Paper SA-05

Electronic Submission of Population PK Analysis Files… What's Your Modus Operandi?

Luai Alzoubi, Divya Kommuru and Sabarinath Sundaram. Pfizer Inc, USA.

ABSTRACT

Population Pharmacokinetic (PopPK) analyses play a critical role in drug development and regulatory decision making. FDA has emphasized the importance of reproducibility in PopPK submissions by highlighting the value of these analyses and the inclusion of data and related files (e.g. coding scripts) in submission packages. All conclusions drawn from the PopPK analysis should be reproducible by the Agency with submitted codes and data. However, submission practices vary across sponsors. Key challenges include integrating heterogeneous data sources, managing sparse PK sampling, and ensuring consistency across studies. Additionally, submission challenges such as aligning documentation formats, meeting evolving regulatory expectations, and ensuring traceability. Pharmacometrics Analysis Report (PMAR) dataset programming plays a vital role in overcoming these issues. This paper will showcase what our organization submits for PopPK Study Reports, and we hope it leads to engagement with other sponsors sharing their expertise with PopPK Submissions, culminating in common approaches and submission packages.

INTRODUCTION

Pharmacokinetics (PK) describes drug exposure following administration of the drug to the patient. PK data includes information on absorption, distribution, metabolism, bioavailability, and excretion of the drug over time. PK evaluation is crucial to understand systemic exposure and to support proper dose selection across patient populations in studies. Lack of understanding of PK can lead to inaccurate dosing and increase development risk downstream.

Pharmacodynamics (PD) describes the relationship between drug concentration and pharmacologic or toxicologic effects. PD endpoints may include biomarkers, efficacy variables, or safety measures. PD reflects the biological response to exposure. PK and PD together describe the dose exposure response relationship used to interpret clinical trial outcomes. Figure 1 illustrates the relationship between pharmacokinetics and pharmacodynamics, the setting of a clinical trial.

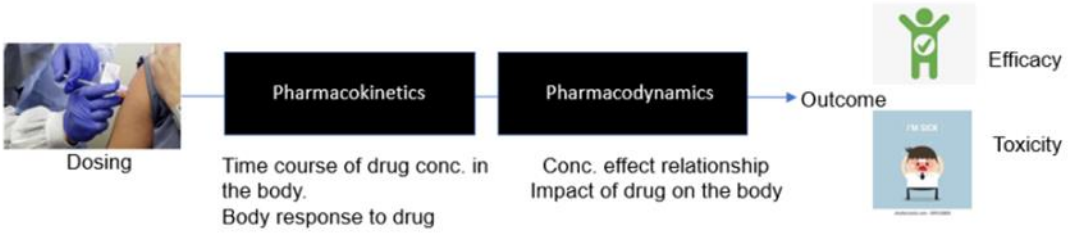


Figure 1: Conceptual PK/PD Framework Linking Drug Administration to Quantifiable Clinical Outcomes

Pharmacometrics integrates PK and PD data to support dosing decisions in clinical development. Drug exposure and response vary across subjects because of intrinsic and extrinsic factors such as age, sex, body size, organ function, disease state, and concomitant medication use. Population-based PK and PK/PD analyses are used to quantify variability and evaluate the impact of these factors on exposure.

Population pharmacokinetic modeling extends individual PK analysis by characterizing typical exposure, inter-individual variability, and covariate effects at the population level. PopPK analyses are used to support dose selection, assess the need for dose adjustments, bridge across studies or populations, and support exposure–response evaluation for efficacy and safety endpoints.

OVERVIEW AND BACKGROUND OF THE POPULATION MODELING ANALYSIS REPORT

The Population Modeling Analysis Report (PMAR) is a structured document used to summarize population PK analyses for internal review and regulatory submission. The PMAR documents the data sources, modeling approach, assumptions, results, and clinical interpretation. Clear documentation within the PMAR allows traceability from clinical data to modeling outputs and supports reproducibility of analyses used to inform development decisions.

One of the primary uses of the PMAR is dose selection. Population PK analyses are used to identify dosing regimens appropriate for the overall population as well as for specific subgroups such as pediatric patients or subjects with renal or hepatic impairment. Observed covariate effects on clearance, volume of distribution, or other PK parameters are used to justify dose adjustments when required. Inter-individual variability in exposure is quantified, and the sources of variability are evaluated to support risk assessment and dose optimization. Common covariates assessed include

demographic factors, measures of organ function, disease characteristics, and concomitant medications.

