

Pharmacokinetics Concentration Data Deciphered – Presenting an Oncology Case Study

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ABSTRACT

Pharmacokinetics (PK) analyses in clinical trials aim to help researchers understand to what degree the given drug is absorbed, distributed, metabolized, and excreted over time. The ability to view concentration as a function of time yields an efficient way to assess the safety of the drug, which is a first key step in any clinical trials.

This paper will walk through a sample case study in an oncology setting to give a high-level overview of how statistical programming teams can transform lab collected PK concentration data into an interim PK concentration (PKC) file, which is then used by clinical pharmacologists as a source of information for deriving PK parameters. We explain in detail how several key variables are derived in the process and the challenges surrounding that effort. We will also clarify how clinical pharmacologists use the PKC file to generate the PK profile of the drug being studied. This will help statistical programmers understand the basic relationship between PK concentration and PK parameter data which in turn may enhance the quality and efficiency in programming datasets in this area.

INTRODUCTION

Pharmacokinetics, or PK, concerns itself with the monitoring of concentration levels of an analyte over time as it passes through the phases of Absorption, Distribution, Metabolism and Excretion in the human body. An analyte can be any body fluid, secretion, or waste product from the body. PK data collection is an integral part of clinical trials as it enables quantifying or measurement of safety and efficacy of the investigational drug/treatment. PK analyses in clinical trials aim to help researchers view analyte concentration as a function of time which is an efficient way to relate safety observations to the levels of an investigational drug. This in turn allows determining the dosage and frequency of drug/treatment administration.

This paper will walk through a sample case study in an oncology trial and outline the steps by which statistical programming teams can process the PK concentrations data into an intermediate PK concentrations file (PKC). This PKC file in turn is then used by clinical pharmacologists for deriving PK parameters. In the process of creating the PKC file, we use the PC data set which is compliant with CDISC standards provided in the SDTM IG.

Study programmers should review the study protocol to understand if there are stated PK objectives for the study. Even a review of an early draft of a protocol may help determine if the approach in this paper is applicable in deriving the PK parameters in the study. The final version of the protocol will have a PK sampling schedule of events, by product, analyte (e.g., ADC, TAb, MMAE, etc.), and visit/timepoint.

PROCESS FLOW

The flowchart in [Figure 1](#) depicts the process/workflow involved in the creation of the PKC file.

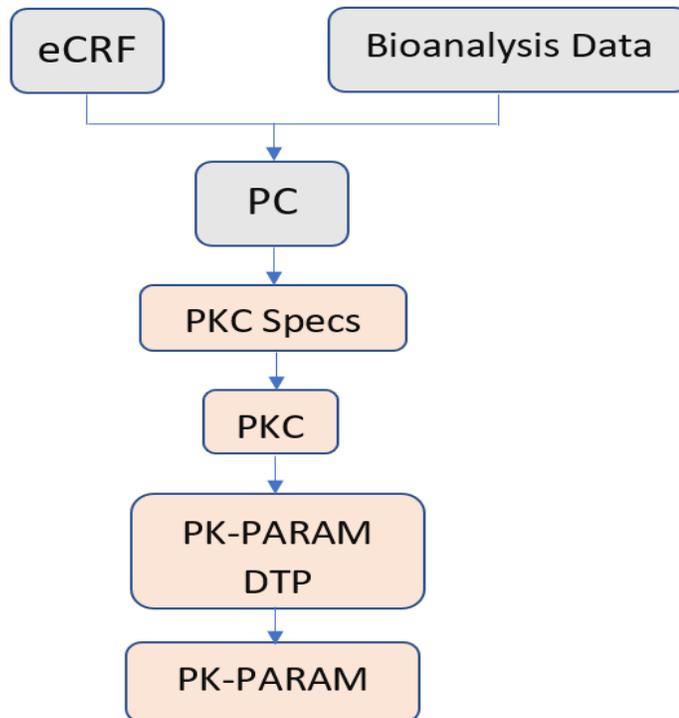


Figure 1. PK workflow

The statistical programming team creates a CDISC-compliant Pharmacokinetics Concentration (PC) dataset using:

- (i) A SAS raw PC data set containing CRF data including original sample timepoint information and subject information from the PC CRF page.
- (ii) Bio-analytical results data provided by lab vendors.

