

Guide to Electronic Submission of Pharmacometric Datasets and Analyses to the Regulatory Authorities

Pooja Kulkarni

Overview

- Introduction to Modelling and Simulation
- Process Roadmap
- Types of analysis
- Analysis pathway
- Analysis materials

In this presentation, we will focus on –

- Data submission
- Analysis submission
- Folder Structure: FDA vs. PMDA

Benefits of Modeling and Simulation in Drug Development

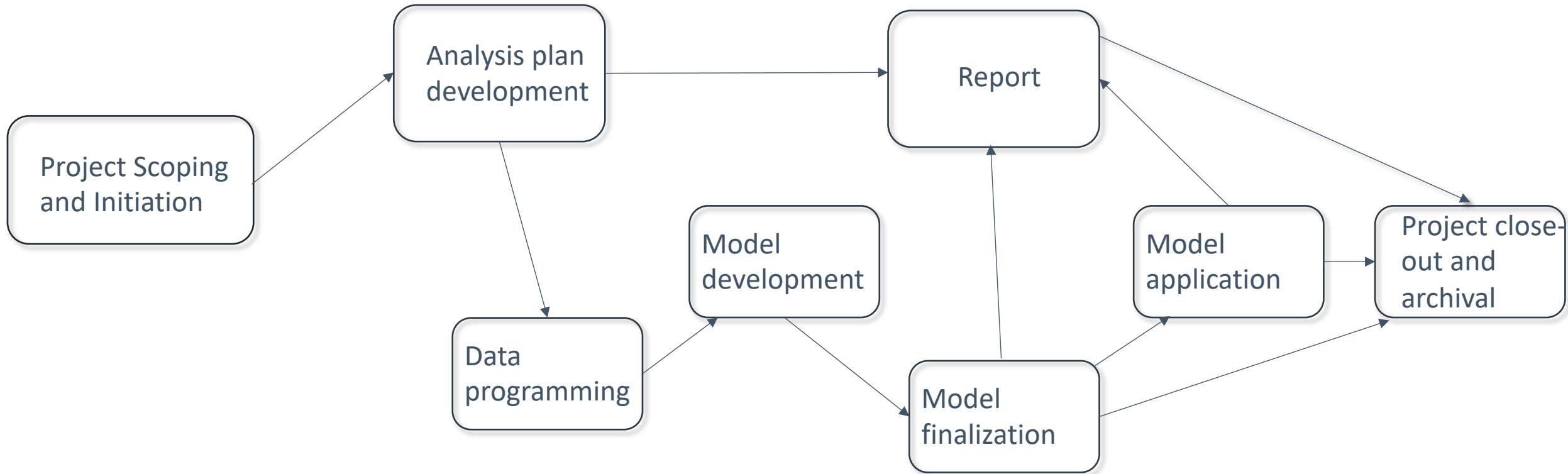
Modeling and simulation is a powerful applied science tool used in **pharmacometric** analysis. This analysis determines the pharmacokinetic characteristics and pharmacokinetic parameters of a given compound. Such parameters include Cmax, Tmax, CL, AUC, half-life, Vd and many other.

Benefits -

- bring **safer** therapies to patients faster
- allows sponsors to make **data-driven** decisions at all stages of drug development
- It systematically takes **risk out** of the drug development process
- It **reduces time and cost**, facilitating earlier approvals.
- It serves as valuable currency with regulators, who use these technologies themselves for review and are helping to lead the M&S revolution.
- Helps in designing safer, targeted and more efficient trials