The PMAR promotes bridging pharmacokinetic data from one population or formulation to another through modeling and simulation. These include extrapolation from healthy volunteers to patients and from intravenous to oral dosing. These types of analyses can lower requirements for future clinical trials. Exposure-response analyses, as part of the PMAR, examine correlations between exposure, efficacy results, and safety observations and are used to establish assessments for dose-response, therapeutic indices, and safety margins.

The PMAR describes the modeling workflow in sufficient detail to allow interpretation of results. This includes a description of the clinical data used, development of the structural and statistical models, evaluation of covariate relationships, and assessment of model performance using standard diagnostic approaches. Simulation results are used to evaluate expected exposure under alternative dosing scenarios and to assess the impact of patient-specific factors.

ROLE OF PMAR ACROSS EARLY AND LATE STAGES OF DRUG DEVELOPMENT

During early-stage development, PMARs are used to support dose selection and study design. Population PK models developed from early clinical studies inform starting doses and escalation strategies in first-in-human trials. In pediatric development, PMARs support dose extrapolation from adult data while accounting for differences in body size and maturation. Modeling may also be applied to guide dosing in special populations prior to conducting dedicated clinical studies, improving efficiency while maintaining patient safety.

In late-stage development, PMARs are used to support dose refinement and confirmation using data from larger and more heterogeneous patient populations. Population PK and PK/PD analyses from Phase II and Phase III studies are used to justify recommended doses, dose adjustments, and guidance for special populations in regulatory submissions. PMARs also support bridging across formulations or regions and provide quantitative input for safety evaluation and post-marketing risk management. Where appropriate, additional data sources may be used as supportive evidence to understand exposure and outcomes in broader clinical use. Table 1 provides a side-by-side comparison of early-stage (Phase I/II) versus late-stage (Phase IIb/III & Registration) clinical development. It highlights key differences in objectives, population characteristics, dose selection, modeling approaches, and regulatory expectations across the two stages

Aspect	Early-Stage Development (Phase I/II)	Late-Stage Development (Phase IIb/III & Registration)
Objective	Guide starting doses, dose escalation, and initial safety	Confirm and refine dosing, support labeling and regulatory decisions
Population	Small, controlled cohorts; often healthy volunteers or limited patient populations	Large, heterogeneous patient populations reflecting intended use
Dose Selection	Establish safe starting doses and escalation schemes	Optimize therapeutic dose, account for inter-patient variability, support dose adjustments
Covariate Analysis	Evaluate key intrinsic/extrinsic factors (age, weight, organ function)	Quantify variability across broader populations, refine special population dosing
Bridging	Extrapolate adult data to pediatrics or special populations	Bridge across formulations, global populations, or real-world settings
Safety Evaluation	Early identification of exposure-safety relationships	Confirm safety margins, identify thresholds for adverse events
Efficacy Assessment	Exploratory exposure-response for efficacy endpoints	Quantitative support for label claims, dose-response validation
Regulatory Use	Inform early clinical development plans and trial design	Support regulatory submissions, labeling, risk management, and post-marketing strategy
Modeling Approach	Focused PK/PD modeling to guide trial design	Comprehensive population PK/PD modeling integrating exposure-response and covariate effects

Table 1: Summary of key distinctions in the use of Population Modeling Analysis Reports (PMARs) across early-stage (Phase I/II) and late-stage (Phase II/III) studies.

ROLES AND RESPONSIBILITIES OF PMAR TO REGULATORY SUBMISSION

PMAR preparation depends on coordinated input from Pharmacometrician, PKPD Programmer, and Regulatory Submission Manager (Figure 2).

ROLE OF PHARMACOMETRICIAN

The pharmacometrician plays a major role in the PMAR process. They author the PMAR and related exposure–response reports, assemble submission-ready model and dataset with complete reproducibility metadata, and ensure that quantitative conclusions align with the CSR and labeling. They lead the end-to-end quantitative strategy, including the development and qualification of population PK/PD and exposure–response models, as well as simulations to justify dosing recommendations.

Pharmacometricians also work with PKPD programmers to transform CDISC (PopPK, PKECG, ER-safety and ER-efficacy) plus the intermediate dataset/source data for the modelling purpose created by the analyst into analysis-ready formats (such as .csv for NONMEM or Phoenix NLME). They contribute to the submission package by creating model code, datasets, reports, and reviewer supporting document.