The two raw data sources from (i) and (ii) are combined to establish how to categorize lab testing information into timepoint slots relative to the timing of dosing.

PKC specs: The clinical pharmacology team requests the study lead for the PKC if required by the study. In Seagen, there is a standard PKC spec developed by a collaboration between Statistical Programming and QPD. Study lead reviews the standard spec and reaches out to QPD to ensure that it addresses the requirements of the study. If needed QPD can update the specs to cater to the needs of the study and finalize the specs.

PKC file: Using the PKC specs and SDTM PC data set as inputs, an Excel file (.xlsx format) is created called PKC file. This Excel file is an exact representation of the PKC SAS data set that is derived from SDTM PC, EX (Exposure) and DM (Demographics). Information from SDTM PC, DM and EX data sets is pooled for the generation of this customized PKC file.

The subsequent sections of this paper enlist and discuss several key variables (besides those present in SDTM PC) that are included in the PKC file. The PKC file serves as an input for the derivation of PK parameters by the clinical pharmacologist. SP generates the PP SDTM data set, using the PK profile as source data.

SOURCE FOR PKC FILE

Statistical programming receives the PK concentration specifications from a Quantitative Pharmacology & Disposition (QPD) representative. PK concentration data is generated as a SAS® data set using CDISC-compliant standard variable names and formats. The SAS® data set is then converted to an Excel file (.xlsx or .csv format) and shared with the QPD group.

PK concentration data is created from multiple SDTM sources. Below are the primary SDTM domains used:

- PC is used to get lab concentration data and derive cycle information
- EX is used to get dosing information
- DM is used to get treatment arm and demographic information
- VS is used to get baseline information such as weight, BMI, etc.

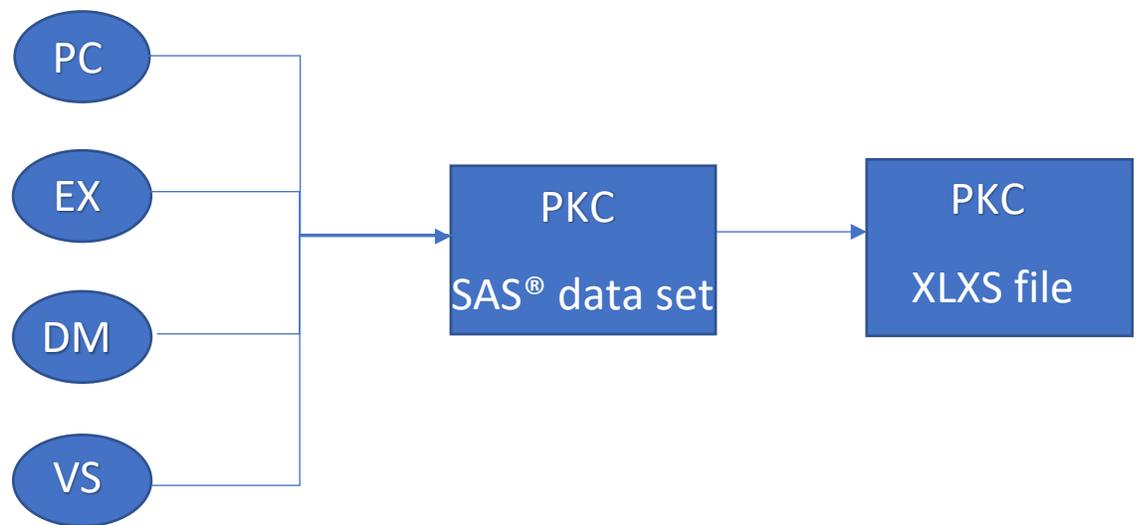


Figure 2. PKC file source

IMPORTANT VARIABLES

In this section, important derived variables in the PKC data set are introduced.

DUPLICATE

A duplicate record is generated from the first record of the following cycle to show as the last record in the current cycle. If the cycle x day 1 (CxD1) dose is skipped, no duplicate record is needed, i.e., if no pre-dose sample record exists then a duplicate record should not be created. Time values for end of infusion records should be based on previous dose or cycle. For the duplicate records, CYCLE is set to the value of the current cycle value and DAY is set to the last day before next cycle. Nominal time relative to infusion (NOMTM) is set to 'START OF INFUSION'.

