

Relating PC and PP Domains using RELREC Records

Dr. Peter Schaefer, Director Product Management, Certara™
peter.schaefer@certara.com

The pharmacokinetics domains for pharmacokinetic concentrations and the resulting pharmacokinetic parameters were added to SDTM in the Version 3.1.2 of the implementation guide. Since the introduction of these domains, companies have started to incorporate the creation of these domains into their pharmacokinetics analysis workflows – and from anecdotal evidence it’s easy to conclude that this is not as straight forward as one would hope. This poster presents the basic principles for the use of RELREC records when implementing the PK domains and explains a couple of special cases that might not be very obvious.

The observed data for pharmacokinetics (PK) analysis of clinical trial study data are tabulated in the PC domain (Pharmacokinetic Concentration) while the typically required dosing information and covariates like age, weight, etc. are found in the DM, SC, VS, and EX domains. The PK parameters that are calculated for each of the time-concentration profiles in the PC domain are tabulated in the PP domain (Pharmacokinetic Parameters).

The PC Domain

The PC domain is a ‘findings’ domain which provides typically multiple records per analyte per subject for each time point. The two main types of records are

- Concentration records, containing the measured concentration for the specified metabolite in the specified specimen
- Sample characteristic records, containing additional data about the measurement, for example, the pH value of the specimen or the volume for a urine sample.

Besides the usual columns to identify the study and subject, the important columns are

- PCSPEC, PCTESTCD, and PCTEST, containing the specimen and the test code and test name for the analyte or specimen characteristic,
- the visit and time columns (like VISITNUM, PCDTC and PCENDTC),
- the reference time that identifies the relevant dosing event (PCTPTREF, PCRFTDTC), and
- the result columns such as PCORRES, PCSTRESC, and PCSTRESN.

A full time-concentration profile for a given study, subject, and dosing event for a specific analyte and specimen will consist of multiple records that are extracted by a primary key such as STUDYID, USUBJID, PCTESTCD, PCSPEC, and PCRFTDTC.

The PP Domain

The PP domain is a ‘findings’ domain which provides one record per PK parameter per time-concentration profile per subject. The PK Parameter is identified by the columns PPTESTCD and PPTEST while the calculated values are reported in the result columns such as PPORRES, PPSTRESC, and PPSTRESN. The primary key for a unique record in the PP domain consists of variables like STUDYID, USUBJID, and PPTESTCD and typically an additional column like PPCAT to identify the analyte.

You don't belong here ...

SDTM is the tabulation standard for observed data and clearly, the content of the PP domain is not observed but calculated. Often we hear that PK parameters should be reported somewhere in the ADaM datasets and not in SDTM. Certainly, there is truth to this argument. However, while the reasons for including these domains in SDTM might be historic and unclear, I don't see that this will be changed soon, if ever. So, I think we should stop arguing, embrace this "stepchild" and learn to love it.

Why RELREC?

Identifying the profile, i.e. the set of records, in the PC domain that was used to calculate a specific PP parameter is critical for reviewing and understanding the PK analysis. So, the relationship must be recorded somewhere in the SDTM datasets. There are a simple situations where the relation can be expressed easily, for example by populating the PPRFTDTC variable with the same value as PCRFTDTC of the related profile and the PPCAT variable with the value from PCTESTCD or PCTEST. This certainly works if there is one analyte and one reference time point.

Relating PC and PP

Obviously, there is a relationship between the records in PC and PP: Each record in PP contains a value that is calculated based on a profile in the PC domain.

An Example

Consider the table below for an example: The rows represent records in the PC domain (these records represent two profiles) and the columns are six records in the PP domain. A checkmark or the ‘x’ indicate whether a certain PC record was used in the calculation of the PP record. For example, to calculate AUC_{∞} and C_{Max} for the parent analyte the PC record P_1.0 was not used but for $t_{1/2}$ the same value was used.

As indicated, the IDVAR of the RELREC record contains the variables that are used to establish the relationship: For relating PP to PC records we suggest to use the --GRPID variables which are optional identifiers that can tie together a block of related records within one domain. In this case, the PCGRPID variable will be used to tag all records from the PC domain that are used for the calculation of a certain set of PK parameters. On

		PP Records				
		AUC_{∞}	C_{Max}	$t_{1/2}$		
PC Records	P_0.5	✓	✓	✓		
	P_1.0	x	x	✓		
	P_2.0	✓	✓	✓		
	P_4.0	✓	✓	✓		
	P_8.0	✓	✓	x		
	M_0.5		✓	✓		
	M_1.0		✓	✓		
	M_2.0	x	✓			
	M_4.0		✓	✓		
	M_8.0		✓	✓		

the other side, the PPGRPID variable is used to tie together the PK parameters that are based on the same set of records from the PC domain. The example requires five values of the PCGRPID variable which are

- PCGRP_P1, identifying P_1.0
- PCGRP_P2, identifying P_8.0
- PCGRP_P, tying together P_0.5, P_2.0, P_4.0
- PCGRP_M1, identifying M_2.0
- PCGRP_M, tying together M_0.5, M_1.0, M_4.0, M_8.0

The required values for the PPGRPID variable are as follows:

- PPGRP_1 for AUC_{∞} and C_{Max} for the parent analyte
- PPGRP_2 for AUC_{∞} and $t_{1/2}$ for the metabolite
- PPGRP_3, indentifying C_{Max} for the metabolite
- PPGRP_4, indentifying $t_{1/2}$ for the parent analyte

With these definitions the RELREC records for the two AUC parameter rows will look like this:

RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
PP	...	PPGRPID	PPGRP_1		A
PC	...	PCGRPID	PCGRP_P		A
PC		PCGRPID	PCGRP_P2		A
PP	...	PPGRPID	PPGRP_12		B
PC	...	PCGRPID	PCGRP_M		B

Basic Principle of the RELREC Dataset

The RELREC dataset was introduced to express relationships between records in different domains. For each relationship, there are always two records in the RELREC dataset required – each record contains a value pointing to the domain and the record that is part of the relationship. The table below depicts the variables that describe a relationship in RELREC and how they are used.

RELREC					
RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
AE	S123456	AESEQ	5		A
CM	S123456	CMSEQ	11		A
CM	S123456	CMSEQ	12		A

Domain identifier for the domain that this RELREC record relates to

A unique identifier in the RELREC dataset for this specific relationship

The variable in the domain that is used to identify the record for the relationship

The value in the IDVAR column that identifies the related records

The use of ‘reference variables’ in RELREC datasets is very flexible and powerful, it allows easily to create one-to-one, one-to-many, and many-to-many relationships between domains: Chapter 8 of the SDTM IG presents multiple examples for RELREC usage.