical role in PKPD and E-R analysis, helping to explain variability in drug exposure and response among individuals. Understanding covariate effects improves dose optimization, enhances model predictability, and supports regulatory decision-making.

Below are some advantages of adding correct co-variates in PK/PD and E-R analysis.

- Including covariates such as age, race, weight, renal function parameters (CrCl, eGFR), Liver Function Tests (ALT, AST, Bilirubin), PK/PD models can quantify sources of variability and predict individualized drug responses.
- It enables dose adjustments for subpopulations like pediatric or renal-impaired patients.
- E-R models incorporating covariates support label recommendations such as “Dose reduction in hepatic impairment" based on liver enzyme levels.
- It helps in identifying risk factors for drug safety and efficacy. It helps to identify subgroups at higher risk of toxicity (e.g., patients with low CYP2D6 activity experiencing higher drug exposure) and ensures safer drug use.

Naming conventions for adding co-variates in ADPPK dataset are as per following.

- <COV>BL for baseline covariate, (e.g., WTBL, BMIBL)
- <COV>N for numerical version of categorical covariate; there is one-to-one relationship between <COV> and <COV>N (e.g., SEXN, RACEN)
- <COV>I for any covariates with imputed values (e.g., WTI, BMII)
- <COV>GRy for grouping covariates (e.g., AGEGR1)

Example of adppk.xpt

ROW	PROJID	STUDYID	USUBJID	TRTA	ADT	ATM	APERIOD	ADY	NFRLT	AFRLT	AMT	DOSE
1	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/3/2023	7:28	1	1	0	0	0	-999
2	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/3/2023	8:05	1	1	0	0	50	50
3	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/3/2023	8:35	1	1	0.5	0.5	0	50
4	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/3/2023	9:05	1	1	1	1	0	50
5	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/3/2023	9:35	1	1	1.5	1.5	0	50
6	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/3/2023	10:05	1	1	2	2	0	50
7	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/3/2023	11:05	1	1	3	3	0	50
8	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/3/2023	12:05	1	1	4	4	0	50
9	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/3/2023	14:05	1	1	6	6	0	50
10	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/3/2023	18:05	1	1	10	10	0	50
11	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/3/2023	20:00	1	1	12	11.92	0	50
12	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/3/2023	20:05	1	1	0	12	50	50
13	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/4/2023	7:26	1	1	24	23.35	0	50
25	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/9/2023	7:27	1	7	0	143.37	0	50
26	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/9/2023	8:05	1	7	0	144	50	50
27	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/9/2023	8:38	1	7	0.5	144.55	0	50
28	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/9/2023	9:10	1	7	1	145.08	0	50
29	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/9/2023	9:35	1	7	1.5	145.5	0	50
30	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/9/2023	10:05	1	7	2	146	0	50
31	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/9/2023	11:05	1	7	3	147	0	50
32	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/9/2023	12:06	1	7	4	148.02	0	50
33	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/9/2023	14:05	1	7	6	150	0	50
34	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/9/2023	18:05	1	7	10	154	0	50
35	POPPK	1712	10011712	POPPK1712_50_mg_BID	5/9/2023	20:00	1	7	12	155.92	0	50

