PharmaSUG 2019 - Paper SS-172

Pharmacokinetic Parameters for Sparse and Intensive Sampling – Nonclinical and Clinical Studies

Shallabh Mehta, PPD

ABSTRACT

Sparse sampling is very common in toxicokinetic studies, where a single blood sample can be collected on a given study day from each animal in a treatment group. Similar case can be seen in a clinical study where not more than one sample can be taken from a human on each study or study day mainly because of the nature of the study for example pediatric or because of difficult procedures involved in obtaining the samples. The purpose of this paper is to present how the process of transforming pharmacokinetic (PK) parameters to Clinical Data Interchange Standards Consortium (CDISC) Standard for Exchange of Nonclinical Data (SEND) Pharmacokinetics Parameters (PP), can be used for CDISC Study Data Tabulation Model Version 1.5 (SDTM) PP, specifically how the pooled PK parameters are formatted to SEND and SDTM PP domains using SEND Implementation Guide 3.1 and SDTM Implementation Guide 3.2.

INTRODUCTION

Pharmacokinetics is described as what the body does to a drug and further refers to the movement of drug into, through and out of the body - the time course of the drug's absorption, distribution, metabolism, and excretion (ADME). In preclinical animal studies, it's not always possible to take excessive blood samples during the study especially from small animals with low available body volumes. In these cases, blood samples from animals in a treatment group are pooled together at predefined timepoints to generate PK parameters from a profile made from samples pooled from multiple animals to characterize the drug exposure in the animal. We see similar cases in clinical studies. Sampling for drug concentrations is usually done in plasma, but for some drugs it is important to determine the drug concentrations at a site of action that is difficult to access. For example, an antibiotic to treat pneumonia needs to reach lung tissue to have its primary effect. Sampling from some tissues can be intrusive, causing the subject discomfort or creating safety issues. Sometimes the sampling process can also be difficult to perform without special training. For example, a drug might need to reach muscle tissue, requiring a muscle biopsy for direct measurement. Similar to the preclinical studies each subject will provide a sample at a prespecified time point for testing and then the samples from multiple subjects at the same time point in each treatment group will be used to construct a singular pooled PK profile and determine the related PK parameters. POOLID is available in SEND Implementation Guide 3.1 to cover cases like these. SDTM Implementation Guide 3.2 mentions POOLID may be used in SDTM PP for similar cases in clinical studies. The paper shows how this approach can be used to generate SDTM PP when pooled data from different subjects are used to generate pooled PK parameters.

UNDERSTANDING PK CONCENTRATIONS AND PK PARAMETERS

PK concentrations are measured at specific times relative to dosing. Based on these concentrations, PK parameters are calculated using non-compartmental (NCA) PK analysis in

Phoenix® WinNonlin® (Certara USA, Inc., Princeton, NJ, USA) or SAS®. Below is an example of PK concentrations being measured at specific timepoints relative to dosing.

Study ID	Subject No.	Group	Matrix	Scheduled Time	Concentrations(ng/mL)
ABC	101	DAY 1	Plasma	Predose	0.0
ABC	101	DAY 1	Plasma	20 mins post-dose	144.8
ABC	101	DAY 1	Plasma	40 Minutes Post-dose	447.8
ABC	101	DAY 1	Plasma	1 hour post-dose	682.0
ABC	101	DAY 1	Plasma	1 hour 5 Minutes post-dose	1024.0
ABC	101	DAY 1	Plasma	1 hour 20 Minutes post-dose	2721.4
ABC	101	DAY 1	Plasma	1.5 hours post-dose	2400.0
ABC	101	DAY 1	Plasma	2 hours post-dose	2000.0
ABC	101	DAY 1	Plasma	3 hours post-dose	1600.0
ABC	101	DAY 1	Plasma	4 hours post-dose	1200.0
ABC	101	DAY 1	Plasma	6 hours post-dose	800.0
ABC	101	DAY 1	Plasma	8 hours post-dose	400.0
ABC	101	DAY 1	Plasma	12 hours post-dose	200.0
ABC	101	DAY 1	Plasma	24 hours post-dose	100.0

Table 1 Pharmacokinetic Sampling Profile

PK parameters are a measure of exposure to an analyte based on the concentration of drug over time in the body. Cmax is the is defined as the highest observed concentration of the drug after dosing in a concentration-time profile and Tmax is the time at which the Maximum Concentration is observed. Area Under the Curve (AUC) represents the total drug exposure integrated over time and is the area under the curve of concentrations from time 0 to last time point (24 hours) as illustrated in the example below.