ROLE OF PKPD PROGRAMMER

The role of a PKPD Programmer is to work with pharmacometricians in order to create, validate, and document specialized analysis datasets and reports to regulatory agencies. They help streamline the submission process by preparing datasets in tandem with database locks, sometimes using "scrambled" or blinded data to facilitate early analysis. They play a critical role in preparation of eCTD (electronic Common Technical Document) process and contribute towards the creation of essential submission package.

ROLE OF REGULATORY SUBMISSION MANAGER

The Regulatory Submission Manager is responsible for planning, coordinating, and executing all activities required to prepare a compliant, high-quality electronic regulatory submission (eCTD). They oversee submission strategy and timelines, ensure that all component are delivered in the correct format, and verify that all documents meet regional regulatory and technical requirements

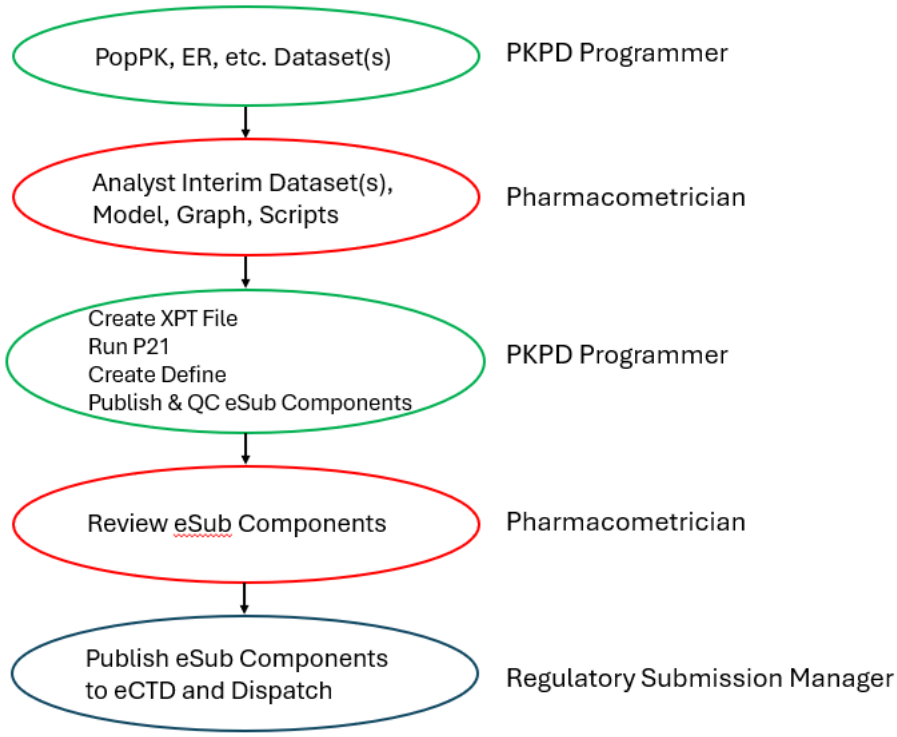


Figure 2: Sequential Workflow for PMAR Development and Submission

ELECTRONIC SUBMISSION (eSub) PROCESS

