Paper DH01

Incorporating Longitudinal Co-Medication Data into Population Pharmacokinetic (POPPK) Analysis Datasets: A Programmer's Perspective

Aschwin van der Giesen, Certara, Oss, The Netherlands
Gerly van der Vleuten, Certara, Oss, The Netherlands

ABSTRACT

This paper explores the integration of time-varying comedication data into a Population Pharmacokinetic (PopPK) dataset. PopPK analysis is critical for understanding variability in drug concentrations within a population receiving clinically relevant doses. The inclusion of comedications, especially those that influence drug metabolism, is essential for accurate modeling of pharmacokinetics (PK) in populations. This paper discusses the methodology for identifying relevant comedication data, addressing common challenges such as incomplete start- and end dates of comedication records, and incorporating these data into a PopPK dataset to improve the precision of drug interaction modeling.

INTRODUCTION

Population Pharmacokinetics (PopPK) refers to the study of variability in drug concentrations within a patient population receiving clinically relevant doses of a drug. This variability is a function of several factors, including genetic differences, disease state, and concomitant medications. PopPK analyses use mathematical models to describe pharmacokinetic (PK) data and pharmacodynamic (PD) outcomes. In a typical PopPK dataset, the inclusion of various covariates—such as patient demographics, disease characteristics, and concomitant medications—can significantly influence the accuracy and reliability of pharmacokinetic predictions.

Concomitant medications (comedications) may play a crucial role in modifying drug metabolism, especially in patient populations outside of controlled clinical trials. Many comedications may have a minimal impact on drug metabolism, while others, particularly those affecting cytochrome P450 (CYP) enzymes, can have substantial effects. The purpose of this paper is to examine how comedication data can be systematically incorporated into a PopPK dataset to model these interactions and enhance the accuracy of PK/PD predictions.

POPULATION PHARMACOKINETIC DATASETS

A PopPK dataset typically contains pharmacokinetic concentration data, dosing information, and covariates such as patient demographics or clinical characteristics. These datasets are used to study how drugs are absorbed, distributed, metabolized, and excreted in a population. Table 1 shows an example of a PopPK dataset.

A typical PopPK dataset is organized into several key domains:

- PK concentration records: These records provide the measured concentration of a drug in the blood or plasma, typically sourced from the ADaM (Analysis Data Model) ADPC domain.
- Dosing records: These records detail the time and dosage of the drug administered to patients, often found in ADEC or ADEX domains.
- Covariate data: These are additional records that include patient information, lab values, and other relevant clinical variables, which are often drawn from ADSL, ADLB, ADVS, or ADCM domains.

For accurate population modeling, it is necessary to combine datasets from different studies with PK data into a comprehensive analysis dataset.

COMEDICATION IMPACT ON DRUG METABOLISM

When moving from Phase I clinical trials to phase III or more diverse patient populations, the likelihood of concomitant medication use increases. Comedications may be administered for various reasons, such as treating co-existing conditions, which can lead to significant change in drug-drug interactions.

Certain drugs, such as CYP3A inhibitors (e.g., tramadol, verapamil, codeine) and inducers (e.g., glucocorticoids, rifampin, phenobarbital), can alter the metabolism of other drugs by affecting enzyme activity. Understanding these interactions is critical for predicting the pharmacokinetics of investigational drugs.

For instance, if a patient is taking a CYP3A inhibitor alongside an investigational drug that is metabolized by CYP3A, the concentration of the investigational drug may increase, leading to potential adverse effects. Conversely, a CYP3A inducer may lower the drug's plasma concentration, reducing its therapeutic efficacy.
Thus, incorporating comedication data into PopPK datasets is vital to correctly model the effect of drug-drug interactions on the pharmacokinetics of the investigational compound.

