Prospective application of a multivariate population optimal design to determine parent and metabolite pharmacokinetic sampling times in a Phase II study.

Ivelina Gueorguieva and Kimberley Jackson

Lilly Research Centre, UK

ABSTRACT

A sparse pharmacokinetic sampling strategy is often applied to studies in Phase II due to logistical and practical considerations in study implementation requiring that a minimum number of samples are taken per patient. It is imperative that enough samples are taken and that these samples are at optimal times. This will ensure the data collected are informative for identifying pharmacokinetic parameters in model development. A number of statistical criteria for model oriented experiments, which maximize the information content of the data, are available. Criteria, based on the Fisher information matrix, whose inverse according to the Rao-Cramer inequality is the lower bound of the variance-covariance matrix of any unbiased estimator of the parameters, have previously been developed for population multivariate and univariate responses [1, 2]. We made use of a software program that was designed specifically to implement these methods [3]. Based upon a previously-developed population pharmacokinetic model that allowed simultaneous estimation of parent and metabolite pharmacokinetic parameters, we explored a D-optimal design for a future study, where optimal, clinically-relevant sampling time points were estimated. To allow more flexibility in study conduct, we proposed a design consisting of clinically-relevant sampling windows based on the optimal time points. This approach balanced the practical and logistical considerations of conducting the study and took into account factors such as the range of doses being studied, timing of samples during the day, potential for BQL concentrations, number of concurrent procedures, etc, against the best design for estimation of both the parent and the metabolite model parameters. This led to a final recommendation for the planned study to include four sampling windows.

[1] Mentré, F., Mallet, A. and Baccar, D. (1997). Optimal design in random-effects regression models. *Biometrika* 84:429-442

[2] Gueorguieva, I., Aarons, L., Jorga, K., Rodgers, T. and Rowland, M. (2006).Optimal design for multivariate response pharmacokinetic models. *J Pharmacokin. Pharmacodyn.* 33(2): 97-124

[3] Gueorguieva, I., Ogungbenro, K., Graham, G., Glatt, S. Aarons, L.(2007). A program for individual and population optimal design for univariate and multivariate response pharmacokinetic-pharmacodynamic models. *Computer Methods and Programs in Biomedicine.* in press, COMM-2619