AS06

Population PK Data Sets – Basic Concepts and Challenges from the Perspective of a SAS Programmer

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ABSTRACT

Population Pharmacokinetic (Pop PK) Data analysis is a recent requirement in drug submission to the regulatory board. The purpose of Pop PK data set is to support PK modeling and simulation by creating a regulatory compliant NONMEM® data set. In this paper, I will be presenting the basic concepts of Pop PK data set and challenges to create a robust Pop PK data set from SAS® programming perspective.

1. INTRODUCTION

1.1 WHAT IS PHARMACOKINETIC (PK)?

Pharmacokinetic is the science that explains how human bodies react with the drug they consume. The reaction includes Absorption, Distribution, Metabolism, and Excretion. The analysis of PK data not only guides drug development, but it also recommends the tailored dosing for individual therapeutic area. The PK analysis results are influenced by several factors such as:

- Physical Environment (Physicochemical properties of the drug)
- Formulation
- Administration route
- Subject's Health Condition
- Covariates such as subject's Age, Sex, Weight
- Food
- Concomitant Medication

1.2 WHAT IS A POPULATION PK ANALYSIS?

Population PK analysis is defined as the study of plasma drug concentrations between subjects across multiple clinical studies when standard dosage regimens are administered. NONMEM® – ready Population pharmacokinetic (hereafter referred to as Pop PK in short) data set is created to support Pop PK modeling and simulation activities that are necessary to assess drug safety, efficacy, and dose-concentration relationship in target population. NON-Linear Mixed Effects Modeling, also known as NONMEM® in short, is one of the leading tools for Pop PK modeling and simulation. The NONMEM® software requires Pop PK dataset to be in a specific format that includes dosing records with actual dosing date and time, dose amount, drug concentration results, and time dependent or time independent variables. Pop PK data set is produced at different stages during drug development cycle as per PK scientists' needs.

The current interest in Pop PK analysis stems from the concern that the PK of new drugs are not studied in relevant populations that is likely to receive the drug at an early enough stage in the drug development program. Recently, Pop PK reports have been an integral part of regulatory submissions and agencies like Food and Drug Administration (FDA) require Pop PK data in transport files generated from SAS® Data sets.

1.3 WHAT ARE THE DIFFERENCES BETWEEN INDIVIDUAL PK AND POP PK DATA ANALYSIS?

Individual PK and Pop PK are two different analysis techniques used to analyze Pharmacokinetic data set. Each method is useful, and each has its advantages and disadvantages. The important features of both techniques are as follows:

Individual PK data set

- It is simple, robust, and uses graphical techniques to display the results.
- It is independent of model and uses data sets from Phase I studies.
- It is not used for predictive work and the analysis time is short.

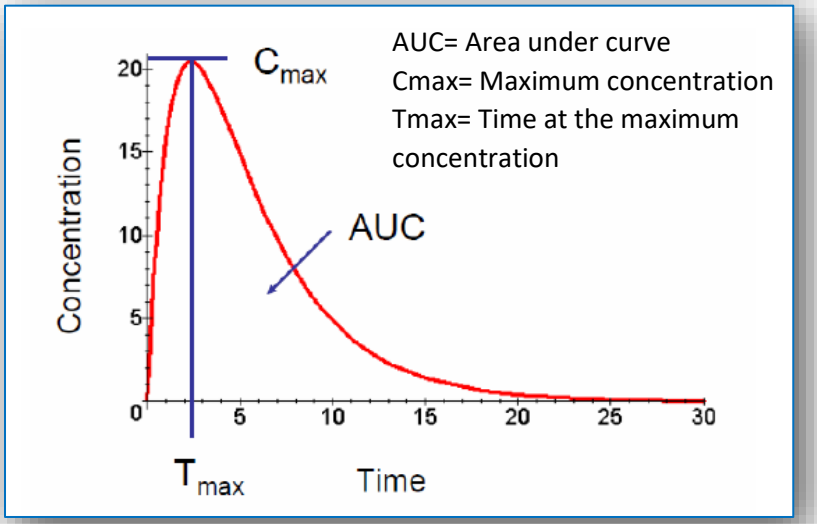


Figure 1: Individual PK Analysis

Pop PK Data set

- It is robust and supports modeling and simulation. It is descriptive and predictive.
- It evaluates the entire population across several clinical studies and determines clearance, volume of distribution, and effect covariates such as age, sex, weight.
- Due to a large and sparse data, the analysis time is longer. Analysis requires SMEs.