CYCLE	DAY	DUPLICATE	NOMTM
1	1		START OF INFUSION
1	1		END OF INFUSION
1	8		START OF INFUSION
1	8		END OF INFUSION
2	21	Y	START OF INFUSION
2	1		START OF INFUSION
2	1		END OF INFUSION
3	21	Y	START OF INFUSION
3	1		START OF INFUSION
5	21	Y	START OF INFUSION
5	1		START OF INFUSION
7	21	Y	START OF INFUSION
7	1		START OF INFUSION
9	21	Y	START OF INFUSION
9	1		START OF INFUSION

Table 1.1 Duplicate variable

WNL_CYCLE

Same as study cycle, except for duplicate records created for which this value is Cycle - 1. The value is always actual cycle - 1 regardless of if the previous cycle was skipped or not. For Unscheduled and EOT visits, WinNonlin Cycle (WNL_CYCLE) should be adjusted to be the same as the previous sample in time.

WNL_CYCLE	CYCLE	DAY	DUPLICATE	NOMTM
1	1	1		START OF INFUSION
1	1	1		END OF INFUSION
1	1	8		START OF INFUSION
1	1	8		END OF INFUSION
1	2	21	Y	START OF INFUSION
2	2	1		START OF INFUSION
2	2	1		END OF INFUSION
2	3	21	Y	START OF INFUSION
3	3	1		START OF INFUSION
4	5	21	Y	START OF INFUSION
5	5	1		START OF INFUSION
6	7	21	Y	START OF INFUSION
7	7	1		START OF INFUSION
8	9	21	Y	START OF INFUSION
9	9	1		START OF INFUSION

Table 1.2 WNL_CYCLE variable

WNL_NGML

Result in ng/mL based on the drug except when concentration is less than LLQ (lower limit of quantification). When the result is less than LLQ, set pre-dose values to zero and post-dose to missing.

WNL_UGML

Result in µg/mL except when concentration is less than LLQ (lower limit of quantification). When the result is less than LLQ, set half of LLQ value.

WNL	CYCLE	DAY	DUPLICATE	NOMTM	WNL_NGML	WNL_UGML	ORGCONC	BLQ	PCLLOQ
1	1	1		START OF INFUSION	0	0.0107	<21.4	1	0.0214
1	1	1		END OF INFUSION	12000	12	12000	0	0.0214
1	1	8		START OF INFUSION	583	0.583	583	0	0.0214
1	1	8		END OF INFUSION	28500	28.5	28500	0	0.0214
1	2	21	Y	START OF INFUSION	237	0.237	237	0	0.0214
2	2	1		START OF INFUSION	237	0.237	237	0	0.0214
2	2	1		END OF INFUSION	31800	31.8	31800	0	0.0214
2	3	21	Y	START OF INFUSION	253	0.253	253	0	0.0214
3	3	1		START OF INFUSION	253	0.253	253	0	0.0214
4	5	21	Y	START OF INFUSION	529	0.529	529	0	0.0214
5	5	1		START OF INFUSION	529	0.529	529	0	0.0214
6	7	21	Y	START OF INFUSION	514	0.514	514	0	0.0214
7	7	1		START OF INFUSION	514	0.514	514	0	0.0214
8	9	21	Y	START OF INFUSION	0	0.0107	<21.4	1	0.0214
9	9	1		START OF INFUSION	0	0.0107	<21.4	1	0.0214

Table 1.3 WNL_NGML and WNL_UGML variables

In [Table 1.3](#), BLQ (Below the Limit of Quantification) is flagged as 1 if PCLLOQ is lower than the original result from the bio-analytics lab (ORGCONC). More than one analyte may be present in the same data file, so PCLLOQ will be different for each analyte.

NOMINAL TIMEPOINT DATETIME SPANS BETWEEN DOSING AND SAMPLE COLLECTION

The first trio of time-based calculations are made from a nominal timepoint perspective. The nominal (planned) timepoints for blood sample collection after a dose starts will vary by study according to the schedule outlined in the protocol. For example, in the study presented in this paper we have: 15 min, 7 days, and 21 days for cycle 1, but only 21 days for cycles thereafter.

