

Case Study #3: Drug X PK-PD Modeling / Simulation

- Pharmacokinetics
 - 3-compartment disposition with extensive tissue distribution and long elimination half-life
 - Linear and non-linear elimination mechanisms
- Pharmacodynamics
 - Slow and prolonged onset of effect with relevant biomarker
 - Described by indirect PD response model (inhibition of synthesis)

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- Data
 - Phase I PK-PD data in target population with extensive sampling
 - 110 patients
 - Multiple dose levels & placebo (by cohort)
 - Multiple routes of administration (IV, SC)

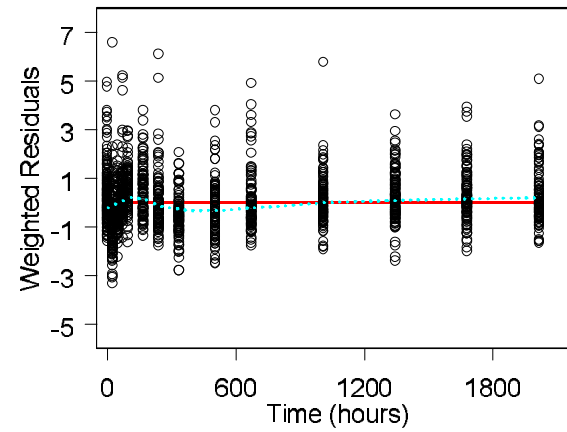
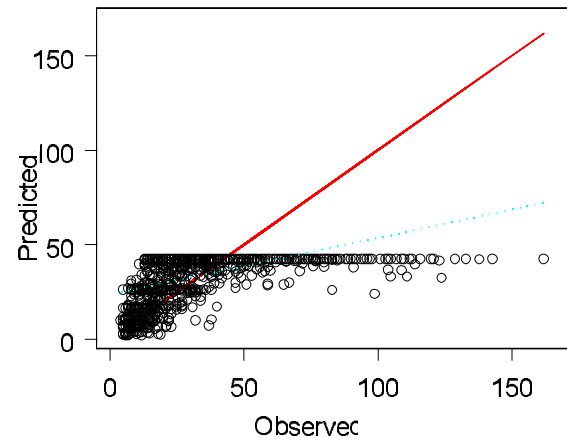
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- Analysis objectives
 - Develop population PK & PK-PD models
 - Estimate exposure-response relationship
- Intended use of model
 - Simulate expected response under various (possibly unstudied) dose and dose regimen conditions
 - Make decisions about dose/regimen for future Phase II – III trials

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- Modeling results
 - 3-compartment PK model with parallel linear/nonlinear elimination results in good fit
 - Final PD model fit is decent, but does reveal some under-prediction at high observations and slight over-prediction at lower concentrations.
 - Precision of PD parameter estimates (%SE) obtained from \$COV step: EC50 (28%), ksyn (11%), kdeg (12%), variance terms (20-40%)

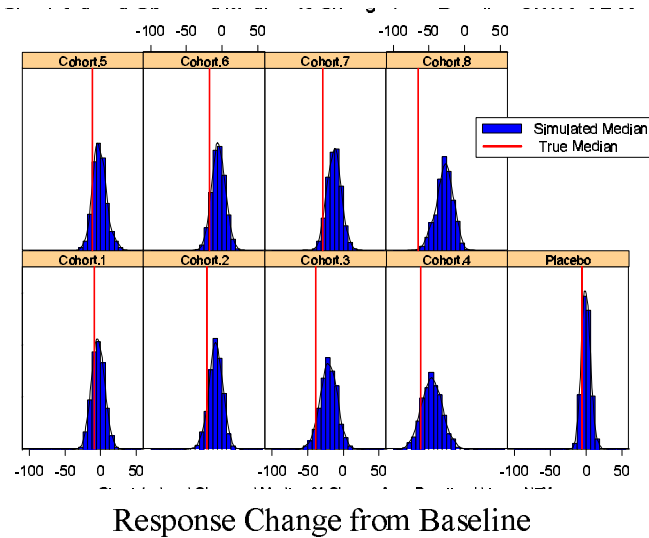
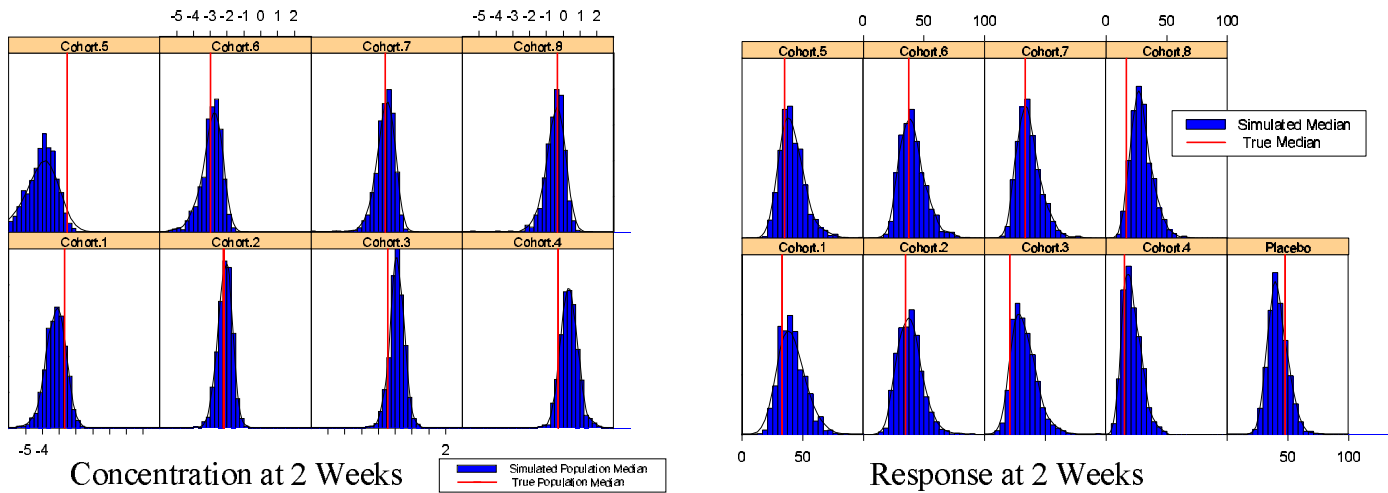
PD Goodness of Fit