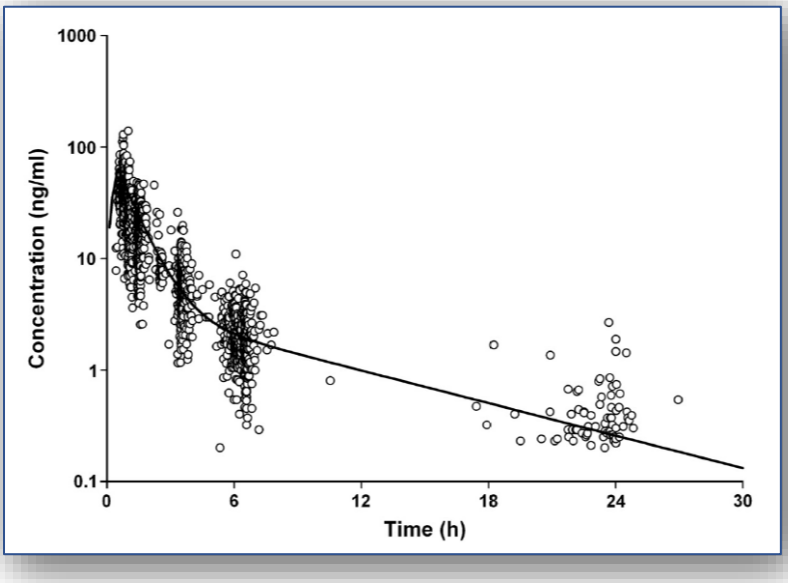


Figure 2: Pop PK Analysis

2. POP PK DATA SET COMPONENTS, VALIDATION, AND STANDARDS

2.1 DATA SET COMPONENTS

Pop PK data set contains required components as well as optional components.

Required components:

- Dosing Data
- PK Concentration Data

Optional components:

- Lab Data
- Biomarker and Efficacy Data
- Demographics Data
- Concomitant Medication Data
- Vital Signs Data
- Antibody Data
- Subject Disposition
- Adverse Events

2.2 DATA VALIDATION

Data validation ensures that the data is accurate and complete, the times of concentration and dosage are accurately recorded in the data, and the data is cross-checked against original patient records. If the data is either missing or incomplete either due to the medical device malfunction or protocol deviations or human error, imputation is necessary and the appropriate rules for imputation are provided in the study documents. Listed below are a few examples of imputation rules:

- Missing dose time information is handled on a case by case basis by imputing it based on prior dosing times or based on recorded PK collection times.
- Missing time for PK sample collection is handled on a case by case basis by imputing it on the dose time and or times of other PK sample collection.
- If drug concentration is missing or below lower limit of quantification, MDV is set to missing.

There are several techniques to validate Pop PK data set. The most common practices are as follows:

- Create independent validation code
- Include proc compare in the validation code
- Isolate each study
- Select the records with key variables
- Check sort order
- Match number of observations
- Validate standard variables
- Validate key variables
- Provide proc compare results and specific details related to differences to production programmer
- Check for program log issues

2.3 DATA STANDARD

Recently, Clinical Data Interchange Standards Consortium (CDISC) standards have been adopted for Pharmacokinetic data. The structure of pharmacokinetic concentrations (PC), pharmacokinetic parameter (PP) SDTM data sets are one record per subject per time point or pharmacokinetic parameter. Analysis – ready, ADPC, and ADPP are based on BDS structure of CDISC ADaM and are created for the purpose of generating displays and for statistical analysis.

Although CDISC ADaM standards for Pop PK data set do not exist, ADaM BDS variables provide sufficient flexibility to support PK analysis. It is critical to maintain consistent standard and data set structure across studies when they are integrated to create a Pop PK analysis data set. With the sponsorship of International Society of Pharmacometrics (ISoP), draft standards for Pop PK data developed by the standards group have completed open review process and the team is planning to hand over the final draft of the standards to CDISC. The industry wide standards for Pop PK data will certainly

provide several benefits such as minimize variability in source data handling rules and algorithms, bring efficiency in programming and consistency across studies and allow the creation of web-based specifications, automated programming and quality control processes.

3. CURRENT PROCESS

Creation of Pop PK data set involves contributions from numerous functions such as Clinical Data Management, Statistics and Programming, Clinical Pharmacology Modeling and Simulation. Clinical Data Management group receives, cleans, and loads data into clinical database from case report forms (CRFs), local and central labs and transfers them to different departments making sure the trial information is blinded. The treatment codes and PK concentration are only released at Database lock (DBL) unless there is early un-blinding to Pop PK data set programmers. Upon receipt of PK samples from different vendors, they are sent to sponsors or other functions within the company by protecting sensitive information. For PK, the sensitive information is shuffled through scrambling so that subject identification or treatment assignments cannot be determined. Techniques used to shuffle PK data should not alter the structure, attributes and formats of the original data. During the data cleaning, data set specifications, input data sets, and Pop PK data set program go through multiple iterations to include changes in the source data sets. The unblinding of PK concentration after DBL leads to more changes in Pop PK data set specifications and SAS® program codes.