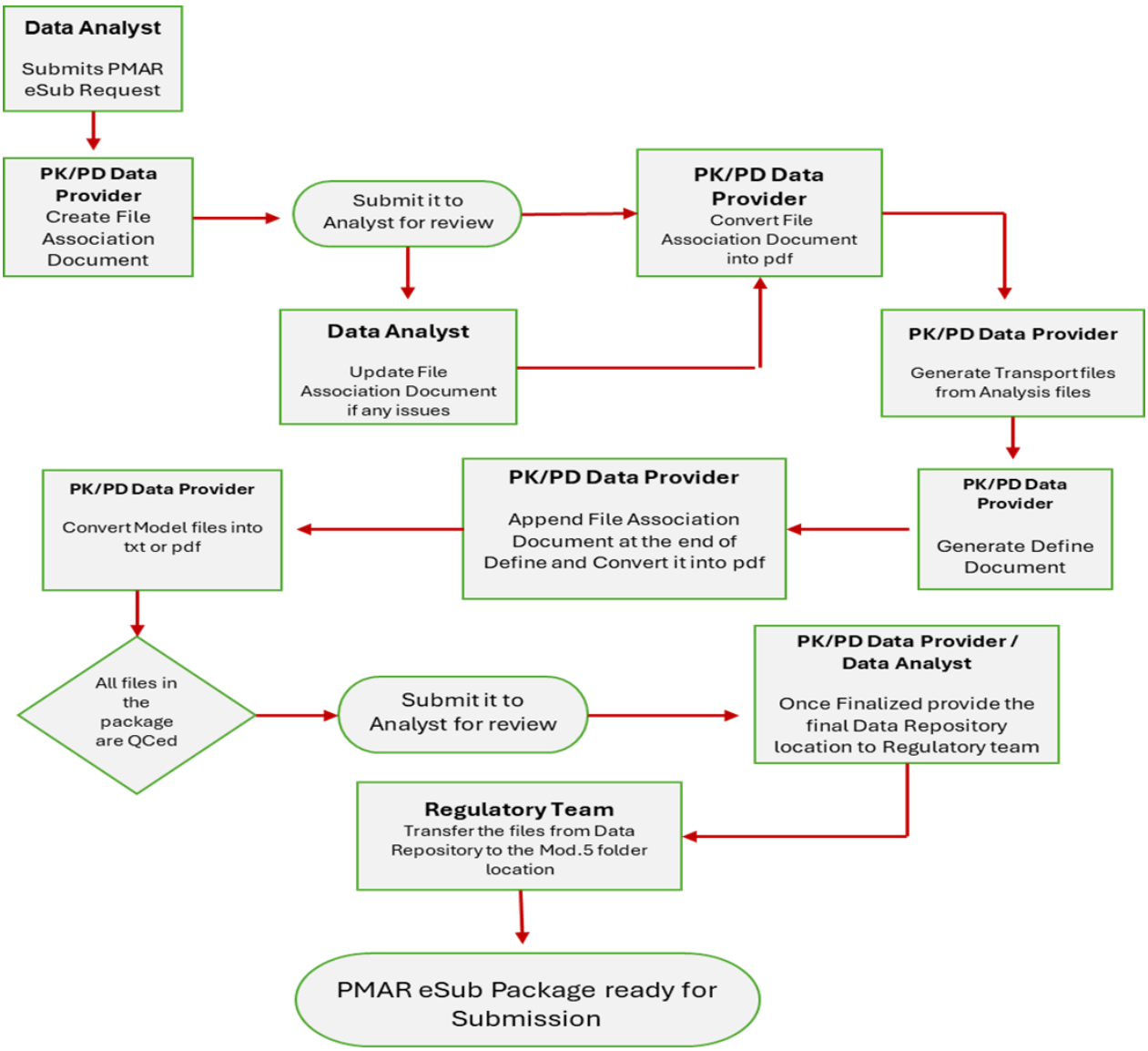
The overall workflow (Figure 3) to support PMAR electronic submission (eSub) delivery involves coordinated planning, data preparation, and cross-functional review to ensure high-quality submission outputs. Each step from dataset readiness through modeling, documentation, QC, and final packaging ensures alignment with regulatory standards and timely delivery.

Pharmacometrician initiates the process by submitting a PMAR eSub Request Form. Request form provides all the needed information and components of submission package to PKPD Data Programmer.

Request details: PMAR report number and description, Compound Name(s), Protocol(s), Therapeutic Area, Reason for request, Timelines and agency due date.

List of all necessary files and scripts for Regulators to re-run the base and final models and outputs must be provided including location of these files.

Analysis Datafile name used for analysis and location. Description, variable labels and associated code lists for all the data files (if any) generated by pharmacometrician.



