CERTARA

Introducing Population Pharmacokinetic Analysis Into Your Early Drug Development Efforts

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Population pharmacokinetic (PopPK) analysis has become a key tool for clinical pharmacology experts when working with data from human subjects. In the recent past, new drug registrations utilized pharmacokinetic (PK) information from healthy volunteers, in whom intensive PK sampling could be performed. In an effort to examine possible dosage adjustments for patients or other subgroups (eg, elderly, children, individuals with compromised liver function, etc) PopPK techniques were developed. Clinical researchers began to utilize these techniques to assist in therapeutic drug monitoring and during the drug development process. PopPK techniques are able to accommodate sparse blood sampling designs in clinical settings common to therapeutic treatment and large Phase 3 clinical trials. Further development of PopPK techniques have focused on trial simulation and optimization as well as supporting dosage recommendations for target patient populations in the absence of dedicated clinical studies. Although many of these applications are late in the drug development effort, the principles and techniques are also applicable in early drug development when making the transition from nonclinical studies to first-in-human clinical trials.

PopPK is based on the principle that the concentration-time profile for each subject can be described with a mathematical model. Systemic drug concentrations (C) are a function time (t) and a set of PK parameters (θ) plus residual error (ε) as shown in Equation 1.

Equation 1: $$C(t) = f(\theta, t) + \varepsilon$$

Each individual subject will have a set of PK parameters based on their individual characteristics and drug concentration information. Thus, in individual model fitting, a full PK profile is required to generate the PK parameters of interest.

PopPK analysis expands upon individual analysis by (1) relating individual PK parameters to a set of theoretical "typical" PK parameters, and (2) quantifying the impact of known information (eg, age, sex, weight, phenotype, etc) on the variability in the individual PK parameters. The relationship between individual and typical PK parameters is illustrated in Equation 2. A new parameter has been added which describes the between-subject variability (η). This parameter describes the distribution of individual PK parameter estimates relative to the population or typical value for that same PK parameter.

Equation 2: $$C(t) = f(\theta, t, \eta) + \varepsilon$$

Further examination of the relationship between the PK parameters (θ) and the between-subject variability parameter (η) is shown in Equation 3. In this equation, the PK parameter for clearance for an individual (CL_i) is a function of a population typical value for clearance (θ) and the random

effect of the individual variance from that typical value (η_i). In this model, the PK parameters are considered the fixed effects, and the between individual variability are the random effects. Thus, the function includes both fixed and random effects making this a mixed-effects model.

In an effort to examine possible dosage adjustments for patient subgroups, elderly, children, liver impaired, PopPK. techniques were developed.

Equation 3:

$$CL_i = \theta * e^{\eta_i}$$

In an effort to minimize the unexplained variability between individual PK parameter estimates, additional fixed effects, sometimes called covariates, can be added to the model as shown in Equation 4. The estimate for individual clearance now includes an adjustment for the weight (WT) of each subject individually using normalization to 70 kg and allometric scaling with an exponent of 0.75. The addition of these covariates is intended to further reduce the random individual variances (η_i) by adding known information.

Equation 4:

$$CL_i = \left[\theta * \left(\frac{WT}{70}\right)^{0.75}\right] * e^{\eta_i}$$

PopPK techniques are a logical extension of single subject PK models. While the population models require more complex statistical systems for evaluation, the underlying principles of examining relationships between PK parameters and observed drug concentrations are consistent between the individual and population techniques.

The following two examples will illustrate the value of implementing PopPK techniques on early development projects to extract additional information that can guide drug development.

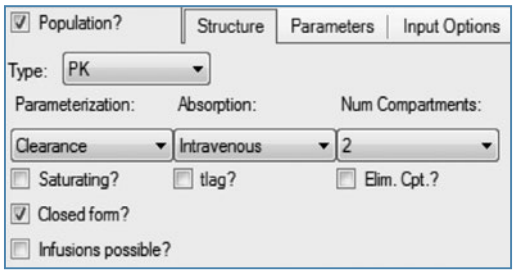
Non-clinical data

Population analysis can also be effective when working with non-clinical data to characterize pharmacokinetics and pharmacodynamics (PK/PD) in a specific species, facilitate allometric scaling across species, and to predict human exposure information. Consider for example an absolute bioavailability study in monkeys. The subcutaneous bioavailability of many peptide therapeutics is predictable from animals to humans, therefore a simple crossover bioavailability study in monkeys might provide information on the rate and extent of absorption for Phase 1 clinical studies. For this type of study, non-compartmental analysis is commonly used to evaluate the concentration-time data, generating measures of exposure (eg, AUC and C_{max}). While this analysis is adequate for the primary focus of the study, the data contains additional value. PopPK analysis can provide additional insights about the between-subject variability, and demographic features that may affect the PK parameters can be extracted from the same concentration-time data.