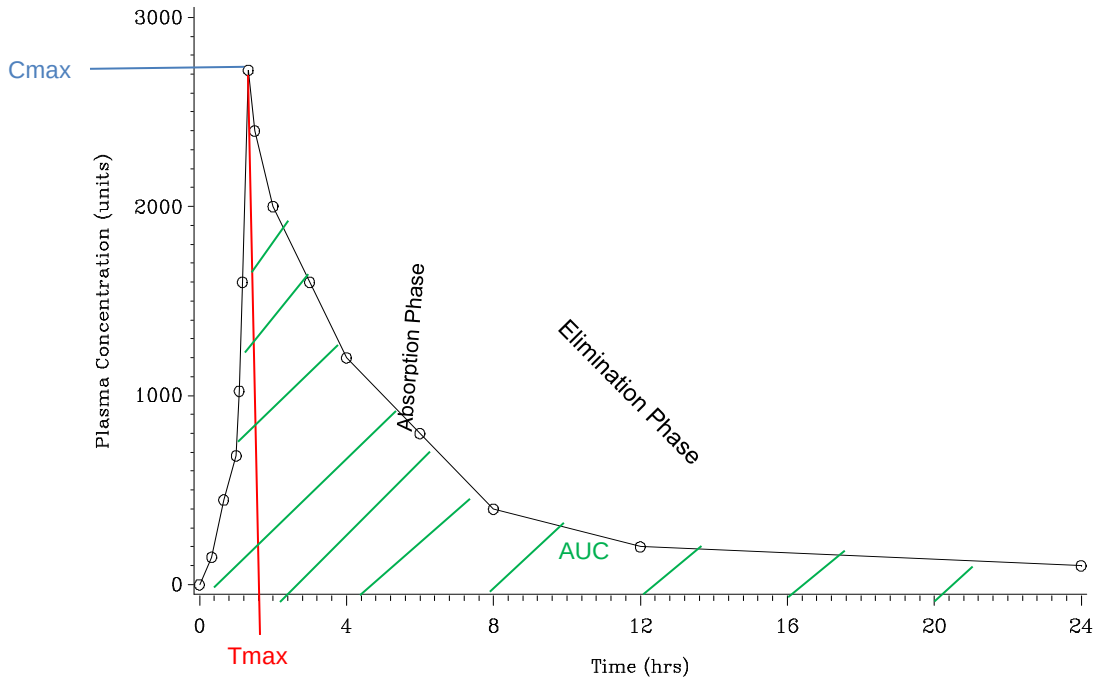

Figure 1 PK Concentrations vs Time Plot

SPARSE SAMPLING

Sparse samples are taken when only a single sample or few samples can be taken from a subject on each study or study day. In these studies, concentrations are pooled from different subjects into 1 PK profile which is used to generate pooled PK parameters.

StudyID	Subject No.	Group	Matrix	Scheduled Time	Concentrations (ng/mL)
ABC	101	DAY 1	Plasma/Fluid	Pre-dose	0
ABC	102	DAY 1	Plasma/Fluid	0.5 hours post-dose	10.0
ABC	103	DAY 1	Plasma/Fluid	1 hour post-dose	20.0
ABC	104	DAY 1	Plasma/Fluid	1.5 hours post-dose	40.0
ABC	105	DAY 1	Plasma/Fluid	2 hours post-dose	60.0
ABC	106	DAY 1	Plasma/Fluid	3 hours post-dose	45.0
ABC	107	DAY 1	Plasma/Fluid	4 hours post-dose	35.0
ABC	108	DAY 1	Plasma/Fluid	6 hours post-dose	20.0
ABC	109	DAY 1	Plasma/Fluid	8 hours post-dose	15.0
ABC	110	DAY 1	Plasma/Fluid	12 hours post-dose	0

Table 2 Sparse Sampling Profile

INTENSIVE SAMPLING

Intensive sampling involves taking several blood samples over a period of time from each subject to determine how the body handles the drug.