*Data Analyst = Pharmacometrician
*PK/PD Data Provider = PK/PD Programmer

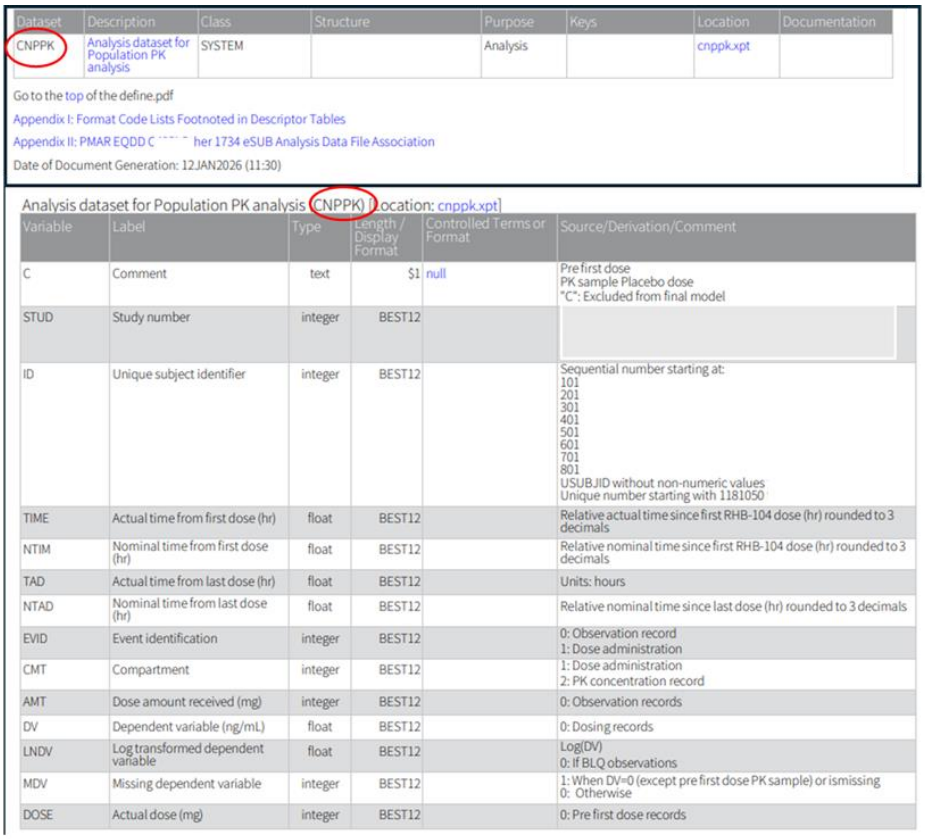
Figure 3: Overall Workflow to Support PMAR eSub Delivery

GENERATING TRANSPORT FILE

The SAS Transport files (XPT files) are how structured data is exchanged, supporting both data and metadata (like labels/formats). Analysis data files (CSV files) are converted to SAS datasets in order to create the transport files. Prior to conversion to SAS datasets the analysis data files need to be reviewed to ensure all the variables names are 8 characters or less. When the analysis data file is read into SAS, variable labels and formats must be defined.

DATA DEFINITION FILE

A define specification document in an electronic submission data package is a crucial file that defines the structure, content, and origin of the analysis datasets used in PK/PD modeling. Pinnacle 21 Enterprise(P21E) is used to extract the metadata directly from existing XPT files to auto-populate an define specification spreadsheet file. This define specification file includes tabs for Datasets, Variables, Value Level Metadata, and Code lists. Once the define specification is populated and imported back into P21, the tool generates the final define file. Below is an example of a define specification spreadsheet file generated from P21E, as shown below (Table 2).



Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
CNPPK	Analysis dataset for Population PK analysis	SYSTEM		Analysis		cnppk.xpt	

Go to the top of the define.pdf
Appendix I: Format Code Lists Footnoted in Descriptor Tables
Appendix II: PMAR EQDD C her 1734 eSUB Analysis Data File Association
Date of Document Generation: 12JAN2026 (11:30)

Analysis dataset for Population PK analysis (CNPPK) [Location: cnppk.xpt]

Variable	Label	Type	Length / Display Format	Controlled Terms or Format	Source/Derivation/Comment
C	Comment	text	$1	null	Pre first dose PK sample Placebo dose "C": Excluded from final model
STUD	Study number	integer	BEST12		
ID	Unique subject identifier	integer	BEST12		Sequential number starting at: 101 201 301 401 501 601 701 801 USUBJID without non-numeric values Unique number starting with 1181050
TIME	Actual time from first dose (hr)	float	BEST12		Relative actual time since first RHB-104 dose (hr) rounded to 3 decimals
NTIM	Nominal time from first dose (hr)	float	BEST12		Relative nominal time since first RHB-104 dose (hr) rounded to 3 decimals
TAD	Actual time from last dose (hr)	float	BEST12		Units: hours
NTAD	Nominal time from last dose (hr)	float	BEST12		Relative nominal time since last dose (hr) rounded to 3 decimals
EVID	Event identification	integer	BEST12		0: Observation record 1: Dose administration
CMT	Compartment	integer	BEST12		1: Dose administration 2: PK concentration record
AMT	Dose amount received (mg)	integer	BEST12		0: Observation records
DV	Dependent variable (ng/mL)	float	BEST12		0: Dosing records
LNDV	Log transformed dependent variable	float	BEST12		Log(DV) 0: If BLQ observations
MDV	Missing dependent variable	integer	BEST12		1: When DV=0 (except pre first dose PK sample) or ismissing 0: Otherwise
DOSE	Actual dose (mg)	integer	BEST12		0: Pre first dose records

