

**Title:** Meta Analyses of Drug X using a Population Pharmacokinetic Approach

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**Objectives:** To develop a population pharmacokinetic (PK) model that describes the data from three clinical trials to identify the covariates that affect the PK of the drug.

**Methods:** Population PK analysis was conducted by pooling data from one clinical trial in which drug X was administered alone as a multiple dose regimen in healthy subjects as well as in patients, and two other trials which used a different formulation of Drug X in patients in combination with another drug. Drug X concentration-time data were analyzed using nonlinear mixed effects modeling approach (NONMEM®) with FOCE. Interoccasion variability was evaluated before covariate selection. Formulation and treatment were assessed as the categorical covariates. Covariates were tested using GAM in Xpose@[1], and further by forward inclusion and backward elimination.

**Results:** A one-compartmental population PK model was developed with a linear elimination process. The absorption of Drug X was best described as a Weibull function for the first dose [2], and first order absorption for the subsequent doses. The bioavailability of Drug X was expressed as a function of dose. Inclusion of inter-occasion variability for clearance significantly improved individual predictions. Formulation was a significant covariate on the first-order absorption rate constant, Gama coefficient in Weibull Function, and bioavailability. The final model was validated with 500 simulations via a posterior predictive check (PPC) approach [3]. Covariates such as age, gender, and body weight did not have any significant effect on the objective function and were not included in the final model.

**Conclusions:** The population PK model for Drug X adequately described the concentration –time profiles obtained in clinical trials. This PK model may be used in future simulations studies.

#### References:

1. Jonsson, E.N. and M.O. Karlsson, *Xpose--an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM*. Comput Methods Programs Biomed, 1999. **58**(1): p. 51-64.
2. Piotrovskii, V.K., *The use of Weibull distribution to describe the in vivo absorption kinetics*. J Pharmacokinet Biopharm, 1987. **15**(6): p. 681-6.
3. Yano, Y., S.L. Beal, and L.B. Sheiner, *Evaluating pharmacokinetic/pharmacodynamic models using the posterior predictive check*. J Pharmacokinet Pharmacodyn, 2001. **28**(2): p. 171-92.