

**Title:** An Improved Approach for Confirmatory Phase III Population Pharmacokinetics Analysis

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**Objectives:** For phase III studies, population pharmacokinetics is a powerful tool for assessing exposure in large populations and identify/quantify important covariates. The typical sparse sampling usually allows for the estimation of only relatively simplistic structural models, but still provides a means to assess covariate influence, e.g., age, sex, and to recommend potential dosing adjustment for drug labeling. The usual exploratory approach may contain certain biases [1] that can lead to unnecessary dosing adjustments. A confirmatory approach has been suggested in a situation of bioequivalence assessment [2]. We herein propose an approach of confirmatory nature aimed specifically at phase III population pharmacokinetics analysis for regulatory submission purpose.

**Methods:** A pre-specified primary analysis is proposed based on phases I/II data and the phase III study design, together with several specific sensitivity analyses. The sensitivity analyses aim to address potential concerns with the primary analysis, which may include misspecification of base and covariate models as well as the robustness with respect to dosing/sampling time inaccuracies. Careful assessment of information in the study design and selected covariates is required prior to launching the analysis. By statistical rationale, this approach eliminates certain biases that may occur in the estimated covariate effects, thereby preventing potential unnecessary dosing adjustment, and also allows for more accurate assessments of uncertainties in the results. For illustrative purpose, the approach was applied to several phase III analyses for regulatory submissions, covering both small molecule and therapeutic protein situations.

**Results:** Differences between the proposed approach and the commonly used extensive exploratory analyses submitted to regulatory agencies were small and consistent with both theoretical predictions and practical expectations. The proposed approach provided a clearer understanding of uncertainties in the conclusions. The analysis time was also substantially shortened because the amount of exploration was vastly reduced.

**Conclusion:** The proposed approach provides a method that is more accurate in statistical theory, and also gives better understanding of uncertainties and robustness from practical considerations. It is also relatively easy to implement with appropriate pre-planning prior to the analysis.

#### **References:**

[1] J. Ribbing and E.N. Jonsson. Power, selection bias and predictive performance of the population pharmacokinetic-covariate model. *Journal of Pharmacokinetics and Pharmacodynamics* 2004; 31:109–134.

[2] C. Hu, K. Moore, Y. Kim and M. Sale. Statistical issues in a modeling approach to assessing bioequivalence or PK similarity with presence of sparsely sampled subjects, *Journal of Pharmacokinetics and Pharmacodynamics*, 33(4): 321-339, 2004.