A list of studies to be pooled, components and covariates to be included, handling of un-blinded and missing data, modeling methods and strategies, definitions, and milestones are explained in PK analysis plan. Once the specification for Pop PK data set is created and source data sets are ready, Pop PK programming activities start. Several back and forth discussions between Pop PK programmers and PK scientists on the available source data and specification during the data set program development stage could lead to specification and data set program updates.

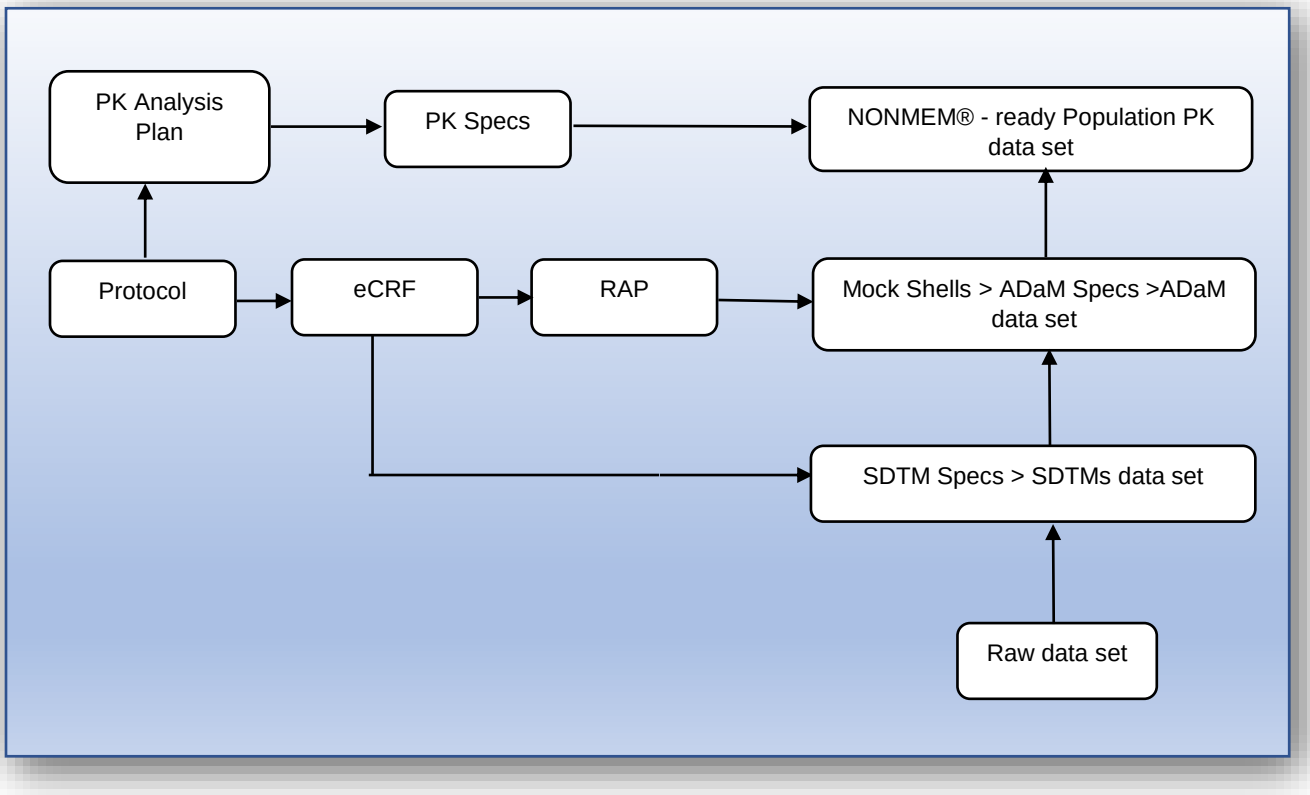


Figure 3: NONMEM® - ready Pop PK data set Workflow

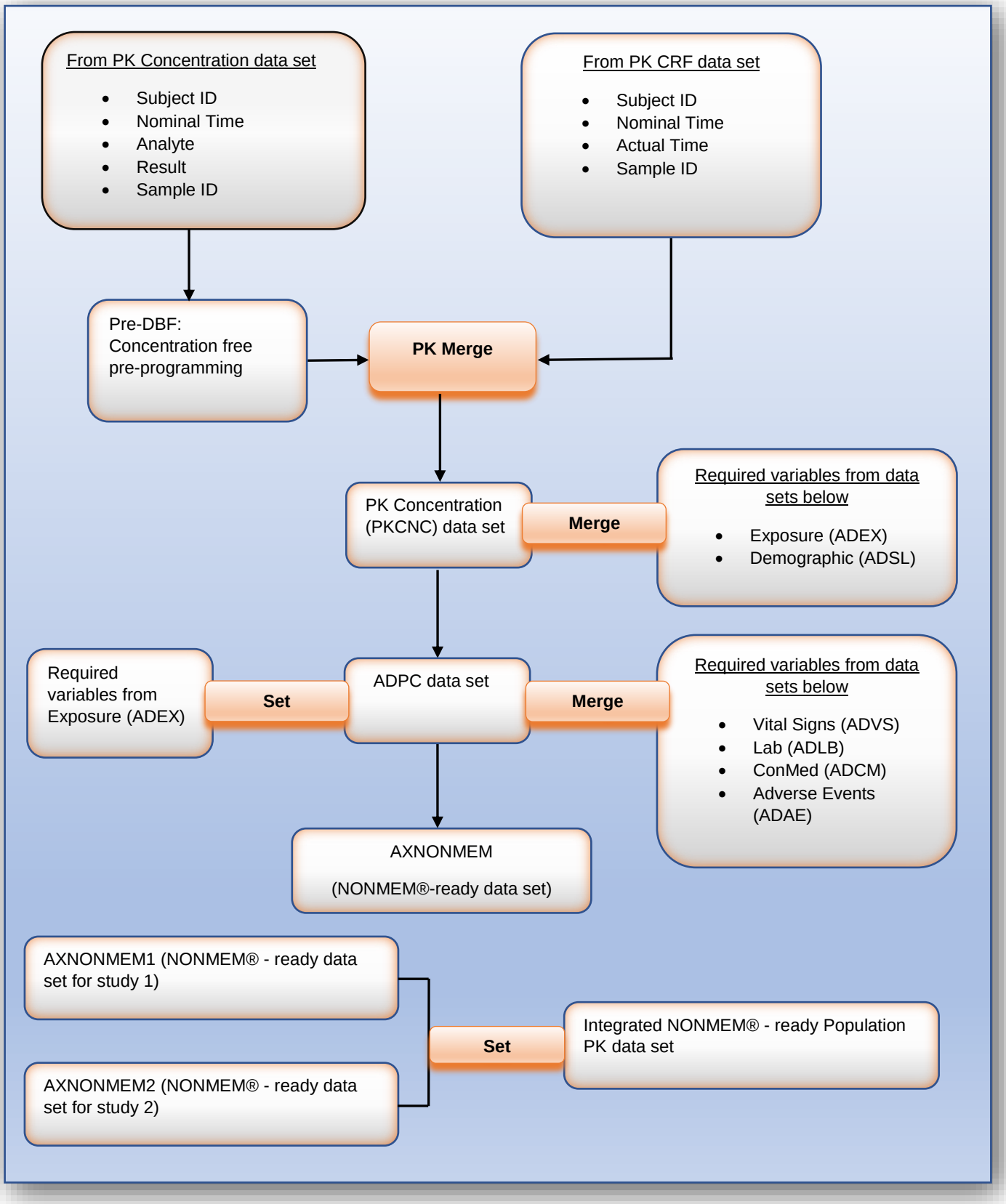


Figure 4: Current process to create Integrated NONMEM® - ready Pop PK data set

4. POP PK NONMEM® SPECIFIC REQUIRED VARIABLES

ID	STUDYID	SUBJID	CMT	EVID	AMT	II	SS	RATE	MDV
1	ABC123456	1	2	0	0	0	0	0	1
1	ABC123456	1	1	1	50	0	0	-2	1
1	ABC123456	1	2	0	0	0	0	0	1
1	ABC123456	1	2	0	0	0	0	0	1
1	ABC123456	1	2	0	0	0	0	0	0
1	ABC123456	1	1	1	200	0	0	-2	1
1	ABC123456	1	2	0	0	0	0	0	0
