J Pharmacokinet Pharmacodyn (2012) 39:727
DOI 10.1007/s10928-012-9272-2

COMMENTARY

Reply to the editor of Journal of Pharmacokinetics and Pharmacodynamics

Chakradhar V. Lagishetty · Pavan Vajjah · Stephen B. Duffull

Received: 24 August 2012 / Accepted: 5 September 2012 / Published online: 2 October 2012

We thank Karlsson and Bergstrand for their comments. We also generally agree with their interpretations of the findings of our work however we do not agree that our findings do not support our conclusions.

The key issue when considering inclusion of a covariate is specification of the model. We know a priori that all models are wrong, and hence we do not know the true covariate model. In this work we have created a misspecification in the covariate models that were used for estimation and shown that even when significant true correlation exists between the parameter and covariate that this does not always transpose to a reduction in BSV. Our conclusion: "In conclusion, it was found that a moderate to strong correlated covariate may not reduce random between subject variability and indeed may inflate the between subject variability due to covariate model misspecification. This would lead to the erroneous conclusion that the covariate was either not important or indeed that appropriate inclusion of the covariate would make the model substantially worse." The message here is, do not believe your models to tell you the right answer. We also show that a misspecified nested model will be fairly robust to misspecification and generally provide appropriate conclusions about the apparent importance of covariates. Note we only considered one nested structure in this work but other structures (including power models) would be of interest.

We leave it up to the modeller to determine whether a covariate should be considered that does not reduce BSV and what the implications of this are, which could include: (1) that the covariate is not relevant to the current analysis or (2) that the covariate model was misspecified and therefore it appears that the covariate is not relevant to the current analysis. We do not suggest including a covariate even if the fit is poor compared to the base model. However if the covariate, on biological grounds, is expected to be important then it is important to consider model misspecification.

We were hoping that a more complex variance–covariance approach to covariate model building would help but this was not apparent across the board and hence we concluded with the general note that these models may be of some value "Incorporating statistical models that account for covariance (covariate–eta interaction) may be useful diagnostically in identifying the variability explained by covariates."

The title statement was chosen when considering covariates of biological importance. We leave it up to the reader whether they agree with our title "A reduction in between subject variability is not mandatory for selecting a new covariate" which was intended to capture the eye of the reader.

C. V. Lagishetty (✉) · S. B. Duffull
School of Pharmacy, University of Otago, Dunedin, New Zealand
e-mail: chakradharshetty@gmail.com

P. Vajjah
Simcyp Ltd, Sheffield, UK