

Title: Evaluation of an alternative approach for multiple-dose population pharmacokinetic data analysis in the presence of noncompliance

Authors: Pankaj Gupta* (1), Matt Hutmacher (2), Bill Frame (1), Raymond Miller (1)

Institutions: (1) Pfizer Global Research and Development, USA

(2) The Ann Arbor Pharmacometrics Group, Ann Arbor, MI, USA

Objectives: To systematically evaluate a promising approach based on the superposition principle, for population PK data analysis under noncompliance.

Methods: A pilot simulation study investigating the aforementioned method has been presented previously (1). A one compartment model with first order absorption and first order elimination was used to generate PK data. Three levels of noncompliance were incorporated ($r = 0, 0.2$ and 0.3 , respectively) where r represents a probability of dose omission at each nominal dose time. Data were simulated using a multiple dose design and analyzed using the conventional methodology (assumption of perfect compliance) followed by the proposed approach which separates estimating the elimination rate from the model based steady-state PK concentration. The two methods were compared with respect to bias (mean error) in and imprecision (mean absolute error) of the parameter estimates. Next, gender was introduced as a covariate on CL. The data were analyzed with and without the inclusion of this covariate to assess the type I error rate. Similarly, power was estimated by simulating under the alternate hypothesis (presence of a covariate) and fitting a base and a covariate model to the simulated data. An empirical distribution constructed under the reduced model was used to obtain a cutoff for the likelihood ratio test to ensure a 5% error rate. NONMEM VI was used for all the analyses.

Results: The simulation study revealed that in the presence of missed doses, the conventional method yielded highly biased and imprecise estimates for the structural and variance parameters when full compliance was assumed. However, dose omission did not significantly influence the performance of the new method as evidenced by the nearly consistent bias and imprecision across the three compliance scenarios. Missed doses severely impacted the estimation of the residual variability, where the me increased from -0.7% ($r=0$) to 376% ($r=0.2$) and the mae from 11% to 376% , for the conventional method. In contrast, the new method demonstrated a superior and consistent performance in these performance measures for the residual variability.

Under 30% noncompliance the conventional method gave a higher cutoff value (4.77) for the type I error rate (95th percentile of the empirical distribution of ΔOFV) compared to a chi square distribution (3.84, 1 degree of freedom). This suggested a potential inflation of type I error estimate if the likelihood ratio test was employed for covariate detection. The two methods showed a decline in power as the underlying noncompliance increased; however the drop was more pronounced for the conventional method (38%) compared to the new one (10%). At $r=0.3$, the difference in power between the two approaches was found to be 20%

Conclusions: The results of the simulation study demonstrate that the new method provides an attractive alternative for outpatient PK data analysis. The salient features of this method are a) no assumption regarding dosing history or steady state is required b) irregularities in dosing are addressed by removing the influence of previous doses on the estimation of elimination rate/clearance c) the method is consistent in performance regardless of the extent of underlying noncompliance.

It is anticipated that this method will prove most useful in late stage development work (outpatient with sparse data), and when such data arising from different dosing regimens/studies are to be pooled for analysis with those collected under more controlled dense sampling designs. Ultimately, the use of this approach will result in greater

confidence in the results from outpatient PK studies which will further facilitate characterization of exposure-response relationships.

References:

- [1]. Gupta P, Hutmacher MM, Frame B, Miller R. A new approach for population pharmacokinetic data analysis under noncompliance. PAGE 16 (2007) Abstr 1136 [www.page-meeting.org/?abstract=1136]
- [2]. Soy D, Beal SL, Sheiner LB. Population one-compartment pharmacokinetic analysis with missing dosage data. *Clin Pharmacol Ther.* 2004 Nov;76(5):441-51.
- [3]. Mu S, Ludden TM. Estimation of population pharmacokinetic parameters in the presence of non-compliance. *J Pharmacokinet Pharmacodyn.* 2003 Feb; 30(1):53-81.
- [4]. Wang W, Husan F, Chow SC. The impact of patient compliance on drug concentration profile in multiple doses. *Stat Med.* 1996 Mar 30; 15(6):659-69.