1	ABC123456	1	2	0	0	0	0	0	0
1	ABC123456	1	2	0	0	0	0	0	0
1	ABC123456	1	2	0	0	0	0	0	0
2	ABC123456	2	2	0	0	0	0	0	1
2	ABC123456	2	1	1	10	0	0	-2	1
2	ABC123456	2	2	0	0	0	0	0	1
2	ABC123456	2	2	0	0	0	0	0	0
2	ABC123456	2	2	0	0	0	0	0	0
3	ABC123456	3	2	0	0	0	0	0	1
3	ABC123456	3	1	1	10	0	0	-2	1
3	ABC123456	3	2	0	0	0	0	0	0
3	ABC123456	3	2	0	0	0	0	0	0
3	ABC123456	3	2	0	0	0	0	0	0

4.1 ID - NONMEM® SUBJECT IDENTIFIER

It is a sequential subject identifier across study after data is sorted by STUDYID, SUBJID, DATE, CMT, EVID. It is entered in all rows for each subject.

4.2 EVID – NONMEM® EVENT ID

It identifies the kind of event the records belong to by assigning them categories. The two available categories are: EVID=1 for records that belong to the Dosing event and EVID=0 for the observation records.

4.3 DV – DEPENDENT VARIABLE

This is a value of an observation. For dosing records and missing results or the results that are below LOQ (NQ), assign the result as missing (“.”). For other observation records, assign the numeric result of the sample or assessment.