NOMCUMTM (Nominal Cumulative Time in Days) from the first dose, <DIFF_Nominal>

NOMCYCTM (Nominal Cycle Time in Days) starting over at each cycle, <DIFF_Nominal>

NOMDSTM (Nominal Dose Time in Days) starting over at each dose, <DIFF_Nominal>

<DIFF_Actual>: the cumulative difference between the actual blood draw datetime and the dosing start.

Cycles start on day 1 of a cycle, and that has an influence on the “Day” value. For example, after an accumulated time of 7 days, that day is Day = 8. “Duplicate” records are different in that they represent the end of the previous cycle, therefore their value of “Day” is the same value as NONCYCTM.

The following are examples of how these variables are calculated:

For the end of infusion for cycle 1 day 1, where the nominal timepoint is 15 minutes, the value for all three variables is derived as: $15/(24*60)=0.0104$

For the start of infusion for cycle 2 day 1, where the nominal timepoint is 7 days, the value for NOMCUMTM is derived as: $7+(0/(24*60))=7$

But the values for NOMCYCTM and NOMDSTM are both affected by the fact that this record is both the start of a new cycle and new dose, thus: $0/(24*60)=0$

For the end of infusion for cycle 2 day 1, where the nominal timepoint is 7 days, the value for NOMCUMTM is derived as: $7+(15/(24*60))=7.0104$

But the values for NOMCYCTM and NOMDSTM are both affected by the fact that this record is both the start of a new cycle and new dose, thus: $15/(24*60)=0.0104$

Nominal Timepoint Name	WNL			Duplicate Record			NOMCUMTM				NOMCYCTM		NOMDSTM	
	Cycle	Day	Record		Full Days	Partial Day	Days	Full Days	Partial Day	Days	Full Days	Partial Day	Days	
Start of Infusion	1	1	1	N	0	0.0000	0.0000	0	0.0000	0.0000	0	0.0000	0.0000	
End of Infusion	1	1	1	N	0	0.0104	0.0104	0	0.0104	0.0104	0	0.0104	0.0104	
Start of Infusion	1	1	8	N	7	0.0000	7.0000	7	0.0000	7.0000	0	0.0000	0.0000	
End of Infusion	1	1	8	N	7	0.0104	7.0104	7	0.0104	7.0104	0	0.0104	0.0104	
Start of Infusion	1	2	21	Y	21	0.0000	21.0000	21	0.0000	21.0000	21	0.0000	21.0000	
Start of Infusion	2	2	1	N	21	0.0000	21.0000	0	-0.0104	0.0000	0	0.0000	0.0000	
End of Infusion	2	2	1	N	21	0.0104	21.0104	0	0.0104	0.0104	0	0.0104	0.0104	
Start of Infusion	2	3	21	Y	42	0.0000	42.0000	21	0.0000	21.0000	21	0.0000	21.0000	
Start of Infusion	3	3	1	N	42	0.0000	42.0000	0	-0.0111	0.0000	0	0.0000	0.0000	
Start of Infusion	4	5	21	Y	84	0.0000	84.0000	21	0.0000	21.0000	21	0.0000	21.0000	
Start of Infusion	5	5	1	N	84	0.0000	84.0000	0	0.0000	0.0000	0	0.0000	0.0000	

Table 1.4 Nominal Timepoint Variables

ACTUAL TIMEPOINT DATETIME SPANS BETWEEN DOSING AND SAMPLE COLLECTION

The second trio of time-based calculations are made from an actual timepoint perspective. The actual (true) timepoints for blood sample collection following each dose varies by study as to their targets (the nominal timepoints) according to the schedule outlined in the protocol. For example, in the study presented in this paper we have: 15 min, 7 days, and 21 days for cycle 1, but only 21 days for cycles thereafter. These are targets, but actual blood draw date and times might not come close to the targets.

ACTCUMTM (Actual Cumulative Time in Days) from the first dose, <DIFF_Actual>

ACTCYCTM (Actual Cycle Time in Days) starting over at each cycle, <DIFF_Actual>

ACTDSTM (Actual Dose Time in Days) starting over at each dose, <DIFF_Actual>

<DIFF_Actual>: the cumulative difference between the actual blood draw datetime and the dosing start.

