A Modeling Approach to Assessing Bioequivalence with Presence of Sparsely Sampled Subjects

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Introduction

- In drug development, similarity of PK (AUC and Cmax) between different populations frequently need to be assessed
  - Patients vs. healthy volunteers
  - Pediatrics vs. adults
- Some subjects may be sparsely sampled, rendering individual evaluation of AUC and Cmax difficult
- Modeling seems a reasonable alternative
- Many ways to model - needs care for analysis to have confirmatory impact

Modeling vs. BE Analysis

- Traditional Modeling: Analysis Depends on Data
  - Seeks “most likely” model and predictions
  - Confidence intervals often qualitative
  - Generally used for hypothesis generation, not confirmation
  - Results may differ by modeler
- BE Analysis: Prespecified Analysis Plan
  - Few, if any, explorations (preliminary tests)
  - Controls type I error
  - Confirmatory
- To have confirmatory impact, a modeling approach needs a prespecified plan suited for BE and more quantitative confidence interval calculation

Application Scenario

- GW433908
  - A phosphate ester prodrug of amprenavir (APV) being developed for HIV treatment
  - Given alone and in conjunction with ritonavir (RTV) to healthy subjects and HIV infected subjects
  - In 4 studies, SS PK samples collected after 14 days
- Sparse sampling in one study in HIV infected subjects
- Need to assess similarity of PK between healthy and HIV-infected subjects
  - For both +/- RTV

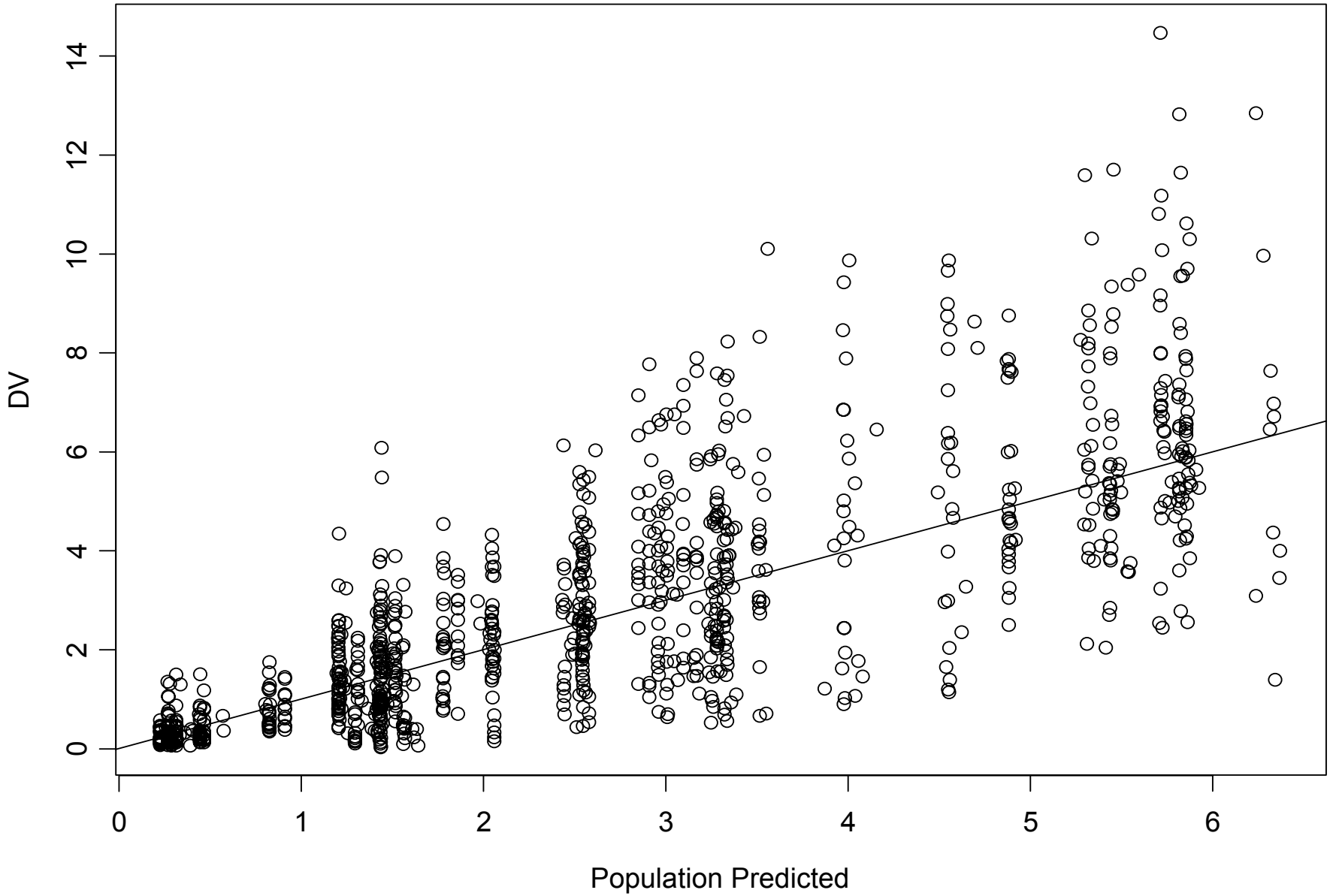
Drug	Pop.	# Subj	Sampling Schedule
GW433908	Healthy	12	0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 h
GW433908	Patient	54	0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 h
+RTV	Healthy	25	0, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 8, 10, 12, 16, and 24 h
+RTV	Patient	37	0, 2, 4 h and 0 h