PopPK principles and techniques are applicable in early drug development when making the transition from non-clinical studies to first-in-human clinical trials.

The same dataset used for non-compartmental analysis in Phoenix WinNonlin can be evaluated using a PopPK model (ie, Phoenix Model) using the non-linear mixed effects (NLME) module. Simply checking the "Population?" box and then selecting the type of parameterization, absorption model, and number of compartments, the user can execute a PopPK model (Figure 1).

Figure 1. PopPK Model Setup using Phoenix NLME.



Using Phoenix NLME, the additional population analysis requires addition of a single workflow object and can be executed without manually coding a complex set of equations.

This two-compartment intravenous model was parameterized using clearance parameters and can be represented by the following sets of equations:

Equation 5:

$$C(t) = \left(a * e^{-\alpha * t} + b * e^{-\beta * t}\right) * (1+\varepsilon)$$

$$V1 = \theta_1 * e^{\eta_1}$$

$$CL = \theta_2 * e^{\eta_2}$$

$$V2 = \theta_3 * e^{\eta_3}$$

$$Q = \theta_4 * e^{\eta_4}$$

where a, b, α, and β are functions of the administered intravenous dose, the volume of distribution of the central (V1) and peripheral (V2) compartments, the clearance (CL), and the intercompartmental clearance (Q) for each individual animal, and ε is the residual random error. θ_1 is the volume of distribution of the central compartment for the population (ie, the "average" monkey), θ_2 is the clearance for the population, θ_3 is the volume of distribution of the peripheral compartment for the population, and θ_4 is the intercompartmental clearance for the population. The between-individual variability parameters for each of the four PK parameters are denoted as η_1, η_2, η_3, and η_4. The basic equation (line 1, Equation 5) is identical to an individual compartmental model. The additional lines provide the population effects for the model.

The resulting model fit is shown in Figure 2 where the individual model fits for two different dose levels run through the middle of the data.

And the model diagnostic plot in Figure 3 illustrates the random distribution of observed versus predicted pairs that lie about the line of unity.

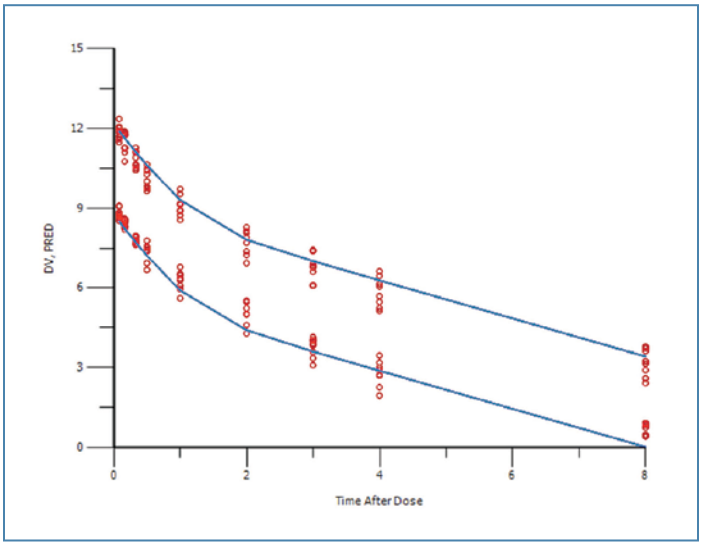


Figure 2. Plasma concentration-time profile for individual observations and population model fits following intravenous injection. Individual observations are shown with red open circles for 2 different dose levels. Population model fits are shown by the blue lines.

