Title: Model Qualification for Exposure Metrics: A Population Pharmacokinetic Example

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Objective: To develop a population PK model that is qualified for metrics of exposure, Cmax (maximum-concentration for observed sampling design) and AUC (area-under-concentration-time for observed sampling design), especially in patients with renal insufficiency

Methods: Plasma concentration-time data from 5 clinical out-patient studies was modeled with a one-compartment 1st-order oral absorption and elimination model. Parameter estimation was performed using the first-order conditional estimation method with interaction in NONMEM version V. Post-hoc random variables (ETA) for each structural model parameter (CL/f, V/f, KA, ALAG1) were plotted versus cockroft-gault (CG) [1] and modified diet in renal disease (MDRD) estimated, glomerular filtration rate (GFR) [2;3], body weight, ideal body weight (IBW), lean body weight (LBW), serum creatinine, age, body mass index (BMI), gender, race, and study. Depending on the trend observed visually in these plots and physiological relevance, covariate relationships were modeled with the structural model parameters.

An objective assessment was needed of the predictive ability of the pop PK model for domain-specific quantities (concentration and summary metrics [AUC & Cmax]) of interest, and to determine whether the model based inferences would have a noticeable effect in substantive inferences to be drawn from the model for patients with renal insufficiency. A stepwise automated approach was adopted to perform model based simulations conditioned on the observed population data (i.e., observed covariate structure and sampling design), the population model, and bootstrapped median (n=1000) population model parameter estimates to address the following questions:

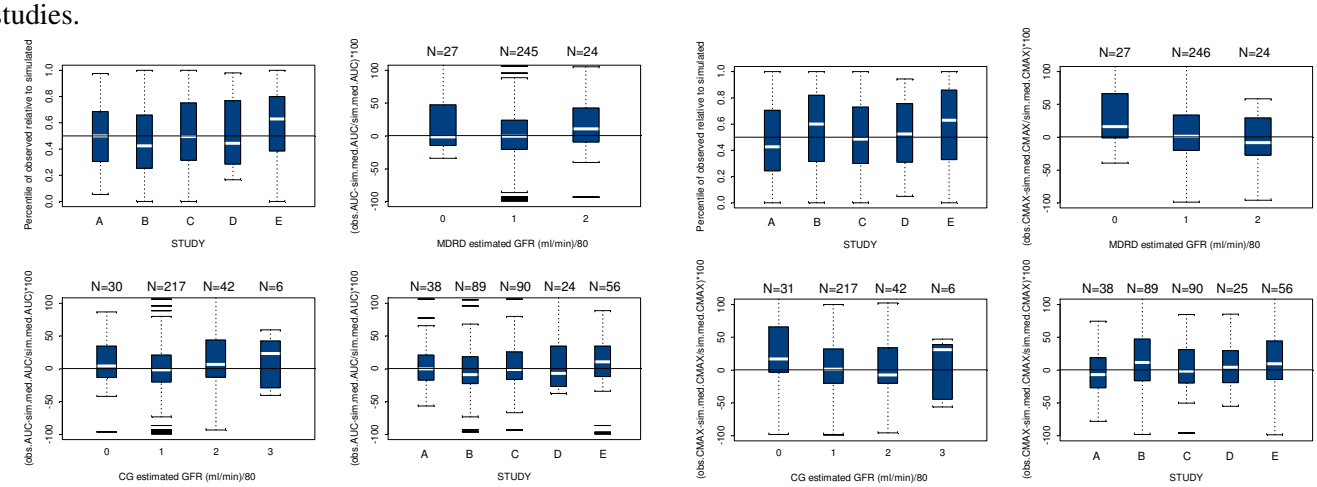
- How typical do observed values of Cmax and AUC appear relative to the predictive distributions of these metrics under the model given the data ?
- How are these deviations related to significant model covariates ?

Posterior predictive distributions of concentrations and metrics were computed by using the degenerate distribution method of Yano et al [4] as estimated by substituting the bootstrapped median of the maximum likelihood estimates (MLE) for the thetas and omegas. Following the model based simulations, a visual comparison of the predictive discrepancy[5] at the level of each concentration per subject and each calculated-metric per subject was implemented.

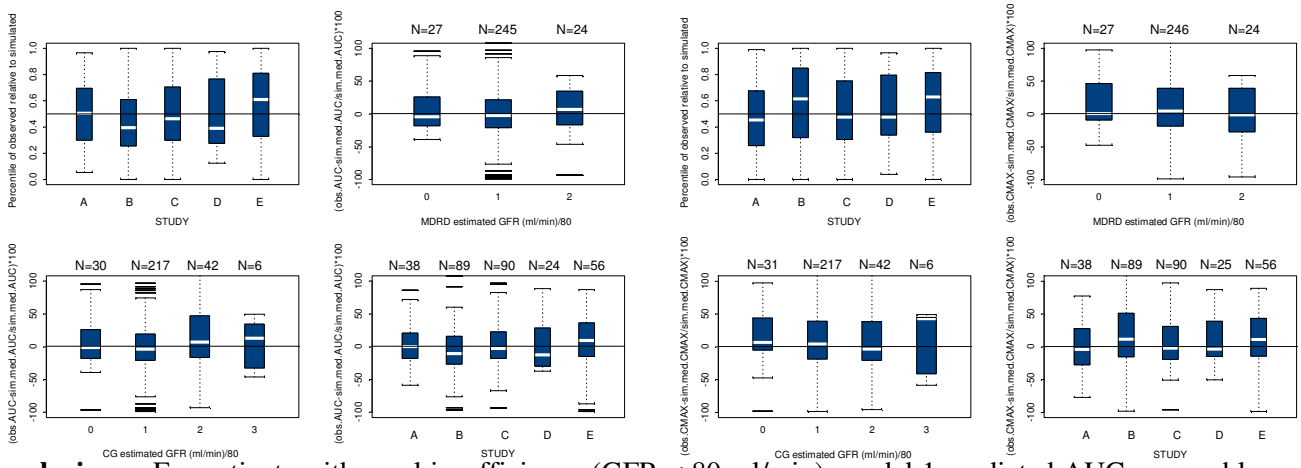
Results: The total apparent clearance (CL/f) was modeled as a composite of renal and non-renal components. The renal component was related to GFR and LBW, and the non-renal component was related to LBW. The apparent volume of distribution (V/f) was incorporated as a function of LBW [model 1].

On observing the relationship of distribution of post-hoc random variable ETA for V/f versus GFR, it was found that with decrease in GFR there is a decrease in V/f (results not shown). The covariate model for V/f was modeled as linearly dependent on GFR for GFR < ‘x’ mL/min (e.g. x=100 ml/min) and as constant for GFR > ‘x’ mL/min [model 2].

Model 1, predictive qualification plots (percentile of observed relative to simulated metric and percent-deviation of simulated from the observed metric) for AUC[left] and CMAX[right] over significant covariates (GFR) and studies.



Model 2, predictive qualification plots (percentile of observed relative to simulated metric and percent-deviation of simulated from the observed metric) for AUC[left] and CMAX[right] over significant covariates (GFR) and studies.



Conclusions: For patients with renal insufficiency (GFR < 80 ml/min), model 1 predicted AUC reasonably well but Cmax was under-predicted. Model 2 predicted both AUC and Cmax reasonably well. Qualification of a model should be performed not only for metric(s) of interest but also on the relevant region of covariate space (e.g. GFR < 'x' ml/min).

References:

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