PMx Process Roadmap

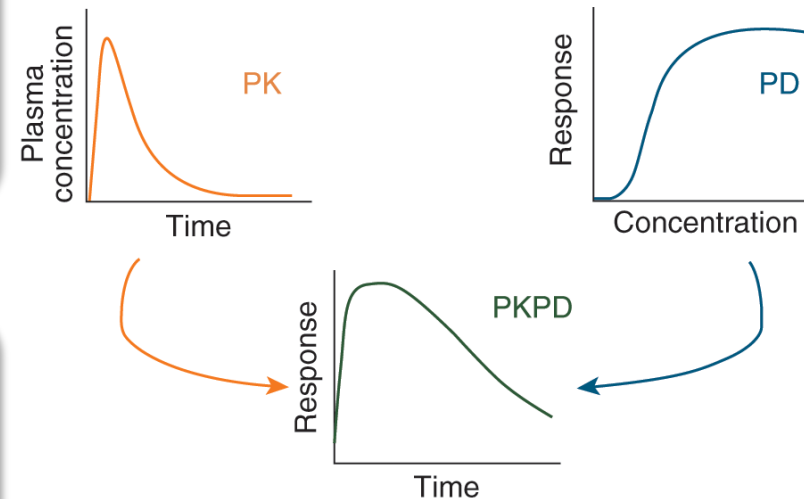


Project team -
PMx Modeler, Lead
Scientific reviewer
Data programmer
Technical writer

Types of analysis

popPK

- Population PK



ER/PKPD

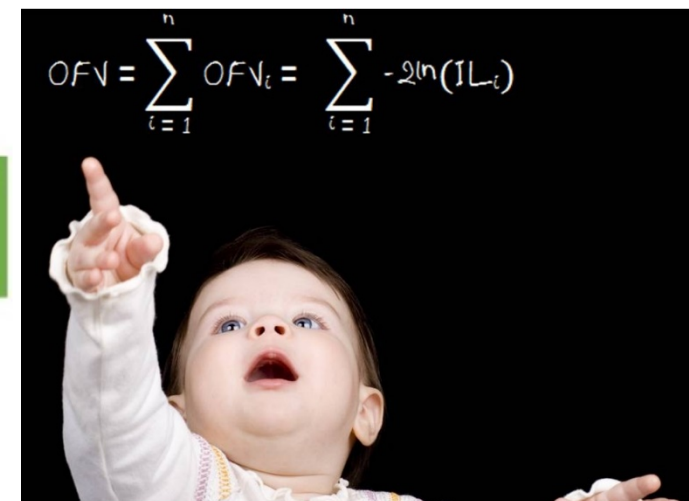
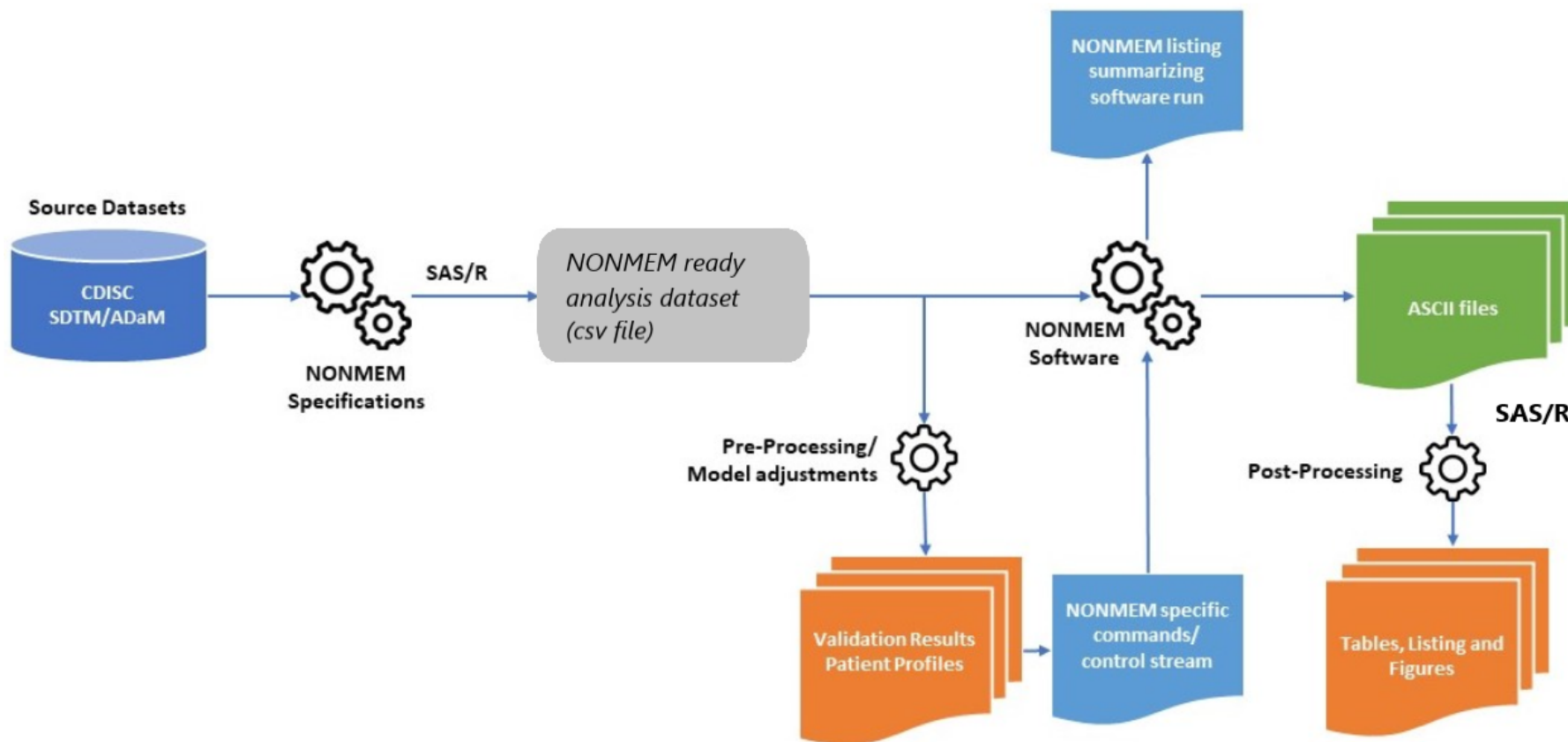
- Exposure-Response (or PKPD) for effectiveness, safety