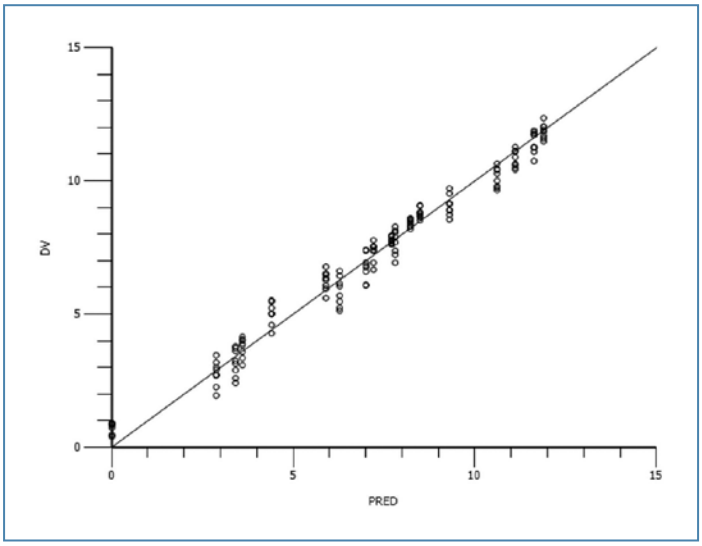
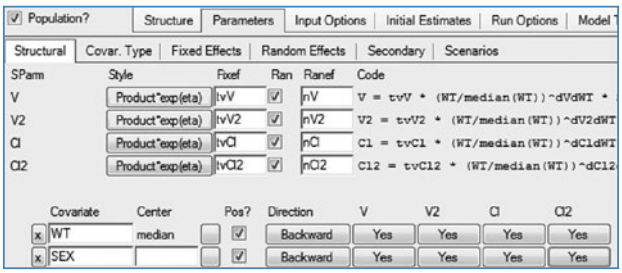


Figure 3. Model diagnostic plot of observed values versus population predicted values (PRED) with the line of unity. The observed value (DV) and PRED pairs generally lie along the line of unity (solid line) with an even distribution on either side of the unity line.

This analysis provides estimates of the clearance and volume of distribution for each individual monkey along with the between-individual variability in those estimates. In addition to the PK parameters, a quick evaluation of gender and body weight suggested that drug clearance is proportional to body weight. This covariate analysis was performed by duplicating the model object used above in the workflow, and pasting a new copy on the workflow space. Simply adding the desired covariates in the structural model setup screen (Figure 4) allowed execution of a covariate search.

Figure 4. Adding covariates in the model setup screen of Phoenix NLME. Two covariates, weight (WT) and gender (SEX), are included in the model. Weight is centered on the median weight. Both covariates are tested on the volume and clearance PK parameters using a backward deletion process.



By executing this model, both weight (WT) and gender (SEX) will be tested as covariates of all four PK parameters (V, V2, CL, CL2 or Q) in the population model. The output of the covariate models is then provided and can be compared to determine the best model fit. In this case, weight was a significant covariate on clearance, suggesting that clearance increases with body weight. The addition of the weight to the model creates improved individual model fits (Figure 5) that explain more of the variability than the population model alone. The improved fits are noticeable at the low concentrations where much better predictions are observed, and the greater alignment of data points along the line of unity (Figure 6).

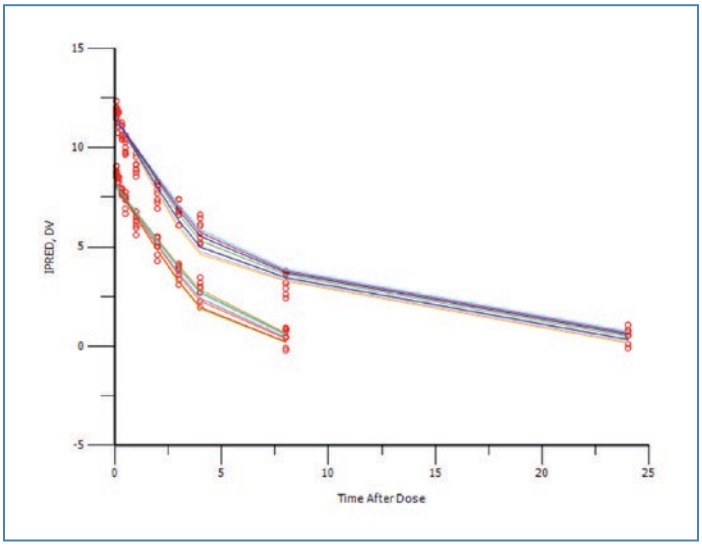


Figure 5. Plasma concentration-time profile for individual observations and individual model fits following intravenous injection. Individual observations are shown with red open circles for two different dose levels. Individual model fits are shown by the multi-colored lines. Compare with Figure 2.