Table 2: Example Data Definition File.

FILE ASSOCIATION DOCUMENT

A File Association Document (Table 3) is created in our process and included in the electronic submission data package, which helps reviewers navigate and understand the background, structure and content of the submission package.

PMAR EQDD CXXXi Other 1734 eSUB PKPD Analysis Data File Association

Report Number	Report Description	Included Studies	Associated Files		
			File Type	File Name in Report[1]	File Name in Submission Package
PMAR-EQDD-CXXXi-Other-1734	Analysis dataset for Population PK analysis	103 105 106 107 108 110 111 112 117 118	Analysis Data file	finalppk.csv	N/A
			Transport file	N/A	poppk.xpt
			Post Processing and Data Manipulation Scripts	PrepSimDataset_v7_pmar1734.R SummarizeSimResult_v7_pmar1734.R	prep-sim-dataset-v7-pmar1734-r.txt summarize-sim-result-v7-pmar1734-r.txt
			Post Processing and Data Manipulation Output Scripts	PK Profile of ODT 75 mg EOD vs QD.png PK Profile of ODT 75 mg EOD with FLCZ vs QD.png SimulatedRimegepantScenarioSummariesforPPKREport_pmar1734_latex.csv	pk-profile-of-odt-75-mg-eod-vs-qd-png.pdf pk-profile-of-odt-75-mg-eod-with-flcz-vs-qd-png.pdf simulated-rimegepant-scenario-summaries-for-ppkre-port-pmar1734-latex.csv
			Base Model File	run7.mod	run7-mod.txt
			Base Output File	run7.lst	run7-lst.txt
			Final Model File	run24.mod	run24-mod.txt
			Final Output File	run24.lst	run24-lst.txt
			R Script File	Run332.r	run332-r.txt

1 File names indicated in the report have been modified to conform to eCTD guidelines for the submission package

Table 3: Example File Association Document

eCTD FOLDER STRUCTURE

The eCTD Module 5 (M5) folder structure organizes clinical study reports and related data for regulatory submissions following an ICH-standardized hierarchy under the M5 directory as shown in below figure. The M5 folder structure is largely harmonized across major regulatory agencies including US FDA, PMDA, Health Canada. Figure 4 Panel (A) illustrates Module 5 folder structure containing PMAR-EQDD analysis datasets, legacy data, and programs. Figure 4 Panel (B) shows how these corresponding components appear in the regulatory eSub package, organized under Clinical Study Reports and associated analysis files