CTS

- Clinical trial simulations



Analysis pathway



Analysis materials needed for submission

- NONMEM ready **analysis dataset** in XPT format
- NONMEM **control stream** (mod files) *
- NONMEM **output files** (cov, ext & lst files) *
- R scripts* for
 - base and final model evaluation
 - model-based simulations
 - creating TLFs

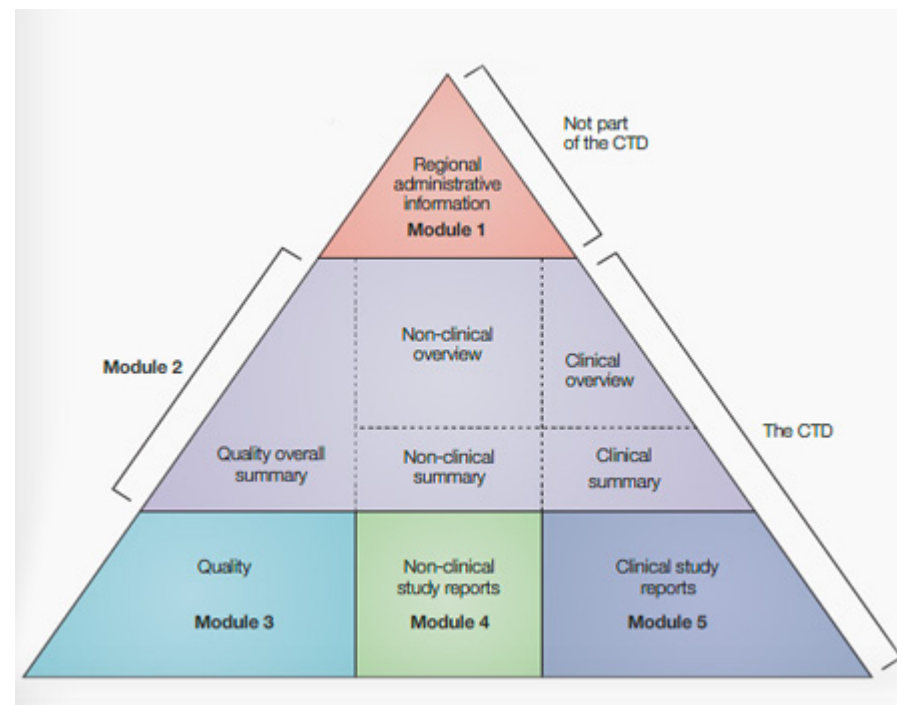
* Submit in ASCII format files

Technical Conformance Guide

<https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/modeldata-format>

In terms of where the code and data should be submitted, the following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1.ctl.txt, run1.lst.txt, plot1.R.txt) with a define pdf file to explain the role of each file

