Title: Immunogenicity in PK of Monoclonal Antibodies**:** Detection and Unbiased Estimation of Model Parameters

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Objectives: To propose and evaluate methods for immunogenicity detection and unbiased estimation of model parameters in the presence of immunogenicity.

Methods: A two-compartment model typical for monoclonal antibodies was used to simulate six-month study with monthly dosing. Sampling included the rich data following the first and the last doses, and trough and peak values for all other doses. Immunogenicity (in 30% of subjects) was simulated as increase in clearance: (a) 5-fold after 2-6 months of dosing; (b) according to a Hill function of time with inter-individual variability in E_{max} and T_{50} parameters. Two methods of accounting for immunogenicity were tested.

The first method introduced the random effect ETA_{err} on the magnitude of the residual error, hypothesizing that subjects with immunogenicity would have higher ETA_{err}. The model was then fitted to the datasets where increasing fractions of subjects with the highest ETA_{err} were removed.

The second method used Nonmem mixture model routine. For the data set (a) it was assumed that the study population consisted of several subpopulations. Subpopulation 1 did not have immunogenicity while the other subpopulations were allowed to have an increase in clearance following i^{th} dose (i=2 to 6). For the data set (b) 2 subpopulations represented non-immunogenic and immunogenic subjects with increase in clearance modeled by Hill function of time.

Results: The parameter estimates of the model that did not account for immunogenic increase of clearance were significantly biased. Introduction of ETA_{err} reduced, but not eliminated bias. High ETA_{err} identified immunogenic subjects. When subjects with high ETA_{err} were removed from the data, bias due to unaccounted immunogenic increase of clearance was eliminated. The mixture models provided the unbiased estimates of the model parameters in both cases (a) and (b). The simulated immunogenic subjects were correctly assigned to the appropriate subpopulations.

Conclusions: For the simulated datasets with rich sampling, the proposed methods identified subjects with immunogenic increase of clearance, provided unbiased individual estimates of onset time and magnitude of immunogenicity, and unbiased estimates of the population parameters. Application to the real data will likely face more difficulties. However, the proposed methods may provide useful tools for detection and evaluation of changes in the PK parameters related to immunogenicity.