For all three of these variables, if the blood draw was before the first dose, cycle, or subsequent dose, respectively (NOMCUMTM, NOMCYCTM, and NOMDSTM), then set to zero.

The [Table 1.5](#) illustrates how the “Actual” time-related variables are calculated.

A note about the colors: Yellow is to indicate that in the calculation of ACTCUMTM the overall first dose date is the only comparator with blood sample collection date. However, for “by Cycle”, it starts over at each cycle (Green). Likewise, for “by Dose” it restarts at each dose (Orange).

Nominal Timepoint Name	WNL			Duplicate Record	Blood Collection		First Dose Overall		ACTCUMTM		First Dose by Cycle		ACTCYCTM		First Dose by Dose		ACTDSTM				
	Cycle	Day	Record		Date	Time	Date	Time	Full Days	Partial Day	Days	Date	Time	Full Days	Partial Day	Days	Date	Time	Full Days	Partial Day	Days
Start of Infusion	1	1	1	N	7/21/2020	11:00 AM	7/21/2020	12:15 PM	0	-0.0521	0.0000	7/21/2020	12:15 PM	0	-0.0521	0.0000	7/21/2020	12:15 PM	0	-0.0521	0.0000
End of Infusion	1	1	1	N	7/21/2020	6:10 PM	7/21/2020	12:15 PM	0	0.2465	0.2465	7/21/2020	12:15 PM	0	0.2465	0.2465	7/21/2020	12:15 PM	0	0.2465	0.2465
Start of Infusion	1	1	8	N	7/28/2020	11:20 AM	7/21/2020	12:15 PM	6	0.9618	6.9618	7/21/2020	12:15 PM	6	0.9618	6.9618	7/28/2020	12:05 PM	0	-0.0312	0.0000
End of Infusion	1	1	8	N	7/28/2020	12:45 PM	7/21/2020	12:15 PM	7	0.0208	7.0208	7/21/2020	12:15 PM	7	0.0208	7.0208	7/28/2020	12:05 PM	0	0.0278	0.0278
Start of Infusion	1	2	21	Y	8/11/2020	8:40 AM	7/21/2020	12:15 PM	20	0.8507	20.8507	7/21/2020	12:15 PM	20	0.8507	20.8507	7/28/2020	12:05 PM	14	-0.1424	13.8576
Start of Infusion	2	2	1	N	8/11/2020	8:40 AM	7/21/2020	12:15 PM	20	0.8507	20.8507	8/11/2020	12:30 PM	0	-0.1597	0.0000	8/11/2020	12:30 PM	0	-0.1597	0.0000
End of Infusion	2	2	1	N	8/11/2020	1:05 PM	7/21/2020	12:15 PM	21	0.0347	21.0347	8/11/2020	12:30 PM	0	0.0243	0.0243	8/11/2020	12:30 PM	0	0.0243	0.0243
Start of Infusion	2	3	21	Y	9/1/2020	8:30 AM	7/21/2020	12:15 PM	41	0.8438	41.8438	8/11/2020	12:30 PM	21	-0.1667	20.8333	8/18/2020	11:15 AM	14	-0.1146	13.8854
Start of Infusion	3	3	1	N	9/1/2020	8:30 AM	7/21/2020	12:15 PM	41	0.8438	41.8438	9/1/2020	12:31 PM	0	-0.1674	0.0000	9/1/2020	12:31 PM	0	-0.1674	0.0000
Start of Infusion	4	5	21	Y	10/13/2020	8:50 AM	7/21/2020	12:15 PM	83	0.8576	83.8576	9/22/2020	12:00 PM	21	-0.1319	20.8691	9/22/2020	1:45 PM	14	-0.2049	13.7951
Start of Infusion	5	5	1	N	10/13/2020	8:50 AM	7/21/2020	12:15 PM	83	0.8576	83.8576	10/14/2020	#####	0	-0.0583	0.0000	10/14/2020	10:14 AM	0	-0.0583	0.0000

Table 1.5 Actual Timepoint Variables

POST-PROCESSING OF PKC DATA

The PKC data set will be used as the source for individual PK profiles. Using drug concentration changes over time, one can calculate a number of key PK parameters. When analyzing pharmacokinetic data, one generally employs Non-compartmental Analysis techniques (NCA). NCA helps us to determine the degree of exposure following administration of a drug (such as AUC), and perhaps the drug's associated pharmacokinetic parameters, such as clearance, elimination half-life, T_{max} , C_{max} , etc. NCA is a simple and quick method for evaluating the exposure of a drug. Usually, Phoenix WinNonlin software is used for NCA, pharmacokinetic/pharmacodynamic modelling and data processing, and for post-analysis processing including statistical tests and bioequivalence analysis, table creation and graphics.