OBSELETE



Dataset recommendations

- SAS Transport Format (XPORT) Version 5
- one dataset per transport file, and the dataset in the transport file should be named the same as the transport file (e.g., 'poppk' and poppk.xpt, 'er' and er.xpt).
- Datasets greater than 5 gigabytes (GB) in size should be split into smaller datasets no larger than 5 GB and should be placed in 'split' folder

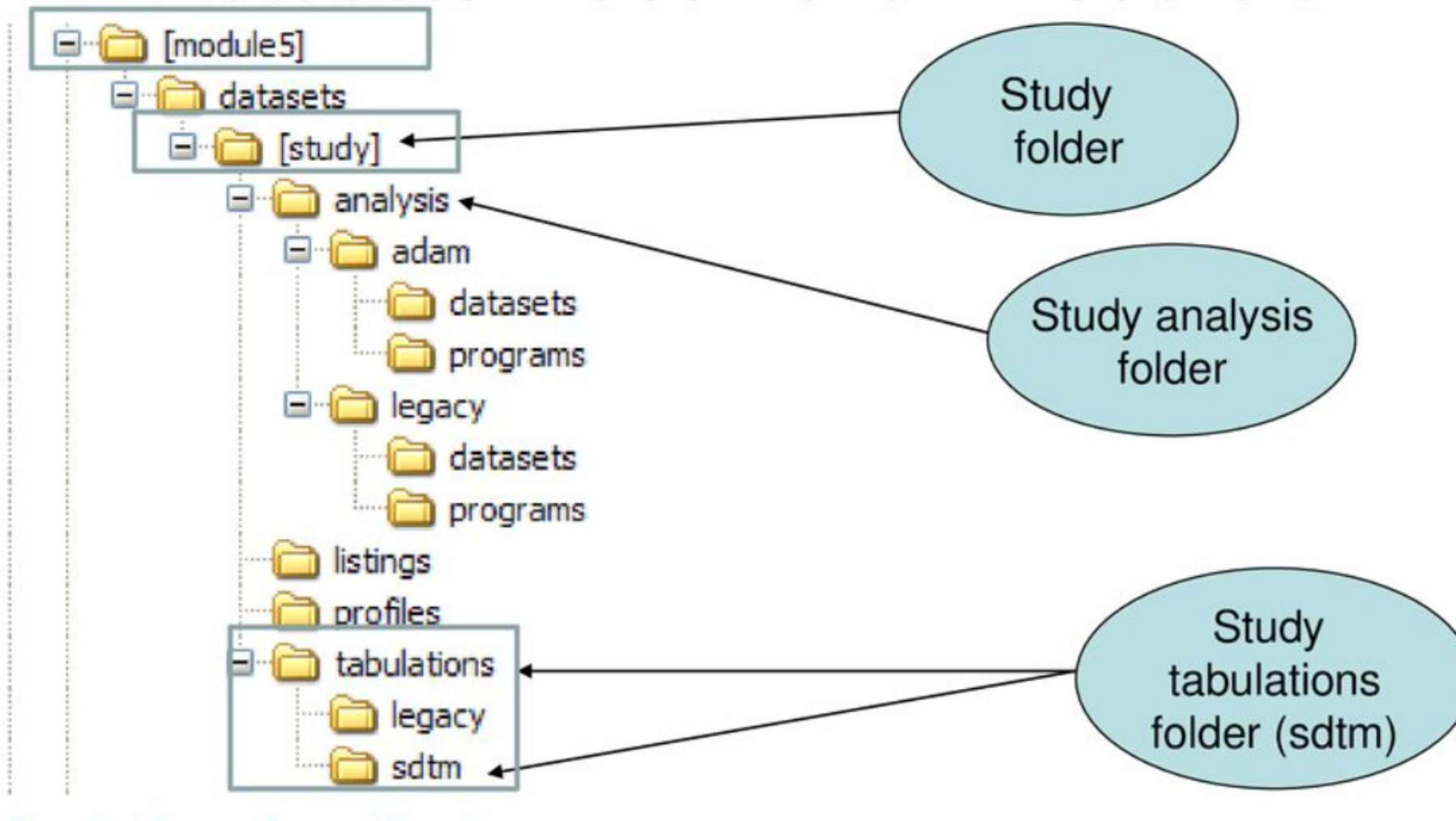
Table 1: Maximum Length of Variables and Dataset Elements