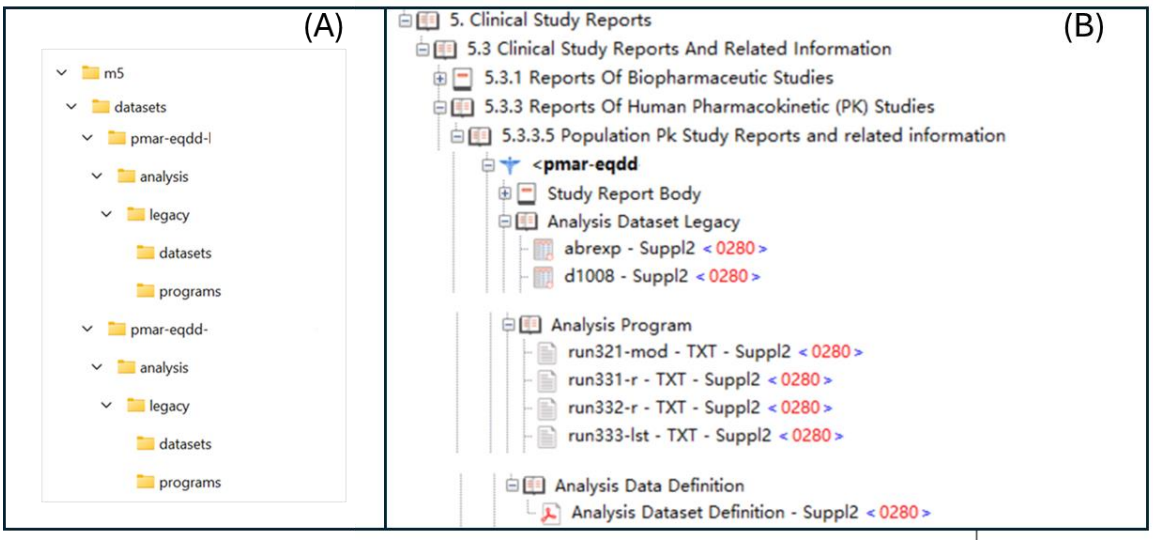


Figure 4: (A) Example M5 Folder structure. (B) Example Submission M5 Folder Content.

Table 4 presents the structured mapping of PMAR eSub components within the eCTD hierarchy.

COMPONENT TYPE	NODE_ NUMBER	NAME	eCTD SEQUENCE	Data_LINK	LEAF_OUTPUT_FILE_NAME
Folder	**5**	**Clinical Study Reports**	0280		
Folder	**5.3**	**Clinical Study Reports**	0280		
Folder	**5.3.3**	**Reports of Human Pharmacokinetic (PK) Studies**	0280		
Folder	**5.3.3.5**	**Population PK Study Reports**	0280		
Folder	**5.3.3.5**	**PMAR-EQDD-DP3-1331 - Population Pharmacokinetic and Pharmacodynamic Model of Marstacima**	0280		
Leaf	5.3.3.5	PMAR-EQDD-DP3-1331 - Population Pharmacokinetic and Pharmacodynamic Model of Marstacimab - Sup	0280		
Document	5.3.3.5	pmar-eqdd-dp3-1331-supplement2-poppk-pkpd	0280	http://gdms.pfizer.com/gdms/drl/objectId/090177e1a46b4485	pmar-eqdd-dp3-1331-suppl2.pdf
Folder	**5.3.3.5**	**Appendices**	0280		
Folder	**5.3.3.5**	**Individual Patient Data Listings**	0280		
Folder	**5.3.3.5**	**Analyses**	0280		
Folder	**5.3.3.5**	**Datasets**	0280		
Leaf	5.3.3.5	Analysis Dataset Definition - Suppl2	0280		
Document	5.3.3.5	define	0280	http://gdms.pfizer.com/gdms/drl/objectId/090177e1a4bb52fc	define.pdf
Leaf	5.3.3.5	abrexp - Suppl2	0280		
Document	5.3.3.5	abrexp	0280	http://gdms.pfizer.com/gdms/drl/objectId/090177e1a4b4ef1f	abrexp.xpt
Leaf	5.3.3.5	d1008 - Suppl2	0280		
Document	5.3.3.5	d1008	0280	http://gdms.pfizer.com/gdms/drl/objectId/090177e1a4b4ef23	d1008.xpt
Folder	**5.3.3.5**	**Programs**	0280		
Leaf	5.3.3.5	run315-lst - TXT - Suppl2	0280		
Document	5.3.3.5	run315-lst.txt	0280	http://gdms.pfizer.com/gdms/drl/objectId/090177e1a4b4ef2f	run315-lst.txt
Leaf	5.3.3.5	run315-mod - TXT - Suppl2	0280		
Document	5.3.3.5	run315-mod.txt	0280	http://gdms.pfizer.com/gdms/drl/objectId/090177e1a4b4ef30	run315-mod.txt
Leaf	5.3.3.5	run320-r - TXT - Suppl2	0280		
Document	5.3.3.5	run320-r.txt	0280	http://gdms.pfizer.com/gdms/drl/objectId/090177e1a4b4ef31	run320-r.txt
Leaf	5.3.3.5	run321-lst - TXT - Suppl2	0280		
Document	5.3.3.5	run321-lst.txt	0280	http://gdms.pfizer.com/gdms/drl/objectId/090177e1a4b4ef32	run321-lst.txt
Leaf	5.3.3.5	run321-mod - TXT - Suppl2	0280		

Table 4: Example Submission US FDA M5 Spreadsheet with Submitted File Names and Locations

CHALLENGES IN PMAR SUBMISSIONS

The most common challenges include:

- Data Set Size and Complexity with the potential to result in long data processing times for large, integrated datasets spanning many clinical trials
- Time Constraints: The urgent or quick turnaround timelines and need to respond rapidly to information requests may require reassignment of resourcing.
- Awareness of different submission requirements between agencies as shown below.

