Title: Effect of Miss-specified Covariance Structures on Estimated Fixed Effect Parameters from Non-Linear Mixed Effects Models for PK Data

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Abstract

Objectives: This paper is an extension of the work done by Pfizer statisticians who reported on the effect of miss-specified covariance structures on linear mixed effects models[1]. They showed that using over-simplified between subject variance structures leads to a marked underestimation of the standard errors of the treatment effect. We are now interested to see if this is true with respect to non-linear mixed effects models which are commonly used in pharmacometrics.

Methods: A computer simulation study was preformed using NONMEM V. We simulated drug concentration data from a first order absorption with oral dosing structural model with 1 compartment disposition and first-order elimination. Statistical models with three different scenarios regarding between subject variability were used for our purpose. Scenario 1 had clearance, volume and Ka as fixed effects and bioavailability (F) as the random effect model in a crossover study design. For the second scenario, the statistical model had clearance and volume as the fixed effects with bioavailability (F) and Ka as random effects. The third scenario had clearance, volume, and Ka as the random effects with bioavailability not estimated (always 1).

Complex and over-simplified covariance structures where fitted for all three scenarios using FOCE in NONMEM.

Estimated population means of the structural parameters derived from over-simplified covariance structures were then compared to those from the complex model on the bases of the bias, standard errors (as estimated in the COV step in NONMEM), and coverage probabilities (based on 90% confidence intervals) for each of the three cases. Bias was estimated as the difference between the true value and the mean estimate (across all of the simulated trials) for a given scenario. Coverage probability was estimated as the proportion of simulated trials where the true parameter value was included in the confidence interval.

Results: Bias was small (less than 22 %) in all of the scenarios. When the estimation model had a covariance structure consistent with the simulated data, the coverage probabilities were approximately 70-90% (90% is expected). These two results (low bias and coverage probabilities) indicated that when the covariance model was correctly specified, the standard errors were approximately correct. Effects of model miss-specification differed for the three scenarios. For scenarios 1 and 2 the coverage's for clearance and volume provided by the over-simplified model were about 20% (compared to the nominal 90%). This result indicated that the standard errors were grossly under-

estimated. However, miss-specification of variance structure had no effect on the standard errors and coverage probabilities for clearance and volume in scenario 3.

Conclusions: Miss-specification of covariance structures did affect the outcome when bioavailability was the random effect in the model, resulting in the drastic underestimation of the standard errors of clearance and volume. Hence, inference based on the corresponding confidence intervals could result in wrong conclusions.

References:

[1] Willavize SA and Morgenthien EA 2006 "Comparison of Models for Average Bioequivalence in Replicated Crossover Designs" Pharmaceutical Statistics 5:201-211. (DOI: 10.1002/pst.212)