Element	Maximum Length in Characters
Variable Name	8
Variable Descriptive Label	40
Dataset Label	40

- Variable Names - only uppercase letters, numbers, and must start with a letter
- Dataset Names - only lowercase letters, numbers, and must start with a letter
- Variable and Dataset Labels - can include punctuation characters, however, special (unbalanced) characters should not be provided

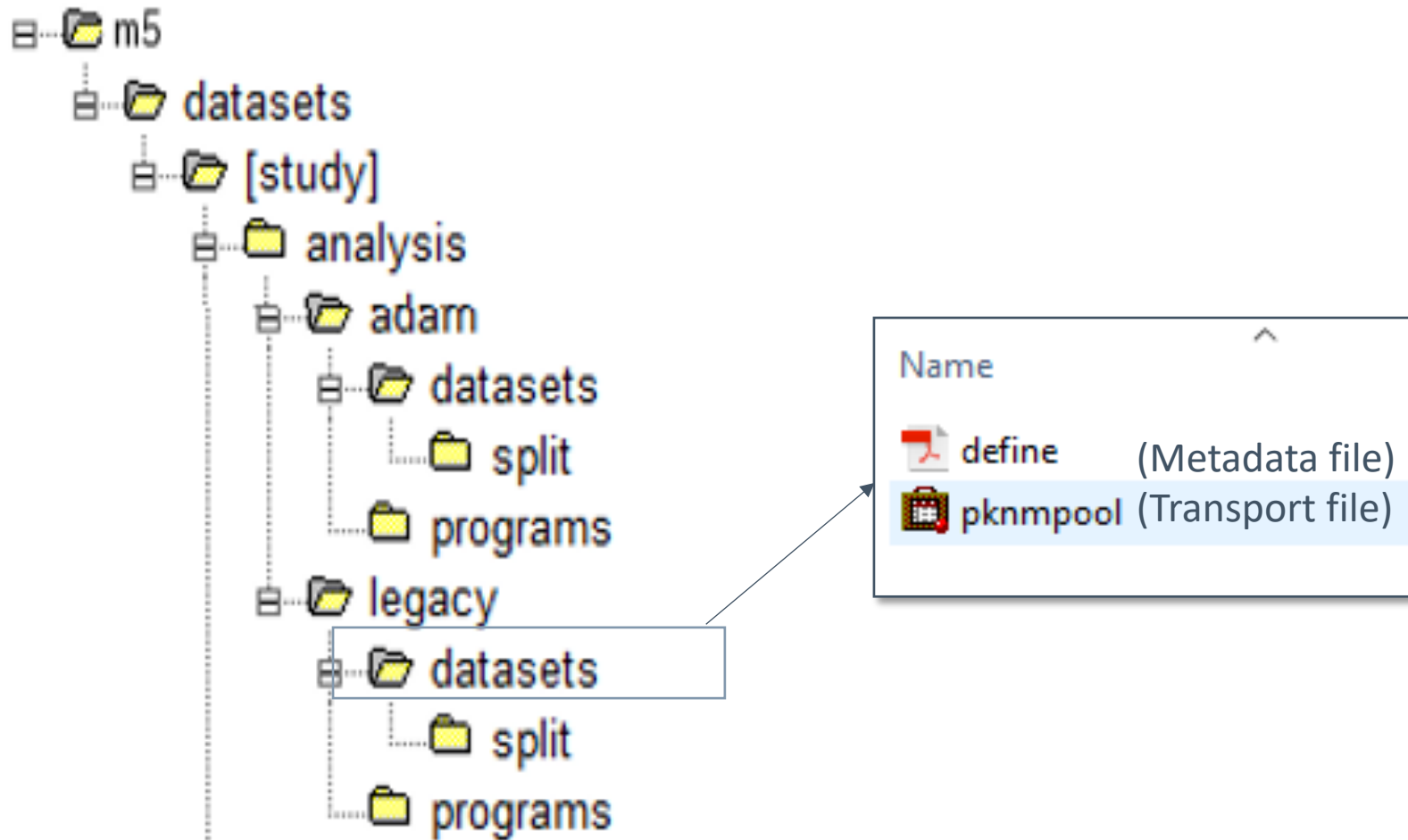
Data and Analysis Submissions

Datasets Placement – Module 5