	US	Japan	Canada
Agency	FDA	PMDA	Health Canada
File format	csv, xpt, r, txt, pdf, png	csv, pdf, txt	.inf and .dat[3]
Documentation	Define	Define, Program Procedure	Supporting Documentation
Agency Website Providing Details on eCTD and eSubmission	U.S. Food and Drug Administration	Pharmaceuticals and Medical Devices Agency	Health Canada - Canada.ca

PMAR eSub PACKAGE CONTENT

A standard PMAR eSub package typically includes Analysis Datasets, Documentation and Metadata, Model files and Programs (FDA - Model | Data Format (**2021**)). Packages are submitted as part of the eCTD, usually in Modules 2 (Summaries) and 5 (Clinical Study Reports). The eCTD is the global, electronic standard for submitting pharmaceutical regulatory information to health authorities.

- Datasets used for model development, model validation, and simulations will be submitted in either SAS Transport (.xpt) or comma-delimited (.csv) format.
- A define file (.pdf) will be provided to describe each dataset, including dataset-level metadata and variable-level definitions. The File Association Document is appended to define, which provides additional detail for the regulatory reviewer regarding the submitted files.
- Model codes/control streams and key output listings will be included for all major stages of model development, such as base structural model, covariates models, final model, validation model.

CONCLUSION

Close collaboration among pharmacometricians, PK/PD programmers, and regulatory submission managers remains essential to ensure accuracy, traceability, and compliance with eCTD requirements. Adopting consistent data standards such as ADPPK and ADER improves efficiency, reduces inconsistencies, and supports robust PopPK and PK/PD analyses. High quality PMAR eSub data packages rely on clear documentation, reproducible datasets, and standardized modeling files that facilitate transparent and efficient regulatory review.

Looking ahead, increased automation of data preparation and model packaging will reduce manual intervention, shorten timelines, and improve reproducibility across submissions. In parallel, AI enabled document generation and validation will streamline the development of model reports, traceability packages, reviewer supporting document , and technical appendices. As these technologies mature, AI driven workflows are expected to further integrate and accelerate key steps within the submission process, ultimately enhancing both efficiency and consistency.

REFERENCES

1) eCTD v4.0 Comprehensive Table of Contents Headings and Hierarchy **(2025)**: eCTD Submission Standards for eCTD v4.0 and Regional M1 | FDA

2) FDA - Model | Data Format **(2021):** Model | Data Format | FDA

3) DRAFT GUIDANCE FOR INDUSTRY Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format **(2004)**: Draft Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format - Canada.ca

4) Revision of Technical Conformance Guide on Electronic Study Data Submissions (April 8, 2024) 000267935.pdf

5) Zou Huixi et al (2020) Application of Pharmacokinetic-Pharmacodynamic Modeling in Drug Delivery: Development and Challenges. Front Pharmacol. 2020 Jul 3;11:997

6) Saumilkumar Tripathi (2025) Optimizing Development and Regulatory Submission of eSUB Package for Exposure-Response and PK/PD Analysis. PHUSE 2025

ACKNOWLEDGEMENTS

We would like to thank our colleagues Akiyuki Suzuki, Gina Costanza, Joshua Phillips, Stuart Pearce, and Christine Rossin for their valuable feedback, constant support, and guidance.

CONTACT INFORMATION

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

Luai R Alzoubi
Pfizer Inc
445 Eastern Point Rd, Groton, CT 06340, US
Luai.Alzoubi@pfizer.com
Work phone: 860-373-6072

Sabarinath Sundaram
Pfizer Inc
445 Eastern Point Rd, Groton, CT 06340, US
Sabarinath.Sundaram@Pfizer.com

Divya Priya Kommuru
Pfizer Inc
445 Eastern Point Rd, Groton, CT 06340, US
Divya.Kommuru@pfizer.com