Study ID	Subject No.	Group	Matrix	Scheduled Time	Concentrations (ng/mL)
ABC	101	DAY 1	Plasma	Pre-dose	0.0
ABC	101	DAY 1	Plasma	0.5 hours post-dose	20.0
ABC	101	DAY 1	Plasma	1 hour post-dose	25.0
ABC	101	DAY 1	Plasma	1.5 hours post-dose	30.0
ABC	101	DAY 1	Plasma	2 hours post-dose	40.0
ABC	101	DAY 1	Plasma	3 hours post-dose	45.0
ABC	101	DAY 1	Plasma	4 hours post-dose	50.0
ABC	101	DAY 1	Plasma	6 hours post-dose	40.0
ABC	101	DAY 1	Plasma	8 hours post-dose	20.0
ABC	101	DAY 1	Plasma	12 hours post-dose	10.0

Table 3 Intensive Sampling Profile

DERIVING PK PARAMETERS FOR SPARSE AND INTENSIVE SAMPLES

For generating PK parameters for sparse samples, the concentrations from different subjects are pooled into 1 PK profile which is used to generate PK parameters. In this case, POOLID is created to be used, instead of USUBJID. In addition to creating SEND/SDTM PP domain, a POOLDEF domain is created to

show the mapping of USUBJID to POOLID. Adding POOLID in SDTM PP generates a warning in OpenCDISC validator “Model permissible variable added into standard domain”, which will need to be explained in SDTM Review Guide as POOLID is a permissible variable that can be added to PP when POOLID is not missing for all records.

We may have a case in a clinical human study where drug concentrations are to be taken from a human organ, which may involve difficult procedures, hence only sparse samples can be taken. In this case, sparse samples are used to generate a pooled PK profile, in turn being used to generate pooled PK parameters. Intensive blood samples are also taken from each subject, to compare the PK parameters from the sparse sample taken from human organ and PK parameters generated from intensive blood samples. A comparison is then made between the pooled PK parameters like Cmax and AUC and individual plasma PK parameters Cmax and AUC respectively to show the relative extent of drug penetration to the site of the desired drug effect. For those studies SDTM PP can be generated populating both USUBJID and POOLID. USUBJID will be used for PK parameters generated using intensive samples and POOLID will be used for PK parameters generated using sparse samples.

Example of how the STDM PP and POOLDEF will look is shown below:

PP

STUDY ID	POOL ID	USUBJID	PPSPEC	PPTESTCD	PPTEST	PPSTRESN	PPSTRESU
ABC	POOL -001		FLUID	CMAX	Max Conc	60	ng/mL
ABC	POOL -001		FLUID	TMAX	Time of CMAX	2	h
ABC	POOL -001		FLUID	AUCALL	AUC All	262.5	ng.h/mL
ABC		ABC-101	PLASMA	CMAX	Max Conc	50	ng/mL
ABC		ABC-101	PLASMA	TMAX	Time of CMAX	4	h
ABC		ABC-101	PLASMA	AUCALL	AUC All	347.5	ng.h/mL

Table 4 SDTM PP Domain

POOLDEF

STUDYID	POOLID	USUBJID
ABC	POOL-001	ABC-101
ABC	POOL-001	ABC-102
ABC	POOL-001	ABC-103
ABC	POOL-001	ABC-104
ABC	POOL-001	ABC-105
ABC	POOL-001	ABC-106
ABC	POOL-001	ABC-107
ABC	POOL-001	ABC-108
ABC	POOL-001	ABC-109

Table 5 SDTM POOLDEF Domain

DISPLAYING POOLED PARAMETERS IN TLFS

SDTM PP can be a source for Tables Listings and Figures (TLF) generated on pooled data as CDISC ADaM standards expect USUBJID to be populated and will generate OpenCDISC error. To overcome this issue, SDTM PP can be used for generation of parameter related TLFs.

CONCLUSION

In summary, POOLID is an identified variable for use in non-clinical studies and it may be used for human clinical trials when appropriate. Pooled PK concentrations are very common for preclinical animal studies but is not very common in human studies. If a case is seen for human studies, POOLID and POOLDEF can be used to transform the PK parameter data into SDTM PP and POOLDEF.

ACKNOWLEDGMENTS

The author would like to thank all PPD PK Management Charles Smith, Carey Hines, Mark Baird, Edward Elam and Jeffrey Wheeler for providing their valuable input for this paper. The author would also like to thank Tripura Malladi for the idea for the topic.

CONTACT INFORMATION

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

Shallabh Mehta
PPD
Shallabh.mehta@ppdi.com

DISCLAIMER

The contents of this paper are the work of the author and do not necessarily represent the opinions, recommendations or practices of PPD.