4.4 MDV – NONMEM® MISSING DATA VALUE

For the observation record, assign a value of 0.
For the record that does not contain a value of an observation, assign a value of 1. For example: Dosing records or Pharmacokinetic record with result lower than LOQ (NQ).

4.5 CMT – NONMEM® COMPARTMENT CODE

Compartment codes for observation or dosing records. CMT=1 for Dosing records and CMT=2 for observation records.

4.6 AMT – NONMEM® AMOUNT OF DRUG ADMINISTERED

For the dosing records, the actual total dose amount administered to a subject is entered. For other records, assign 0 or missing (“.”).

4.7 RATE – RATE OF DRUG INFUSION

4.8 II – NONMEM® Inter-dose interval

It is defined as the time between implied doses.

4.9 SS – STEADY – STATE DATA ITEM

It implies that the dose and regimen combination is at steady-state and the assigned values are either 0 or 1.

5. POP PK TIME RELATED VARIABLES

ID	STUDYID	SUBJID	DATETIME	NOMT	NOMTLD	RTFD	RTLD
1	ABC123456	1	11/09/2009 08:55:00	.	.	-0.083333333	.
1	ABC123456	1	11/09/2009 09:00:00	0	0	0	0
1	ABC123456	1	11/09/2009 09:15:00	0.25	0.25	0.25	0.25
1	ABC123456	1	11/09/2009 09:30:00	0.5	0.5	0.5	0.5
1	ABC123456	1	11/09/2009 10:00:00	1	1	1	1
1	ABC123456	1	11/23/2009 09:00:00	336	0	336	0
1	ABC123456	1	11/23/2009 09:15:00	336.25	0.25	336.25	0.25
1	ABC123456	1	11/23/2009 09:30:00	336.5	0.5	336.5	0.5
1	ABC123456	1	11/23/2009 10:02:00	337	1	337.03333333	1.0333333333
1	ABC123456	1	11/23/2009 11:00:00	338	2	338	2
2	ABC123456	2	10/26/2009 09:55:00	.	.	-0.083333333	.
2	ABC123456	2	10/26/2009 10:00:00	0	0	0	0
2	ABC123456	2	10/26/2009 10:16:00	0.25	0.25	0.2666666667	0.2666666667
2	ABC123456	2	10/26/2009 10:30:00	0.5	0.5	0.5	0.5
2	ABC123456	2	10/26/2009 11:01:00	1	1	1.0166666667	1.0166666667
3	ABC123456	3	10/26/2009 10:55:00	.	.	-0.083333333	.
3	ABC123456	3	10/26/2009 11:00:00	0	0	0	0
3	ABC123456	3	10/26/2009 11:15:00	0.25	0.25	0.25	0.25
3	ABC123456	3	10/26/2009 11:30:00	0.5	0.5	0.5	0.5
3	ABC123456	3	10/26/2009 12:01:00	1	1	1.0166666667	1.0166666667

5.1 DATETIME – DATE AND TIME OF RECORD

Date of record is in date format of mm/dd/yyyy (e.g., 12/30/2019). Time of record is in hh:mm:ss format (e.g., 04:30:25).

5.2 NOMT – NOMINAL TIME SINCE FIRST IP (INVESTIGATIONAL PRODUCT) DOSE

It represents scheduled time of study relative to first dose. For the first dosing records, assign NOMT=0.

5.3 NOMTLD – NOMINAL TIME SINCE LAST IP DOSE PRIOR TO SAMPLE

It represents scheduled time of study relative to last IP dose prior to sample. For dosing records, assign NOMTLD=0

5.4 RTFD – RELATIVE TIME FROM FIRST IP DOSE TO CURRENT SAMPLE TIME

It is the actual time from first dose of IP.

5.5 RTLD – RELATIVE TIME FROM LAST IP DOSE PRIOR TO SAMPLE

It is the actual time from last dose of IP prior to sample.

6. CHALLENGES IN POP PK DATA SET CREATION FROM PROGRAMMING PERSPECTIVE

6.1 INCONSISTENCIES IN INPUT DATA SET STRUCTURE AND STANDARDS

Extra time and efforts are needed from Pop PK programmers if there are inconsistencies between source data set structures and formats. For instance, If the PK concentration data set structure is not consistent with the structure of the CRF PK data set, then it becomes necessary to manipulate them so that they can be merged.
Another layer of complexity is added to Pop PK programming if there are no consistent standards such as imputation rules, inclusion and exclusion criteria across studies. Thus, it is important to use industry wide consistent rules and algorithms to minimize the variability on how PK teams across Pharmaceutical industry handle data issues. The industry wide consistent standards will also help bring efficiency in programming and consistency across studies and compounds because Pop PK analysis is done on a pooled dataset from several studies.