STUDYN	SUBJID	TRTAN	TRTPN	NDOSE	DOSE	AMT	NTIME	TIME	DVID	DV	MDV	AGE	BHT	BALT	ADATE	ATIME	USUBJID
12345	987654321	1	1	315	315	.	0	0	1	.	1	37	168	21	2011-06-24	08:56:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	315	0	0	0	.	1	37	168	21	2011-06-24	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	0.5	0.5	1	203.47	0	37	168	21	2011-06-24	09:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	1	1	1	1584.81	0	37	168	21	2011-06-24	10:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	1.5	1.5	1	1656.16	0	37	168	21	2011-06-24	10:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	2	2	1	1365.05	0	37	168	21	2011-06-24	11:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	3	3	1	1419.27	0	37	168	21	2011-06-24	12:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	4	4	1	708.63	0	37	168	21	2011-06-24	13:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	5	5	1	578.77	0	37	168	21	2011-06-24	14:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	6	6	1	451.77	0	37	168	21	2011-06-24	15:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	8	8	1	294.8	0	37	168	21	2011-06-24	17:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	10	10	1	192.05	0	37	168	21	2011-06-24	19:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	12	12	1	114.14	0	37	168	21	2011-06-24	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	16	16	1	57.35	0	37	168	21	2011-06-25	01:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	24	24	1	19.39	0	37	168	21	2011-06-25	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	36	36	1	7.07	0	37	168	21	2011-06-25	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	48	47.83	1	3.9	0	37	168	21	2011-06-26	08:50:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	144	143.92	1	.	1	37	168	21	2011-06-30	08:55:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	315	144	144	0	.	1	37	168	21	2011-06-30	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	144.5	144.5	1	25.81	0	37	168	21	2011-06-30	09:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	145	145	1	423.23	0	37	168	21	2011-06-30	10:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	145.5	145.5	1	370.43	0	37	168	21	2011-06-30	10:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	146	146	1	377.56	0	37	168	21	2011-06-30	11:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	147	147	1	497.43	0	37	168	21	2011-06-30	12:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	148	148	1	440.35	0	37	168	21	2011-06-30	13:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	149	149	1	321.91	0	37	168	21	2011-06-30	14:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	150	150	1	237.72	0	37	168	21	2011-06-30	15:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	152	152	1	149.24	0	37	168	21	2011-06-30	17:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	154	154.02	1	103.72	0	37	168	21	2011-06-30	19:01:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	156	156	1	63.05	0	37	168	21	2011-06-30	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	160	160	1	35.94	0	37	168	21	2011-07-01	01:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	168	168	1	16.1	0	37	168	21	2011-07-01	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	180	180	1	8	0	37	168	21	2011-07-01	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	192	192	1	4.19	0	37	168	21	2011-07-02	09:00:00	ABC12345-987-654-321

Table 1: Example of a PopPK analysis dataset. Depicting subject identifiers, treatment information, time-course information, PK concentrations, subject level information (demographics, vital signs, and laboratory measurements).

METHODOLOGY FOR INCORPORATING COMEDICATION DATA

IDENTIFYING RELEVANT COMEDICATION RECORDS

The first step in incorporating comedication data into a PopPK dataset is identifying which medications are likely to impact the metabolism of the investigational drug. This process involves reviewing the clinical trial's concomitant medication (CM) domain, which includes records of administered drugs, their doses, and administration times.

To determine the metabolic impact of these drugs, we rely on external drug interaction databases, such as the FDA Drug Interaction database or Certara's Drug Interactions Database. These resources provide information on which comedications are known to interact with the investigational drug through the modulation of metabolic enzymes, such as CYP450 enzymes.

Once we identify the relevant comedications, we can extract standardized drug names (WHO drug names or ATC codes) and match them to the CM domain data.

HANDLING MISSING OR INCOMPLETE DATA

A common challenge when working with comedication data is the presence of incomplete or missing start and end dates for medication administration. In such cases, assumptions are made to impute these dates. For example:

- For missing start dates, the first day of the month or the first month of the year may be assumed.
- For missing end dates, the last day of the month or year is assumed.
- If a medication is marked as "ONGOING," the current date can be used as the end date.

An example of a comedication (CM) domain, is depicted in Table 2.

HANDLING OVERLAPPING COMEDICATION RECORDS

Overlapping comedication records are another challenge. In many instances, a patient may be prescribed multiple medications with the same potency that overlap in time but vary in therapeutic class. To address this, we pool overlapping records of the same potency by creating a single, consolidated record for each subject, which reflects the overall potency or effect of the various comedications during that time period. An example is shown in table 3.