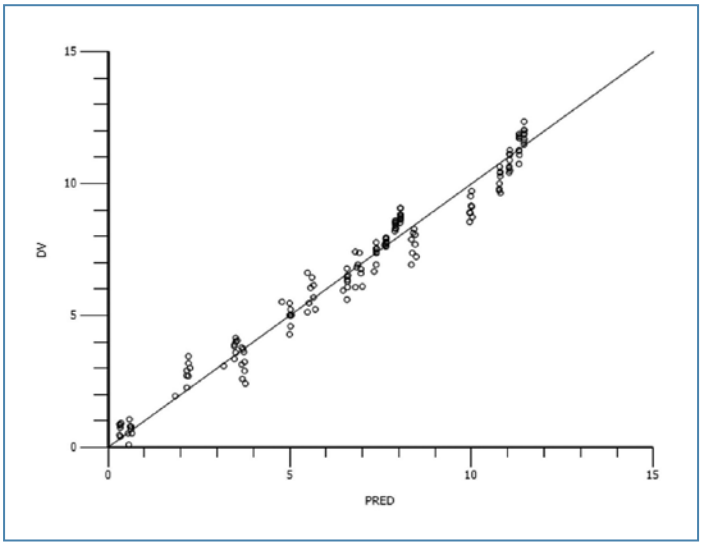


Figure 6. Model diagnostic plot of observed values (DV) versus PRED with the line of unity for the covariate model WT~CL. The DV and PRED pairs generally lie along the line of unity (solid line) with an even distribution on either side of the unity line. Compare with Figure 3.

Total analysis time was less than 10 minutes, including the minimization process, post-processing of 37 plots and 22 data tables, and preparation of summary text files.

As a researcher incorporates population modeling into the non-clinical data analysis, new insights can be gained. Information regarding the variability in PK parameters can be estimated across species to give insight into expected variability in human subjects and help in planning for future studies in animals. Covariates can be tested for significance, which may provide mechanistic insights, as well as information about potential effects in humans. Using Phoenix NLME, the additional population analysis requires addition of a single workflow object and can be executed without manually coding a complex set of equations.

Early clinical data

First-in-human studies are designed to assess the safety, tolerability and PK of drug candidates through a series of distinct cohorts of volunteers who receive escalating doses. While the primary focus of these studies is to evaluate the safety of the drug candidate in human subjects, they often generate a wealth of PK data. Standard PK analysis for first-in-human studies include the use of non-compartmental analysis to generate estimates for drug exposure (AUC, C_{max}), and elimination (CL, $t_{1/2)}$. By applying the principles of PopPK analysis, significantly more information can be gathered from this PK data.

A large first-in-human study was conducted with an intravenous agent that was administered at multiple doses and multiple infusion rates to give 13 unique dosing regimens. Plasma concentration-time data (2029 samples) was available from 56 subjects that comprised a parent drug and a primary metabolite. A combined parent-metabolite PK model was built to simultaneously describe the plasma concentration data for the parent drug and the metabolite (Figure 7).

This model estimates the clearance of both the parent drug and the metabolite as well as the formation rate of the metabolite M1, which is an irreversible process. Using the graphical modeling feature of Phoenix NLME, this model was constructed (Figure 8). Utilizing the non-compartmental analysis dataset, the population model was executed by assigning parent drug concentration column to the CObsPar object (Concentration Observation Parent), and the metabolite concentration column to the CObsMe object. Phoenix NLME provided initial estimates and initiated the model fitting process.

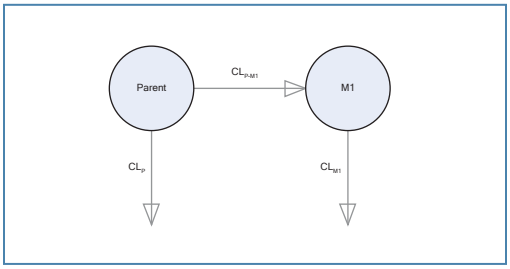


Figure 7. Model schematic for parent-metabolite model. Following intravenous infusion of the parent drug, there are two clearance processes: conversion of the parent to metabolite ($CL_{P\text{-}M1}$) and other clearance of the parent (CL_P). The metabolite has a single clearance mechanism (CL_{M1}).

The tight integration of NLME within the Phoenix platform provides the user with a single, easy-to-use tool for PK/PD analysis from early non-clinical work through clinical trials.