ROW	FORM	COHORT	AGE	SEX	RACE	WTBL	BMIBL	DV	MDV	EVID	II	ADDL
1	140	1	32	1	2	69.8	22.6	0	0	0	0	0
2	140	1	32	1	2	69.8	22.6	-999	1	1	0	0
3	140	1	32	1	2	69.8	22.6	457	0	0	0	0
4	140	1	32	1	2	69.8	22.6	541	0	0	0	0
5	140	1	32	1	2	69.8	22.6	1050	0	0	0	0
6	140	1	32	1	2	69.8	22.6	1920	0	0	0	0
7	140	1	32	1	2	69.8	22.6	2390	0	0	0	0
8	140	1	32	1	2	69.8	22.6	1490	0	0	0	0
9	140	1	32	1	2	69.8	22.6	1180	0	0	0	0
10	140	1	32	1	2	69.8	22.6	350	0	0	0	0
11	140	1	32	1	2	69.8	22.6	252	0	0	0	0
12	140	1	32	1	2	69.8	22.6	-999	1	1	0	0
13	140	1	32	1	2	69.8	22.6	524	0	0	0	0
25	140	1	32	1	2	69.8	22.6	696	0	0	0	0
26	140	1	32	1	2	69.8	22.6	-999	1	1	0	0
27	140	1	32	1	2	69.8	22.6	1170	0	0	0	0
28	140	1	32	1	2	69.8	22.6	1430	0	0	0	0
29	140	1	32	1	2	69.8	22.6	1580	0	0	0	0
30	140	1	32	1	2	69.8	22.6	1470	0	0	0	0
31	140	1	32	1	2	69.8	22.6	1730	0	0	0	0
32	140	1	32	1	2	69.8	22.6	2070	0	0	0	0
33	140	1	32	1	2	69.8	22.6	2270	0	0	0	0
34	140	1	32	1	2	69.8	22.6	916	0	0	0	0
35	140	1	32	1	2	69.8	22.6	771	0	0	0	0

Pinnacle 21 (P21) is a widely used validation tool, helping to assess ADPPK dataset for CDISC ADaM compliance before regulatory submission.

Key Aspects of Pinnacle 21 Compliance for ADPPK:

- Ensures all variable names, labels, and formats align with ADaM IG (Implementation Guide).
- Checks for missing required variables (e.g., USUBJID, PARAMCD, AVAL, ATPT).
- Ensures linkage between ADPPK and source SDTM/ADAM datasets (e.g., EX, PC, ADSL, ADLB).
- Validates ATPT, ATPTN, ADY, ATIME, ensuring correct PK time alignment.
- Confirms ADPPK follows BDS (Basic Data Structure) rules required for ADaM datasets.

Common Issues Identified by Pinnacle 21 in ADPPK:

- Missing Required Variables (e.g., PARAMCD, VISIT, DOSE)
- Incorrect Data Types (e.g., character vs. numeric mismatches)
- Issues with 1:1 mapping of PARAMN, PARAMCD and PARAM
- Lack of Traceability to SDTM (e.g., missing USUBJID mapping)

Performing a Pinnacle 21 compliance check on ADPPK datasets ensures adherence to regulatory expectations, reducing submission risks and potential regulatory queries. By addressing validation findings early, organizations can improve data quality and streamline PK/PD and E-R regulatory submissions for efficient approval.

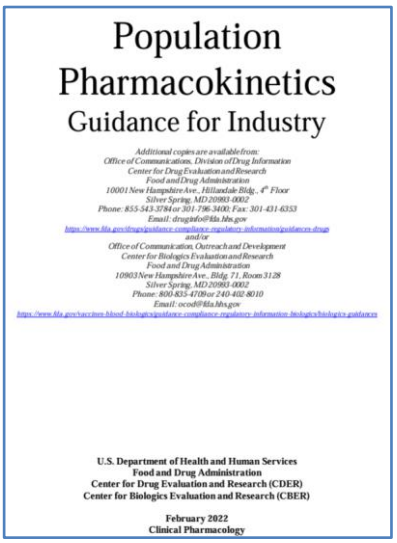
REGULATORY GUIDANCE FOR PK/PD and E-R analysis