Analysis Plan (Prespecified)

- Model Building
  - A plan specifying the criteria for choosing structural models and covariates
    - Testing only covariates (RTV, weight and AAG) that were likely to influence PK
  - Maintain subject population (similar to formulation in BE) effects in all structural model parameters, without testing their significance
- Assessing Confidence Interval
  - Model parameters give estimates of AUC and Cmax ratios
  - Using bootstrap to obtain confidence intervals of AUC and Cmax ratios

Model Building Result

- An oral two-compartment model was selected, using NONMEM (FOCE + INTER)
- 2 Covariates Affecting Structural Model Parameters
  - Subject population (healthy vs. infected, prespecified)
  - RTV on only CL (indicated by previous experience, expected)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Population Predicted

Confidence Interval Computation

- 3,000 bootstrap runs conducted
  - 149 did not converge
  - 108 had $COV fail
  - Remaining 2743 runs used
  - AUC and Cmax ratios computed from parameter estimates
- 90% confidence intervals obtained from 5% and 95% percentiles from bootstrapping distribution

Variable	5% percentile	Median	95% percentile
AUC – Healthy- GW433908	13.462	15.251	17.327
AUC – Healthy - GW433908+RTV	59.362	65.187	71.173
AUC – HIV-infected- GW433908	14.049	15.855	17.745
AUC – HIV-infected- GW433908+RTV	60.518	67.460	74.763
Ratio of AUC (HIV-infected / Healthy)	0.908	1.041	1.174
Cmax – Healthy- GW433908	2.791	3.181	3.588
Cmax – Healthy - GW433908+RTV	5.348	5.865	6.402
Cmax – HIV-infected- GW433908	3.081	3.535	4.025
Cmax – HIV-infected - GW433908+RTV	5.791	6.391	7.063
Ratio of Cmax, GW433908 only (HIV-infected/ Healthy)	0.951	1.108	1.297
Ratio of Cmax, GW433908+ RTV (HIV-infected/ Healthy)	0.956	1.088	1.244

Confidence Interval Results

- AUC ratios meets 80-125% criteria
- Cmax ratio meets 80-125% criteria for GW433908 given alone
- For GW433908 given with RTV, upper bound of Cmax ratio at 129.7%, exceeding 125%
  - Cmax in HIV infected subjects is slightly higher than in healthy volunteers, although the difference was considered clinically insignificant
- Overall, analysis confirmed similarity in amprenavir PK between healthy and HIV infected subjects

Effect of Model Exploration

- Excluding the influence of subject population (formulation) effect on any structural model parameter obscures differences between subject populations
  - Results biased towards concluding equivalence
- Model exploration costs degrees of freedom, thus adversely affects type I error / power
  - Formally accounting model exploration is theoretically possible but difficult to implement
- However, more accurate model favorably affects type I error / power
- Striking a balance within analysis plan

Conclusion

- Modeling can be useful for BE-type of assessment when subjects are sparsely sampled
- Care is needed to maintain BE principle in controlling type I error
  - Limiting model explorations
  - Maintain formulation (subject population) effects on model parameters
  - Focus on computing confidence intervals
  - Must have a detailed, prespecified analysis plan