6.2 FREQUENT CHANGES TO THE SPECIFICATION

PK scientists create Pop PK specifications from the study protocols and the CRFs before the real data is available. The initial specifications do not cover all data scenarios in a study and frequent changes to specification occur throughout the Pop PK data set creation process necessitating multiple reviews by the programming and PK team which might impact critical timelines.

6.3 AVAILABILITY OF PK CONCENTRATION DATA

PK concentration data is available only after DBF but, the Pop PK programmers have to prepare program codes ahead of time without the real concentration data and they need to get acquainted with the real data as soon as it is available. The completeness of input data set drives the entire process and therefore the data management activities such as data cleanup, issue resolution etc. should be aligned with the Pop PK data development timelines.

6.4 DATA PROCESSING TIME

Data processing time for integrated Pop PK data set is long due to the volume of the data. The processing time also varies depending upon the number of studies being integrated.

6.5 SCRAMBLING

The data after scrambling is not realistic and not as per the expectation of PK scientist. Initial setup is time consuming and requires extra resources from multiple functions.

7. CONCLUSION

Pop PK data analysis occurs throughout the life cycle of the clinical study/studies. The results from Pop PK analysis is critical for determining the long-term dosing regimen for future patients. Programs and models are prepared well in advance so that final Pop PK analysis reports can be submitted to regulatory agencies on time. However, changes in source data sets at different stages demand extra time and efforts from several functions jeopardizing critical timelines. To meet aggressive timelines and several challenges, thorough guidelines are important for a dedicated Programming group that understands source data issues, complicated derivations and NONMEM® modeling concepts and requirements. Due to lack of consistent standards, there is still a lot of variability on how different companies create Pop PK datasets. Therefore, an industry wide standard has become necessary.