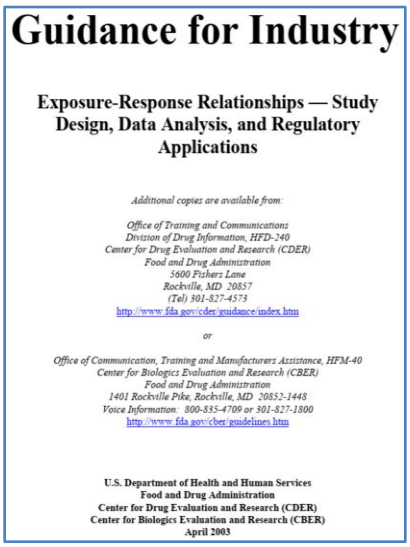
Regulatory agencies such as the FDA, EMA and PMDA have issued guidelines to ensure consistency, reliability, and transparency in Population PK and exposure-response (E-R) analysis. These guidelines provide frameworks for study design, data analysis, model validation, and regulatory submission. Staying up-to-date with these regulatory guidelines is essential for PK/PD scientists, pharmacometricians, and regulatory teams to ensure compliance, streamline submissions, and optimize drug development.

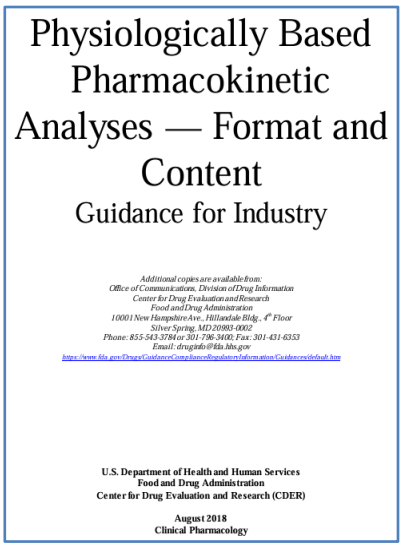
Advantages of adhering to these regulatory guidance

- Regulatory guidance aligns study designs, data analysis, and reporting with agency expectations, increasing the likelihood of faster approvals with minimal review cycles.
- Following guidelines ensure uniform data processing, model selection, and validation, leading to reproducible and scientifically sound conclusions.
- Regulatory-compliant PK/PD and E-R analyses help optimize dose selection, particularly for special populations (pediatrics, elderly, renal/hepatic impairment), improving safety and efficacy.
- Guidelines encourage the use of physiologically-based pharmacokinetic (PBPK) modeling, Bayesian approaches, and machine learning to enhance model-based drug development (MBDD), reducing trial burden.
- Following ICH and FDA/EMA PMDA guidance ensures that PK/PD and E-R analyses meet the expectations of multiple regulatory agencies, streamlining global submissions.
- Adhering to CDISC ADaM ADPPK, SDTM, and eCTD guidelines ensure that datasets meet electronic submission standards, reducing the risk of regulatory rejection.

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


Population Pharmacokinetics
Guidance for Industry
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
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
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2018
Clinical Pharmacology

EMA Guidance Webpage :
https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics

PMDA Guidance Webpage :
https://www.pmda.go.jp/english/review-services/regulatory-info/0008.html

CONTENT AND FOLDER STRUCTURE FOR REGULATORY SUBMISSIONS (eSUB Package)

Regulatory agencies require structured submission of PK/PD and E-R analysis for New Drug Applications (NDAs) and Biologics License Applications (BLAs). The submission package should follow CDISC standards (ADaM.ADPPK, Define.xml) and electronic submission guidelines (eCTD format). Following is the comprehensive list of required items to be included to create an effective eSUB package.

Pharmacometric analysis reports for new drug applications (NDAs) and biologic license applications (BLAs) can be submitted in eCTD Module 5.3.3.5

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 Steam 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)

ANALYSIS DATASETS :

The ADaM Subject-Level Analysis Dataset (ADSL) is an essential component of the PK/PD and Exposure-Response (E-R) analysis electronic submission (eSUB) package. It is mandatory dataset for any regulatory submission and serves as the foundation dataset that links demographic, treatment, and baseline characteristics to PK/PD data, ensuring traceability, consistency, and regulatory compliance in population pharmacokinetics (PopPK) and E-R modeling. Usually, this dataset is directly copied from CSR analysis datasets folder and then used to derive required variables and to include core variables for Population PK analysis dataset ADPPK.