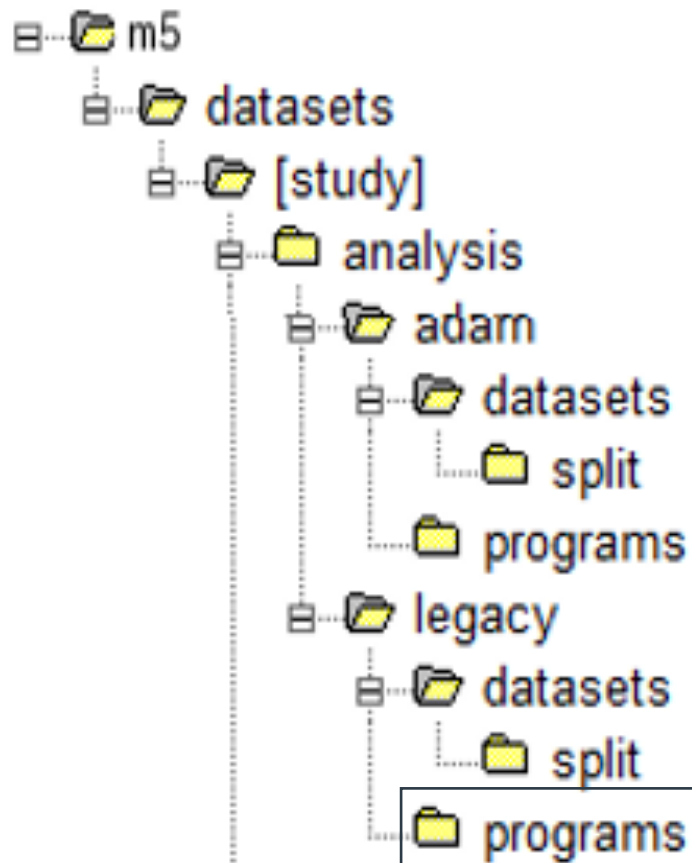
Data submission

Pharmacometric submission materials are always placed under 'legacy' folder



Analysis submission

[study] can be individual study or pooled studies, can be named accordingly –
study123-poppk
Drug-name-poppk



Analysis materials will be stored here

- define
- diagnostics-base-r
- diagnostics-final-r
- revieweraid
- run253-cov
- run253-ext
- run253-lst
- run253-mod
- run253-multi-scm
- run253-tab
- run253-uni-scm