APPENDIX – EXAMPLE OF A NONMEM® - READY POP PK DATA SET

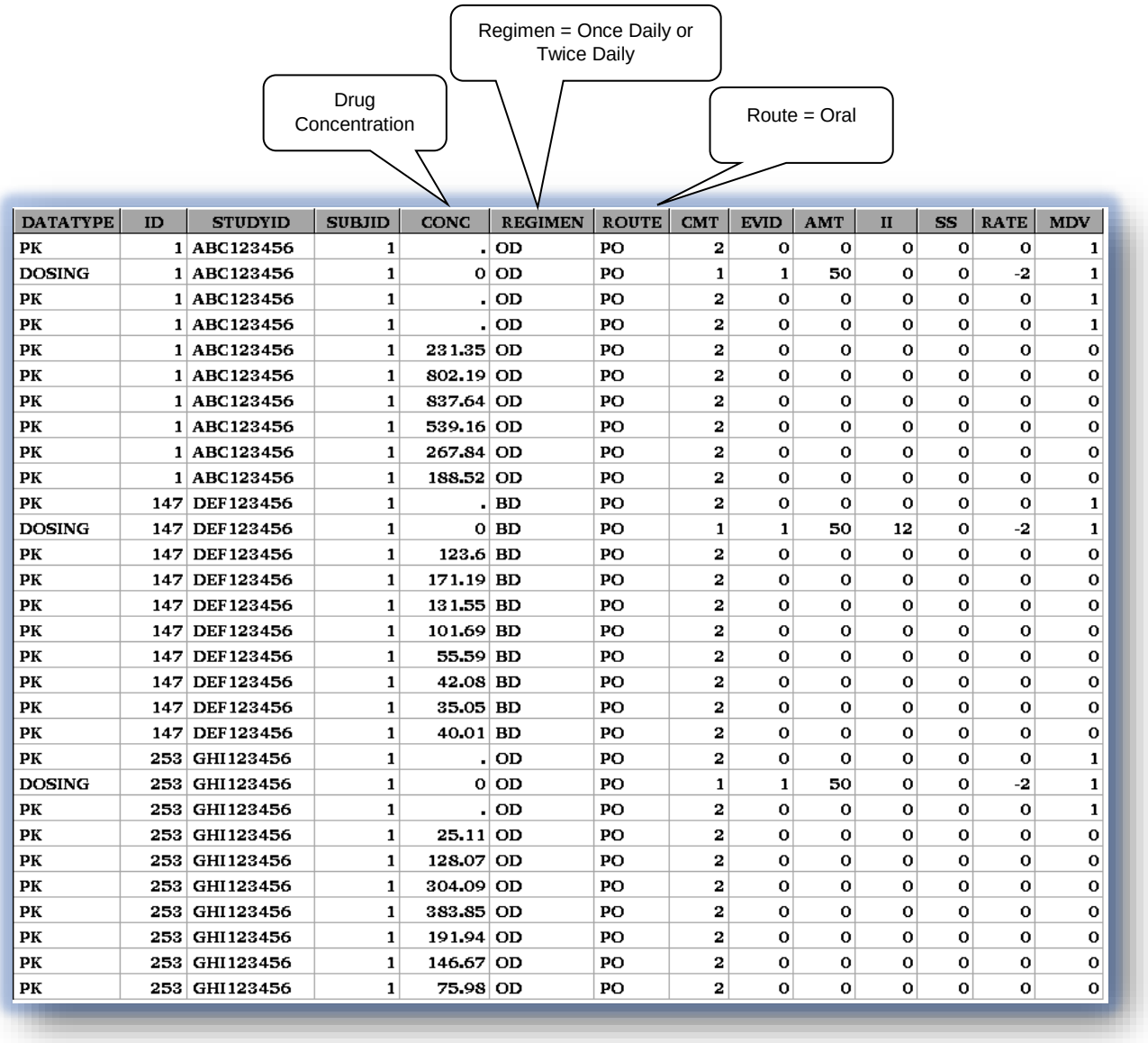
Use of Proton Pump Inhibitor

Baseline Creatinine Clearance

DATATYPE	ID	STUDYID	SUBJID	AGE	SEX	RACE	HT	WT	BMI	CMED	PPI	CRCL	FOOD	SMOKE
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
DOSING	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
DOSING	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker
DOSING	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker
PK	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker
PK	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker
PK	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker
PK	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker
PK	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker
PK	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker
PK	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker
PK	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker

Notes/Consideration:

- Creatinine Clearance (CRCL) is calculated based on the Cockcroft-Gault equation.
  Clearance is defined as the volume of plasma which is completely cleared of drug per unit time.
- Unit for CRCL is mL/min
- If CRCL='.' then impute to -99
- Blood volume of distribution (Vd) is calculated as the ratio of the total amount of drug in body and the concentration of drug in blood.



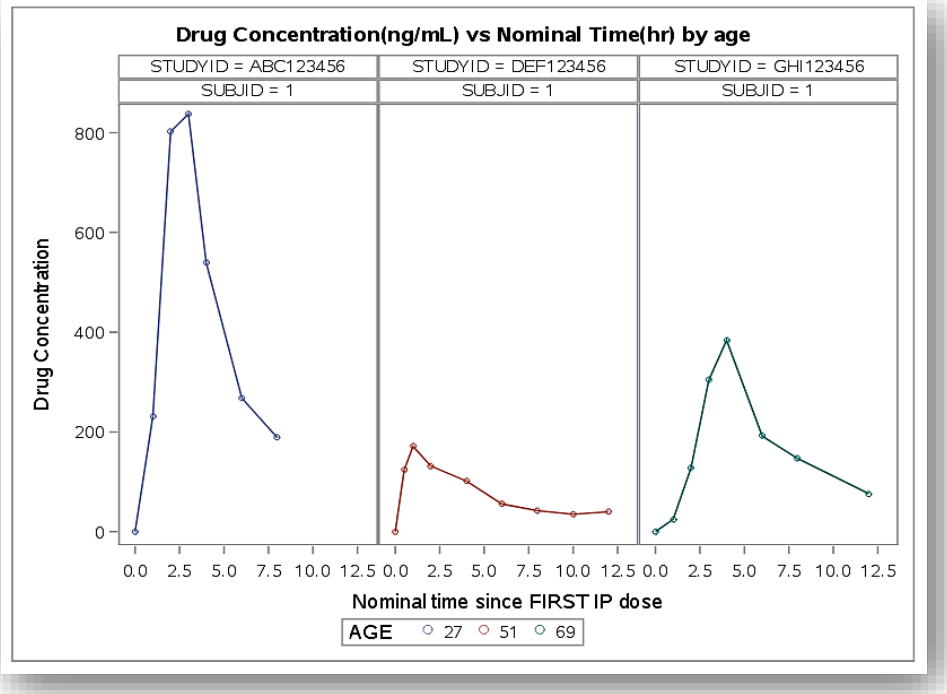
DATATYPE	ID	STUDYID	SUBJID	CONC	REGIMEN	ROUTE	CMT	EVID	AMT	II	SS	RATE	MDV
PK	1	ABC123456	1	.	OD	PO	2	0	0	0	0	0	1
DOSING	1	ABC123456	1	0	OD	PO	1	1	50	0	0	-2	1
PK	1	ABC123456	1	.	OD	PO	2	0	0	0	0	0	1
PK	1	ABC123456	1	.	OD	PO	2	0	0	0	0	0	1
PK	1	ABC123456	1	231.35	OD	PO	2	0	0	0	0	0	0
PK	1	ABC123456	1	802.19	OD	PO	2	0	0	0	0	0	0
PK	1	ABC123456	1	837.64	OD	PO	2	0	0	0	0	0	0
PK	1	ABC123456	1	539.16	OD	PO	2	0	0	0	0	0	0
PK	1	ABC123456	1	267.84	OD	PO	2	0	0	0	0	0	0
PK	1	ABC123456	1	188.52	OD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	.	BD	PO	2	0	0	0	0	0	1
DOSING	147	DEF123456	1	0	BD	PO	1	1	50	12	0	-2	1
PK	147	DEF123456	1	123.6	BD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	171.19	BD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	131.55	BD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	101.69	BD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	55.59	BD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	42.08	BD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	35.05	BD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	40.01	BD	PO	2	0	0	0	0	0	0
PK	253	GHI123456	1	.	OD	PO	2	0	0	0	0	0	1
DOSING	253	GHI123456	1	0	OD	PO	1	1	50	0	0	-2	1
PK	253	GHI123456	1	.	OD	PO	2	0	0	0	0	0	1
PK	253	GHI123456	1	25.11	OD	PO	2	0	0	0	0	0	0
PK	253	GHI123456	1	128.07	OD	PO	2	0	0	0	0	0	0
PK	253	GHI123456	1	304.09	OD	PO	2	0	0	0	0	0	0
PK	253	GHI123456	1	383.85	OD	PO	2	0	0	0	0	0	0
PK	253	GHI123456	1	191.94	OD	PO	2	0	0	0	0	0	0
PK	253	GHI123456	1	146.67	OD	PO	2	0	0	0	0	0	0
PK	253	GHI123456	1	75.98	OD	PO	2	0	0	0	0	0	0