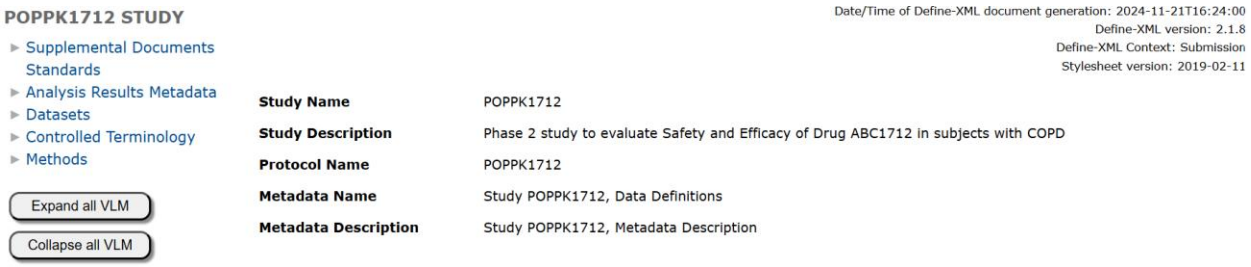
Earlier, Population PK analysis dataset used to be created and submitted as non-standard analysis dataset. However, based on recent available guidance from CDISC on creating a Population PK analysis dataset ADPPK has solved this problem. This dataset is now created and submitted as standard analysis dataset along with ADSL which serves as an input dataset for NONMEM analysis. There may be any other analysis datasets from CSR analysis included in PK/PD or E-R analysis electronic submission package if they are used as source dataset for creating ADPPK to perform POPPK or E-R modeling. Regulatory agencies do not have any preference for using ADAM datasets over SDTM datasets as source for creating ADPPK. However, for consistency, it is always advised to use ADAM datasets as source because they are the most recent version of data used for Safety/Efficacy analysis and have derived variables in alignment with statistical analysis plan.

DEFINE.xml :

For PK/PD and E-R analysis, earlier, Define.pdf was to be submitted to regulatory due to lack of availability on standards and compliance checks. But as now ADaM BDS guidance is available on creating and submitting standard ADPPK analysis dataset, submitting Define.xml is recommended. Define.xml is machine readable file and provides metadata to regulatory reviewers and

ensures that they can interpret and validate dataset variables, derivations and transformations. It establishes lineage between source SDTM and ADAM datasets which helps in reproducing PK/PD and E-R analysis, facilitating efficient regulatory review.

Sample Define.xml file for PKPD Submission



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

ANALYSIS DATA REVIEWER's GUIDE (ADRG) :

The PK/PD analysis data package differs from the standard analysis data package prepared for Clinical Study Reports (CSR) for Efficacy and Safety. The PK/PD Analysis Data Reviewer's Guide (ADRG) serves as a structured document designed to facilitate regulatory review by providing clear and concise instructions. ADRG is an essential component of the ADaM electronic data submission package and is developed following the PHUSE ADRG template. Since a significant portion of the PK/PD analysis datasets is derived from the study's CSR analysis datasets, the ADRG for the PK/PD database is primarily based on the CSR ADRG, with modifications to accommodate the unique aspects of PK/PD data. As per ADRG template, Section 1.4 of the ADRG (Source Data Used for Analysis Dataset Creation) provides a comprehensive explanation of the dataset derivation process.
For FDA regulatory submission, the ADRG must be saved as adrg.pdf, ensuring compliance with the FDA Portable Document Format (PDF) Specifications and created with the 'Optimize for Fast Web View' option to ensure efficient document processing and accessibility.