After consolidating comedication records, the dataset no longer needs to track individual medications. Instead, the focus shifts to the potency of comedications and their classification as inhibitors or inducers of specific enzymes. This simplifies the dataset and enhances its utility for pharmacokinetic analysis.

USUBJID	CMDECOD	CMSCAT	CMDOSE	CMDOSU	CMDOSFRQ	CMROUTE	CMSTDTC	CMENDTC	CMSTDY	CMENDY	CMENRF
ABC12345-987-654-321	ROSUVASTATIN	Prior	20	mg	QD	ORAL			.	.	ONGOING
ABC12345-987-654-321	ALLOPURINOL	Prior	300	mg	QD	ORAL	2019-12-30		-63	.	ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	309	mL	ONCE	INTRAVENOUS	2020-01-05	2020-01-05	-57	-57	
ABC12345-987-654-321	SACCHARATED IRON OXIDE	Prior	1	IU	PRN	INTRAVENOUS	2020-01-06	2020-04-18	-56	48	
ABC12345-987-654-321	ACICLOVIR	Prior	400	mg	BID	ORAL	2020-01-07		-55	.	ONGOING
ABC12345-987-654-321	VORICONAZOLE	Prior	200	mg	BID	ORAL	2020-01-07		-55	.	ONGOING
ABC12345-987-654-321	AMOXICILLIN;CLAVULANIC ACID	Prior	.	mg	BID	ORAL	2020-01-08		-54	.	ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	201	mL	ONCE	INTRAVENOUS	2020-01-08	2020-01-08	-54	-54	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	244	mL	ONCE	INTRAVENOUS	2020-01-12	2020-01-12	-50	-50	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	201	mL	ONCE	INTRAVENOUS	2020-01-14	2020-01-14	-48	-48	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	230	mL	ONCE	INTRAVENOUS	2020-01-18	2020-01-18	-44	-44	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	217	mL	ONCE	INTRAVENOUS	2020-01-20	2020-01-20	-42	-42	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	216	mL	ONCE	INTRAVENOUS	2020-01-21	2020-01-21	-41	-41	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	203	mL	ONCE	INTRAVENOUS	2020-01-25	2020-01-25	-37	-37	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	212	mL	ONCE	INTRAVENOUS	2020-02-02	2020-02-02	-29	-29	
ABC12345-987-654-321	METHYLPREDNISOLONE	Prior	32	mg	OTHER	ORAL	2020-02-05		-26	.	ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	219	mL	ONCE	INTRAVENOUS	2020-02-05	2020-02-05	-26	-26	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	302	mL	ONCE	INTRAVENOUS	2020-02-06	2020-02-06	-25	-25	
ABC12345-987-654-321	SULFAMETHOXAZOLE;TRIMETHOPRIM	Prior	1	OTHER	QD	ORAL	2020-02-10		-21	.	ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	241	mL	ONCE	INTRAVENOUS	2020-02-10	2020-02-10	-21	-21	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	273	mL	ONCE	INTRAVENOUS	2020-02-15	2020-02-15	-16	-16	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	208	mL	ONCE	INTRAVENOUS	2020-02-18	2020-02-18	-13	-13	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	220	mL	ONCE	INTRAVENOUS	2020-02-18	2020-02-18	-13	-13	
ABC12345-987-654-321	INSULIN	Prior	1	OTHER	PRN	SUBCUTANEOUS	2020-02-19		-12	.	ONGOING
ABC12345-987-654-321	INSULIN ASPART	Prior	6	OTHER	TID	SUBCUTANEOUS	2020-02-19		-12	.	ONGOING
ABC12345-987-654-321	METFORMIN	Prior	1000	mg	BID	ORAL	2020-02-19	2020-03-15	-12	14	
ABC12345-987-654-321	HYDROXYCARBAMIDE	Prior	1000	mg	QD	ORAL	2020-02-25	2020-02-28	-6	-3	
ABC12345-987-654-321	FAMOTIDINE	Prior	20	mg	PRN	ORAL	2020-02-25	2020-03-10	-6	9	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	204	mL	ONCE	INTRAVENOUS	2020-03-01	2020-03-01	-1	-1	
ABC12345-987-654-321	OSELTAMIVIR PHOSPHATE	Prior	75	mg	QD	ORAL	2020-03-01	2020-03-10	-1	9	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Concomitant	344	mL	ONCE	INTRAVENOUS	2020-03-03	2020-03-03	2	2	

Table 2: Example of a comedication (CM) domain, including examples of incomplete or missing start and end dates for medication administration.