Accompanying documents

Datasets

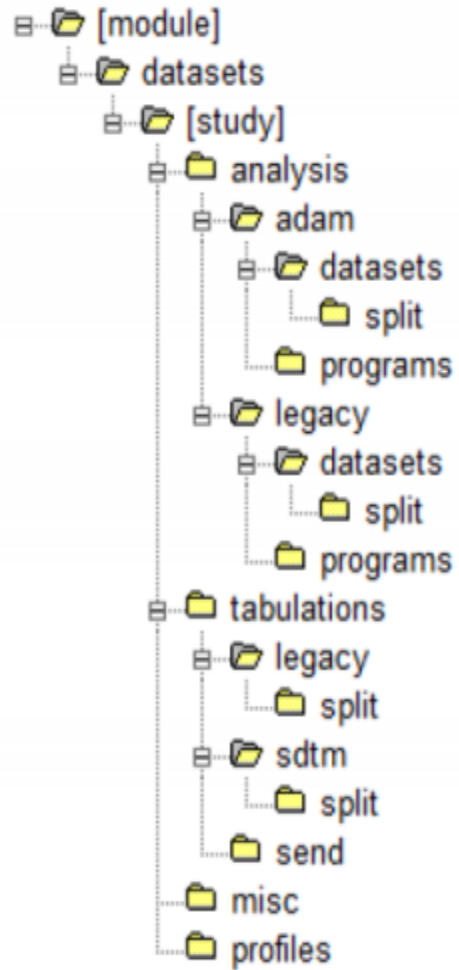
- define.pdf (not define.xml thankfully 😊)

Analyses

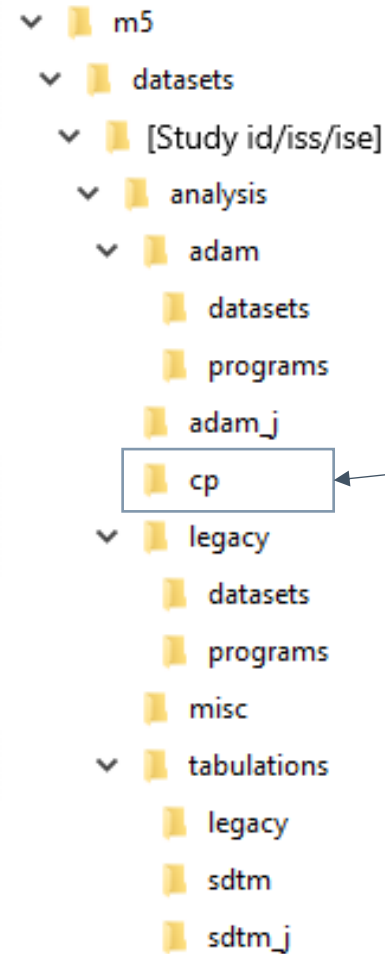
- define.pdf
- revieweraid.pdf (flow of running the code)

Folder Structure: FDA vs. PMDA

FDA



PMDA



PMDA: Low line “_” [U+005F] is allowed for folder and file names

Folder for storing electronic study data on clinical pharmacology in formats other than the CDISC standard.

References

The Benefits of Modeling and Simulation in Drug Development

(accessible at https://www.certara.com/app/uploads/2020/06/WP_BenefitsOfBiosimulation-1-1.pdf)

IN SILICO CLINICAL TRIALS - EXPLAINED!

<https://www.vph-institute.org/news/avicenna-in-silico-clinical-trials-explained.html>

NONMEM Dataset Generation

<https://centreum.com/nonmem/>

Covariate Model Building and Evaluation in NONMEM

<https://www.med.upenn.edu/kmas/Mats/Matsindex.htm>

Data Submissions Douglas Warfield www.fda.gov

STUDY DATA TECHNICAL CONFORMANCE GUIDE (October 2019)

Model/Data Format

(accessible at <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/modeldata-format>)

Electronic Common Technical Document (eCTD):Overview and Submission

https://www.accessdata.fda.gov/cder/eCTD/backgr/backgr/fd_02_01_0030.htm

Process optimization for efficient and smooth e-data submissions to both FDA and PMDA (Sakai, Eri. *et al.* accessible at

<https://pdfs.semanticscholar.org/ad7/ee39ea7f5ee933b44fbe35533d42dee35c01.pdf>)

Revision of Technical Conformance Guide on Electronic Study Data Submissions

<https://www.pmda.go.jp/files/000229468.pdf>

ACKNOWLEDGMENTS

I would like to thank all my colleagues at Certara for their inputs, support and guidance.

Questions?