Section 5.2 of PK/PD Analysis Data Reviewer's Guide :

Dataset Dataset Label	Class -SubClass	Efficacy	Safety	Baseline or other subject characteristics	PK/PD	Primary Objective	Structure
ADSL Subject-Level Analysis Dataset	Subject Level Analysis Dataset	X	X	X			One record per study, per subject
ADPPK Population PK Analysis Dataset	Basic Data Structure Population Pharmacokinetic Analysis	X	X		X		One record per subject per parameter (analyte) per analysis timepoint per event (dosing or observation)

Vital components of PKPD or E-R Analysis ADRG

MODEL SCRIPTS AND SAS/R PROGRAMS :

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-pklan-dose.txt ……

In addition to the above, project files (e.g., .rmd, .phxproj) can also be included in the package. It is recommended to keep all the files and program names in lower case. There are some differences in requirements between different regulatory agencies. Thus, it is always advised to refer to the latest applicable regulatory guidance documents while preparing an electronic submission package. Content and requirements can be confirmed in a pre-submission meeting with the regulatory agency to avoid potential re-work which can delay the decision.

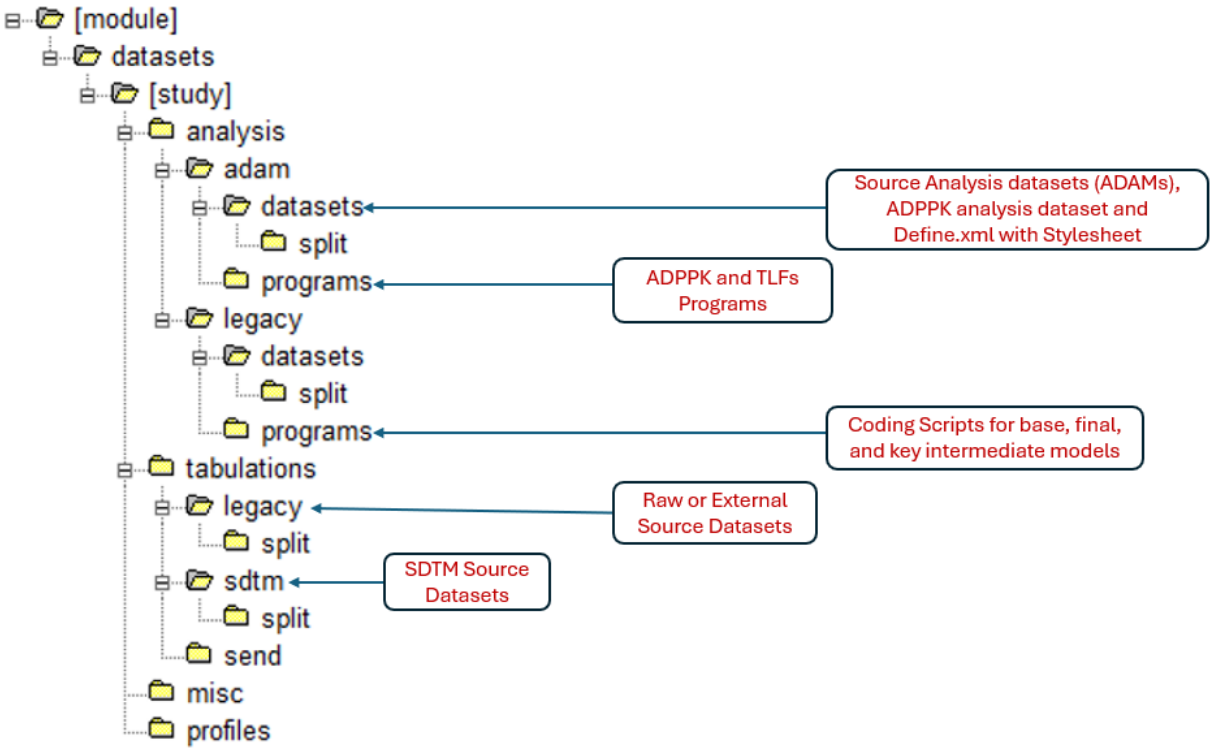
FOLDER STRUCTURE

The Electronic Common Technical Document (eCTD) is the standard format for submitting applications, amendments, supplements, and non-clinical / clinical study reports to regulatory agencies such as FDA, EMA, PMDA, and others. The following image highlights the required folder structure as per FDA technical conformance guide Module 5 (M5).