USUBJID	CMDECOD	CMSTDTC	CMENDTC	INH	IND
ABC12345-987-654-321	METFORMIN	2020-02-19	2020-03-15	MODERATE	
ABC12345-987-654-321	ACICLOVIR	2020-02-21	2020-03-11	MODERATE	
ABC12345-987-654-321	METFORMIN	2020-03-01	2020-03-21	MODERATE	
ABC12345-987-654-321	HYDROXYCARBAMIDE	2020-02-25	2020-02-28	WEAK	
ABC12345-987-654-321	FAMOTIDINE	2020-02-25	2020-03-10		MODERATE
ABC12345-987-654-321	RITONAVIR	2020-03-01	2020-03-10		STRONG
ABC12345-987-654-321	OSELTAMIVIR PHOSPHATE	2020-03-11	2020-03-21		WEAK

Table 3: Example of overlapping comedication records. The first three lines in this table have the same inhibitory potency (MODERATE) and have overlap in CMSTDTC & CMENDTC.

STUDYN	SUBJID	TRTAN	TRTPN	NDOSE	DOSE	AMT	NTIME	TIME	DVID	DV	MDV	AGE	BHT	BALT	IND_WEAK	IND_MOD	IND_STR	INH_WEAK	INH_MOD	INH_STR	ADATE	ATIME	USUBJID
12345	987654321	1	1	315	315	.	0	0	1	.	1	37	168	21	0	0	0	1	1	0	2011-06-24	08:56:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	315	0	0	0	.	1	37	168	21	0	0	0	1	1	0	2011-06-24	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	0.5	0.5	1	203.47	0	37	168	21	0	0	0	1	1	0	2011-06-24	09:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	1	1	1	1584.81	0	37	168	21	0	0	0	1	1	0	2011-06-24	10:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	1.5	1.5	1	1656.16	0	37	168	21	0	0	0	1	1	0	2011-06-24	10:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	2	2	1	1365.05	0	37	168	21	0	0	0	1	1	0	2011-06-24	11:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	3	3	1	1419.27	0	37	168	21	0	0	0	1	1	0	2011-06-24	12:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	4	4	1	708.63	0	37	168	21	0	0	0	1	1	0	2011-06-24	13:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	5	5	1	578.77	0	37	168	21	0	0	0	1	1	0	2011-06-24	14:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	6	6	1	451.77	0	37	168	21	0	0	0	1	1	0	2011-06-24	15:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	8	8	1	294.8	0	37	168	21	0	0	0	1	1	0	2011-06-24	17:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	10	10	1	192.05	0	37	168	21	0	0	0	1	1	0	2011-06-24	19:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	12	12	1	114.14	0	37	168	21	0	0	0	1	1	0	2011-06-24	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	16	16	1	57.35	0	37	168	21	0	0	1	1	1	1	2011-06-25	01:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	24	24	1	19.39	0	37	168	21	0	0	1	1	1	1	2011-06-25	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	36	36	1	7.07	0	37	168	21	0	0	1	1	1	1	2011-06-25	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	48	47.83	1	3.9	0	37	168	21	0	0	1	1	1	1	2011-06-26	08:50:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	144	143.92	1	.	1	37	168	21	0	1	1	1	0	0	2011-06-30	08:55:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	315	144	144	0	.	1	37	168	21	0	1	1	1	0	0	2011-06-30	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	144.5	144.5	1	25.81	0	37	168	21	0	1	1	1	0	0	2011-06-30	09:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	145	145	1	423.23	0	37	168	21	0	1	1	1	0	0	2011-06-30	10:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	145.5	145.5	1	370.43	0	37	168	21	0	1	1	1	0	0	2011-06-30	10:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	146	146	1	377.56	0	37	168	21	0	1	1	1	0	0	2011-06-30	11:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	147	147	1	497.43	0	37	168	21	0	1	1	1	0	0	2011-06-30	12:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	148	148	1	440.35	0	37	168	21	0	1	1	1	0	0	2011-06-30	13:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	149	149	1	321.91	0	37	168	21	0	1	1	1	0	0	2011-06-30	14:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	150	150	1	237.72	0	37	168	21	0	1	1	1	0	0	2011-06-30	15:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	152	152	1	149.24	0	37	168	21	0	1	1	1	0	0	2011-06-30	17:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	154	154.02	1	103.72	0	37	168	21	0	1	1	1	0	0	2011-06-30	19:01:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	156	156	1	63.05	0	37	168	21	0	1	1	1	0	0	2011-06-30	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	160	160	1	35.94	0	37	168	21	0	1	1	1	0	0	2011-07-01	01:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	168	168	1	16.1	0	37	168	21	0	1	1	1	0	0	2011-07-01	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	180	180	1	8	0	37	168	21	0	1	1	1	0	0	2011-07-01	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	192	192	1	4.19	0	37	168	21	0	1	1	1	0	0	2011-07-02	09:00:00	ABC12345-987-654-321

