Estimation of Population PK Measures: Selection of Sampling Grids

Valerii Fedorov and Sergei Leonov

GlaxoSmithKline, Collegeville, PA

ABSTRACT

In clinical pharmacokinetic (PK) studies multiple blood samples are taken for each enrolled patient, and various population PK measures, such as area under the curve (AUC), maximal concentration (Cmax) and time to maximal concentration (Tmax) are estimated. In this talk we compare a model-based approach, where parameters of a compartmental model are estimated and the explicit formulae for PK measures are used, and an empirical, or model-independent, approach, where numerical integration algorithms are used for AUC and sample estimates for Cmax and Tmax.

In our earlier studies we have discussed how to optimize sampling schemes for compartmental models (model-based approach) and showed that the number of collected samples may be reduced with minimal loss of precision; see Fedorov, Gagnon and Leonov (2002), Gagnon and Leonov (2005). Moreover, once costs are introduced (e.g. costs of enrolling patients and costs of analyzing samples) then sampling schemes with smaller number of samples which mix sampling sequences may outperform more dense sampling schemes.

Since regulatory agencies usually require the model-independent estimation of PK measures, this presentation will focus on the empirical approach while using the model-based approach as a benchmark. We show how to split a single sampling grid into two or more subsets, which substantially reduces the number of samples taken for each patient, but often has little effect on the precision of estimation of PK measures in terms of mean squared error (MSE). For a number of special cases we derive explicit formulae for the MSE of the empirical estimator of AUC. When costs are taken into account, these formulas allow the optimal selection of the number of patients and samples per patient.

References:

Fedorov, V., Gagnon, R. and Leonov, S. (2002). Design of experiments with unknown parameters in variance. *Appl. Stoch. Models Bus. Ind.* v.18, 207-218.

Gagnon, R., and Leonov, S. (2005). Optimal population designs for PK models with serial sampling. *J. Biopharm. Stat.* v. 15 (1), 143-163.