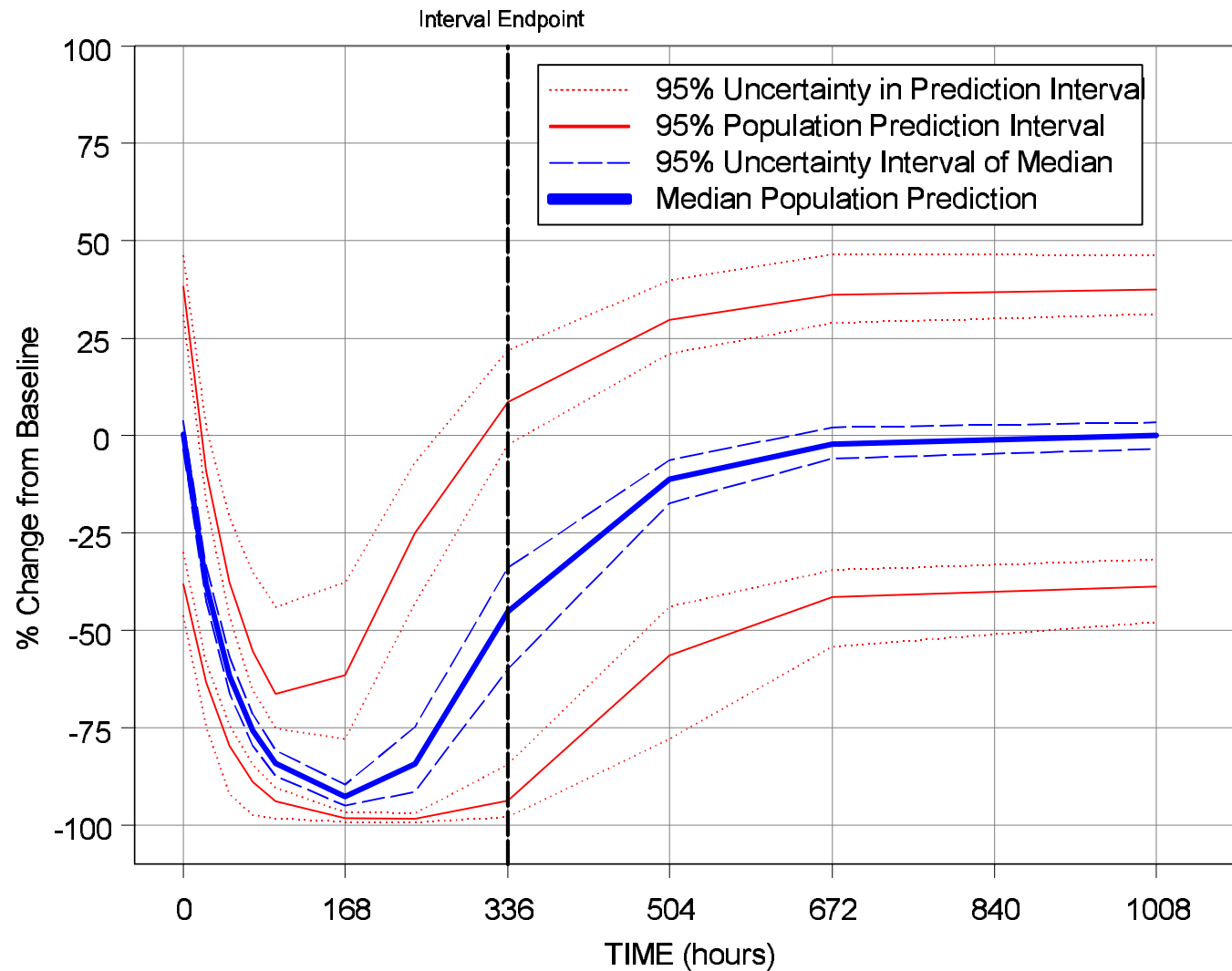
Case Study Questions

1. Which method(s) of model selection and/or evaluation would you select? Why?
2. Describe the implementation of the method(s).
3. How would you make decisions based upon the results of the model evaluation method(s)? Which statistics or metrics would you use to guide decision making?

Predictive Check



Simulation with Uncertainty (new dose and regimen)



Global Sensitivity Analysis