Table 4: Example of a PPK analysis dataset incorporating longitudinal comedication data.

REDUCING DATA COMPLEXITY

Once we have identified the relevant comedication records, determined their potency, and imputed any missing start and end dates, we are ready to merge this information into the Population Pharmacokinetic (PopPK) dataset.

To do this, we merge the comedication data with the PopPK dataset by subject identifier (USUBJID) and date (ADATE). The merged dataset is then sorted by both USUBJID and ADATE to ensure the data is organized in chronological order for each subject.

LAST OBSERVATION CARRIED FORWARD (LOCF) METHODOLOGY

At this point, the next step involves employing a Last Observation Carried Forward (LOCF) approach. This technique compares each dosing or observation record in the PopPK dataset against the comedication dosing periods. If a dosing or observation record falls within the timeframe of an active comedication (i.e., the start and end dates of the comedication record overlap with the dosing period), the potency of the comedication (inhibitor or inducer) is assigned to the corresponding record.

The LOCF approach ensures that the impact of comedications is carried through for all relevant dosing and observation events within the specified period. This way, we account for any changes in drug metabolism that could have occurred due to comedication use during the dosing period. An example of an analysis dataset incorporating longitudinal comedication data can be found in Table 4.

ADVANCED CONSIDERATIONS

Incorporating comedication data into a PopPK dataset can be achieved by following the above steps. However, there are additional complexities at play that are worth consindering. Two of such examples are described below:

LAG TIME AND DRUG HALF_LIFE

One complexity in incorporating comedication data is considering the lag time in the onset and cessation of drug effects. For example, does the clinical effect of a comedication begin immediately after administration? For drugs with long half-lives, the effect may persist well after the medication is discontinued.

To address this, we can introduce secondary start- and end-date variables that account for the lag in the drug's clinical effect. These variables can be adjusted by adding days to the start and/or end dates, based on known pharmacokinetic properties of the drugs involved

DRUG CO_ADMINISTRATION EFFECTS

In some cases, two drugs may be co-administered, and their combined effect may differ from the sum of their individual effects. For example, co-administration of Lesinurad and Allopurinol can alter the pharmacokinetic profile of each drug. In these cases, the programmer will need to confirm whether both compounds are administered in an overlapping fashion to capture the combined impact of co-administered drugs.

CONCLUSION

The incorporation of time-varying comedication data into a PopPK dataset is essential for accurately modeling drug-drug interactions and predicting the pharmacokinetics of investigational drugs in patient populations. While several challenges exist, such as incomplete data and overlapping records, these can be addressed through careful data management and assumptions. By accurately accounting for comedication effects, we can improve the precision of PopPK modeling, thereby facilitating safer and more effective drug development.

CONTACT INFORMATION

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

Author Name: Aschwin van der Giesen
Company: Certara
Address: Kloosterstraat 9, 5349 AB Oss
Email: aschwin.vandergiesen@certara.com
Website: www.certara.com