NCA will determine the following directly from the PKC data:

- C_{max} : Maximum observed concentration (units = concentration)
- T_{max} : The time where the maximum concentration was observed (units = time)
- AUC: The area under the curve (units = time \times plasma concentration)
- Volume of distribution (V_d)
- Systemic clearance (CL)
- Terminal half-life ($t_{1/2}$)

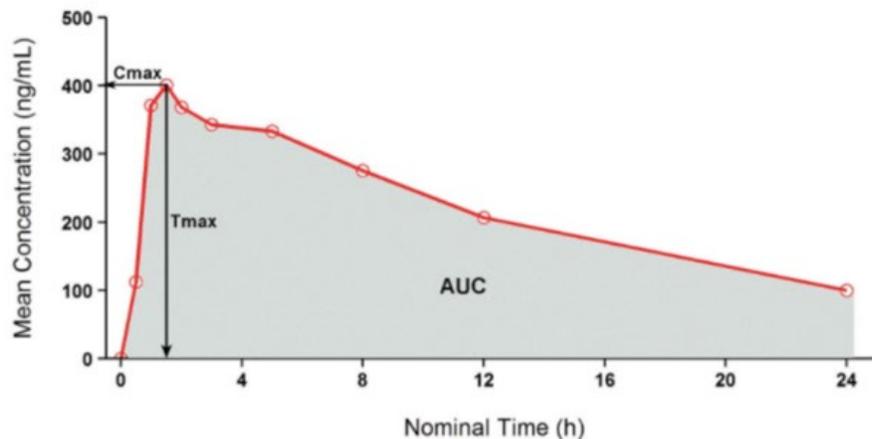


Figure 3. Mean concentration profile by nominal time

Symbol	Definition
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last} , as estimated using the linear regression from λ_z determination. $AUC_{0-\infty} = AUC_{0-t} + C_{last\ pred} / \lambda_z$. Units: ng*h/mL.
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. $AUC_{extra\%} = (\text{extrapolated area} / AUC_{0-\infty}) * 100$. The predicted $AUC_{0-\infty}$ should be used. Units: %.
CL/f	The apparent total body clearance of drug following extravascular administration. $CL/f = \text{Dose}_{p.o.} / AUC_{0-\infty}$. The predicted $AUC_{0-\infty}$ should be used. The dose amounts to be used for this calculation are 5 mg for bisoprolol and 5 mg for amlodipine. Units: L/h.
C_{max}	Maximum observed concentration, taken directly from the observed concentration-time profile. Units: ng/mL.
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the first occurrence in case of multiple/identical C_{max} values). Units: h.
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2) / \lambda_z$. Units: h.
$V_{z/f}$	The apparent volume of distribution during the terminal phase following extravascular administration $V_{z/f} = \text{Dose} / (AUC_{0-\infty} * \lambda_z)$ following single dose. Units: L.
λ_z	Terminal elimination rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve. Units: h^{-1} .

Table 2. Pharmacokinetics parameters

The data underlying this PK profile created for each qualified subject will be delivered back to the statistical programmers, who will map these to the PP domain.

CONCLUSION

Pharmacokinetics data is a critical component in understanding drug safety. In this paper we discussed basic concepts of Pharmacokinetics and the steps involved in creating the PKC data set from the CDISC standard source data. One of the biggest challenges in the process of creating this PKC data set is understanding the nominal and actual timepoints, which we explained here. The underlying concepts about non-compartmental analysis and the PK parameters also discussed here will provide insight into PP domain parameters. In our company we are standardizing the PKC creation process by coming up with a standard template for PKC specs and through a holistic macro which can be used to calculate all the time point variables (based on the study protocol and the actual blood collection time), bringing in the exposure data, covariant information and PK data.

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