Total analysis time was less than 10 minutes, which includes the minimization process (estimation of parameters), post-processing of 37 plots and 22 data tables, and preparation of summary text files. The base model was further refined by adding weight as a covariate of the volume of distribution and the clearance of the parent drug using the same method described above for the non-clinical data.

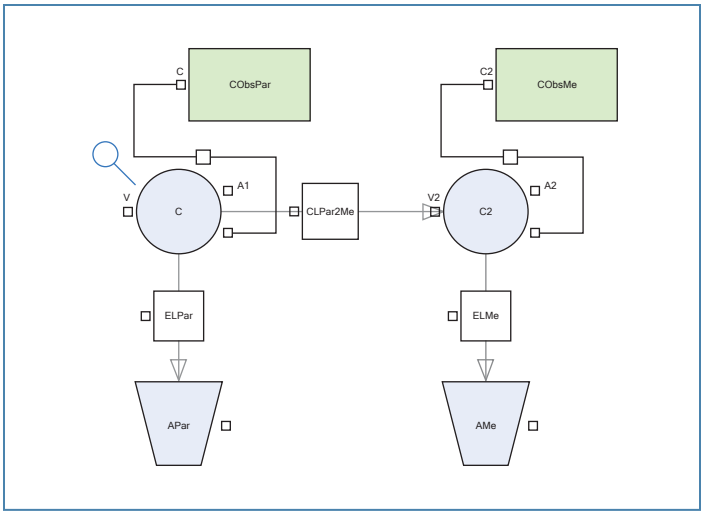


Figure 8. Phoenix NLME graphical model editor for parent-metabolite model. Central compartment for parent (C) and metabolite (C2) are shown with grey circles. Elimination compartments (eg, urine) for parent (APar) and metabolite (AMe) are shown with grey trapezoids. The green rectangles represent the concentration observations for parent (CObsPar) and metabolite (CObsMe). The clearance parameters for clearance of the parent drug (CLpar), conversion of the parent to the metabolite (CLPar2Me), and clearance of the metabolite (CLMe) are indicated by the open squares.

The resulting model provided a reasonable fit of the observed data (Figure 9). This model established the proportion of parent drug converted to metabolite relative to the total parent-drug clearance; a fact that was not known from the non-compartmental analysis alone. The final parent-metabolite PopPK model was used to simulate the plasma concentration-time profile for a multiple dose Phase 2 study in a patient population. These simulations were critical to demonstrate that the metabolite, which was associated with some animal toxicity, would not accumulate significantly following multiple doses.

Conclusion

Drug development is a complex, multidisciplinary effort that requires integration of many diverse pieces of information with the purpose of establishing definitive data of the safety and efficacy of a drug product. Thus, the most valuable asset of any pharmaceutical organization is the data generated from studies with a drug product.

As shown in these two examples, standard pharmacokinetic studies can be analyzed with PopPK techniques to extract additional information. By developing these models early in the drug development effort, the models can be refined and optimized as more data is collected.

The tight integration of the NLME module within the Phoenix platform provides the user with a single, easy-to-use tool for PK/PD analysis from early non-clinical work through Phase 3 clinical trials.

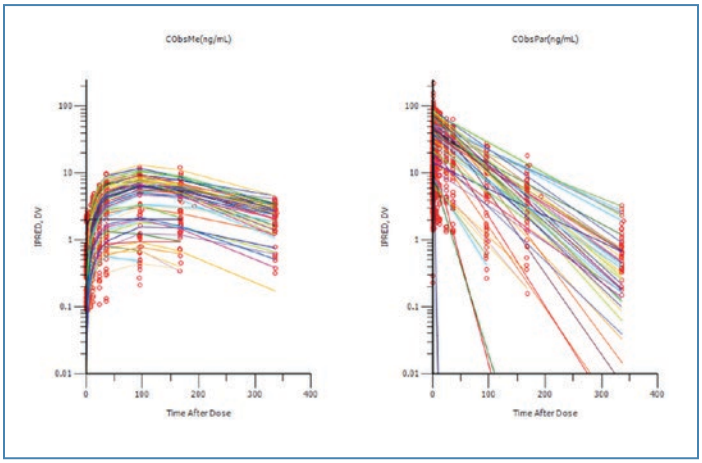


Figure 9. Individual observations and predictions versus time after initiation of infusion. Plot on the left represents the metabolite concentration observations (red circles), individual predicted concentration-time curves (multicolored lines) relative to the time after dose. Plot on the right represents the same data for the parent drug.

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