Development and Evaluation of New Model-Based Bioequivalence Statistical Approaches for Pharmacokinetic Studies with Sparse Sampling

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Introduction and objectives: In traditional bioequivalence (BE) analysis, two one-sided tests (TOST) are conducted on the area under the concentration-time curve (AUC) and the maximal concentration (Cmax), generally derived from pharmacokinetics (PK) studies with rich sampling, which is not always feasible. Our previous work, on a model-based (MB) TOST showed a type I error inflation on design with sparse sampling due to underestimation of the treatment effect on asymptotic standard error (SE) [1]. Here we propose and evaluate, through simulations, two alternative approaches on parallel designs.

Methods: We implemented a MB TOST using i) an empirical SE (or confidence interval, CI) from a parametric bootstrap method, and ii) a CI from the *a posteriori* distribution of the treatment effect sampled by Hamiltonian Monte Carlo (HMC) [2] using Stan [3]. These two approaches were evaluated on scenarios with rich or sparse sampling and moderate between subject variability (BSV, 15-30%), using the saemix R package.

Results: For the scenario with spare sampling, we confirmed that the MB TOST with asymptotic SE obtains inflated type I error estimates. MB TOST with bootstrap SE or HMC CI showed more accurate type I error estimates, i.e., included in the 95% prediction interval around 0.05 for 500 simulations = [0.0326;0.0729].

All three approaches of MB TOST showed sufficient power (between 0.76 and 1) under the scenarios with rich or sparse sampling.

Conclusions and perspectives: We explored and assessed approaches which are less sensitive to the type I error inflation on PK studies with sparse sampling as compared to that of the MB TOST with an asymptotic SE. Implementation of these approaches may provide alternative BE assessment methodologies in situations when conventional BE approaches with rich sampling are not feasible such as BE studies for ophthalmic drug products.

References:

[1] Dubois et al. (2011). Stat Med, 30, 2582-2600.
[2] Ueckert et al. (2015). ACoP meeting.
[3] Stan Development Team (2016). RStan: the R interface to stan, version 2.12.0.