Notes/Consideration:

- Assign CONC=0 for dosing records.
- No sample (NS), insufficient sample (IS) and no result (NR) records are excluded from data set.
- CONC='.' for PK records < LOQ (i.e. if drug conc is NQ).
- Unit for CONC is ng/mL

Hour is the unit of Time Dependent Variables – NOMT, NOMTLD, RTFD, RTLD

DATATYPE	ID	STUDYID	SUBJID	DATETIME	DAY	NDAY	NOMT	NOMTLD	RTFD	RTLD
PK	1	ABC123456	1	11/09/2009 08:55:00	1	.	.	.	-.08	.
DOSING	1	ABC123456	1	11/09/2009 09:00:00	1	1	0	0	0	0
PK	1	ABC123456	1	11/09/2009 09:15:00	1	1	0.25	0.25	0.25	0.25
PK	1	ABC123456	1	11/09/2009 09:30:00	1	1	0.5	0.5	0.5	0.5
PK	1	ABC123456	1	11/09/2009 10:00:00	1	1	1	1	1	1
PK	1	ABC123456	1	11/09/2009 11:00:00	1	1	2	2	2	2
PK	1	ABC123456	1	11/09/2009 12:00:00	1	1	3	3	3	3
PK	1	ABC123456	1	11/09/2009 13:00:00	1	1	4	4	4	4
PK	1	ABC123456	1	11/09/2009 15:00:00	1	1	6	6	6	6
PK	1	ABC123456	1	11/09/2009 17:00:00	1	1	8	8	8	8
PK	147	DEF123456	1	04/11/2014 08:43:00	1	.	.	.	-.37	.
DOSING	147	DEF123456	1	04/11/2014 09:05:00	1	1	0	0	0	0
PK	147	DEF123456	1	04/11/2014 09:34:00	1	1	0.5	0.5	0.48	0.48333
PK	147	DEF123456	1	04/11/2014 10:04:00	1	1	1	1	0.98	0.98333
PK	147	DEF123456	1	04/11/2014 11:04:00	1	1	2	2	1.98	1.98333
PK	147	DEF123456	1	04/11/2014 13:04:00	1	1	4	4	3.98	3.98333
PK	147	DEF123456	1	04/11/2014 15:04:00	1	1	6	6	5.98	5.98333
PK	147	DEF123456	1	04/11/2014 17:04:00	1	1	8	8	7.98	7.98333
PK	147	DEF123456	1	04/11/2014 19:04:00	1	1	10	10	9.98	9.98333
PK	147	DEF123456	1	04/11/2014 21:01:00	1	1	12	12	11.9	11.9333
PK	253	GHI123456	1	11/13/2011 08:59:00	1	.	.	.	-.02	.
DOSING	253	GHI123456	1	11/13/2011 09:00:00	1	1	0	0	0	0
PK	253	GHI123456	1	11/13/2011 09:30:00	1	1	0.5	0.5	0.5	0.5
PK	253	GHI123456	1	11/13/2011 10:00:00	1	1	1	1	1	1
PK	253	GHI123456	1	11/13/2011 11:00:00	1	1	2	2	2	2
PK	253	GHI123456	1	11/13/2011 12:00:00	1	1	3	3	3	3
PK	253	GHI123456	1	11/13/2011 13:00:00	1	1	4	4	4	4
PK	253	GHI123456	1	11/13/2011 15:00:00	1	1	6	6	6	6
PK	253	GHI123456	1	11/13/2011 17:00:00	1	1	8	8	8	8
PK	253	GHI123456	1	11/13/2011 21:00:00	1	1	12	12	12	12



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TRADEMARKS