According to ADaM Implementation Guide (ADaMIG) v1.1, when an analysis dataset includes an ADaM-compliant datasets, the complete set of analysis datasets must be stored within the /adam folder. If analysis datasets are ADAM non-compliant then these datasets should be placed in the /legacy folder. Any coding scripts created by pharmacometrician and used in analysis are placed in the /programs sub-folder within /legacy folder. The PK/PD data package is submitted separately as an independent study within Module 5 of the eCTD structure. The following files are included within the /datasets folder.

- ADSL and ADPPK ADaM .xpt files
- Analysis Data Reviewer's Guide (adrg.pdf)
- Define.xml metadata file
- Stylesheet (define2-0-0.xsl)

Additionally, all Model Scripts mentioned above, SAS or R programs (saved in .txt format) used for generating analysis datasets, safety or efficacy summaries, and graphical outputs are stored within the /programs folder.
This structured approach ensures compliance with regulatory requirements and facilitates efficient data review by regulatory agencies.



CONCLUSION

Efficient regulatory submission of the eSUB package for Exposure-Response (E-R) and Pharmacokinetics/ Pharmacodynamics (PK/PD) analysis is crucial for ensuring compliance, data traceability, and streamlined regulatory review. By following regulatory guidance from agencies such as the FDA, EMA, and PMDA, and adhering to CDISC ADaM standards, pharma researchers can enhance data consistency and facilitate seamless evaluations of drug safety and efficacy. A well-structured eSUB package including ADSL and ADPPK datasets, define.xml, Analysis Data Reviewer's Guide (ADRG), and NONMEM model files supports efficient decision-making by regulatory reviewers, reducing the risk of delays and requests for additional data. Standardized data formats ensure that critical PK/PD and E-R relationships are clearly presented, aiding dose optimization and risk- benefits assessments. E-R Analysis Datasets are different and currently there are no standards for same because of various endpoints based on specific Therapeutic Area. This dataset and corresponding program still need to be included in eSUB package within legacy/datasets folder.
By leveraging best practices in data standardization, automation, and structured documentation, pharmaceutical companies can significantly improve the efficiency of regulatory submissions, ultimately expediting the drug development process and bringing new therapies to patients faster. Future advancements in model-informed drug development (MIDD), real-world data integration, and AI-driven automation will further enhance regulatory submissions, fostering innovation in Pharmacometric analysis. The implementation of the standard data structure for PKPD and

E-R analysis is expected to improve data quality, facilitate tool development, accelerate collaboration across pharmacometrics community and enhance communication with the regulatory agencies.

REFERENCES

Basic Data Structure for ADaM PopPK Implementation Guide v1.0
https://www.cdisc.org/standards/foundational/adam/basic-data-structure-adam-poppk-implementation-guide-v1-0

The Specification for File Format Types Using eCTD Specifications
https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd

FDA Model | Data Format
https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format

FDA Industry Guidance
Population Pharmacokinetics
www.fda.gov/media/71364/download

FDA Industry Guidance
Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications
www.fda.gov/media/71277/download

ACKNOWLEDGMENTS

I would like to thank all my colleagues at Ephicacy who shared their experiences, read my drafts, and gave me valuable and constructive feedback. Thank you for your support.

CONTACT INFORMATION

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

Author Name: Saumilkumar Tripathi
Company: Ephicacy Lifescience Analytics
Address: No. 6, 2nd Floor,
2nd Main, Arekere,
Off Bannerghatta Road,
Bengaluru - 560076,
Karnataka, India.
Work Phone: +91-8390914975
Email: saumil.tripathi@ephicacy.com
Website: https://www.ephicacy.com/