



# International Workshop on Uncertainty and Variability in Physiologically Based Pharmacokinetic (PBPK) Models

October 31 - November 2, 2006 Research Triangle Park, NC

## Detailed Charges to the Breakout Groups

### Overall Charge Questions

1. What are past/current practices, their strengths/limitations?
2. What should be considered “best” practices?
3. What could be done *now* to improve/ expand use of “best” practices?
4. What needs to be done medium-/long- term to further improve the characterization of uncertainty and variability in PBPK modeling?
5. What needs to be included in reports of modeling activities, so that models are transparent for evaluation and use.

### Model Specification (Group 1)

#### Scope

- Deterministic model structure (mathematical representation of biological system and data)
  - Degree of lumping across and within tissues
  - Biological processes within/between compartments
  - Metabolic pathways
  - Evaluating alternative model structures
- Statistical model structure for parameter and data uncertainty and variability (overlap with Groups 2, 3)
  - Intra- and inter- subject/experiment/group variability
  - Structure of errors between data and model predictions
  - Representation of biological and statistical interdependencies, correlations, and autocorrelations

#### Key Issues

- To what extent should model structure be tailored to database differences across species?
  - Amount of data (rodents >> humans)
  - Nature of data (in vivo vs. in vitro; direct vs. surrogate/ extrapolated).
  - Ensuring model and parameters are identifiable (role of statistical/sensitivity analyses?)
- Evaluating alternative models
  - What statistical methods are useful for comparing models?
  - How to weigh parsimony vs. completeness vs. desired use?
- How to integrate the statistical model for uncertainty and variability into model development?

## **Model Calibration (Groups 2A/2B)**

### **Scope**

- Methodology for estimating parameters
  - Parameters to be estimated from *in vivo* kinetic data
  - Parameters to be fixed at literature/*in vitro* values
  - Estimating central tendencies, uncertainty, and variability
- Statistical structure for parameter and data uncertainty and variability (overlap with Groups 1 and 3)
  - Intra- and inter- subject/experiment/group variability
  - Structure of errors between data and model predictions
  - Representation of biological and statistical interdependencies, correlations, and autocorrelations
- Evaluation of consistency between model and data
  - Evidence for model's predictive power ("Validation")
  - Comparing alternative models

## **Model Calibration (Groups 2A/2B)**

### **Key Issues I (Group 2A starts here)**

- To what extent should *in vivo* data be used for estimating parameters vs. "validating" the model?
  - Validation only
  - Split data into "calibration/validation" sets
  - Estimation only.
  - Other methods (e.g., cross-validation?)
- What depth/rigor of statistical model and parameter calibration is necessary?
  - When is it useful and practical to use a formal statistical population approach (e.g., Bayesian) to estimate all parameters from all datasets simultaneously?
  - When are less intensive approaches (e.g., fit-by-eye, fix some/fit others, sequential) sufficient?

### **Key Issues II (Group 2B starts here)**

- Implementation of the statistical model
  - When is it justifiable not to include all the data?
  - What sources of uncertainty/variability (Intra- and inter- subject/experiment/group, measurement error, model error) to include (and how!)?
  - How to account for a variety of data collection issues?
    - Different experimental designs (longitudinal, serial sacrifice, closed chamber, number of data points)
    - Availability of individual vs. aggregated data
  - What statistical method(s) are the most appropriate/practical?
- How to evaluate model performance (deviance between predictions and data)?
  - Absolute ("is this good enough?")
  - Relative ("is A better than B?"), while accounting for degree of model parsimony

## **Model Prediction (Group 3)**

### **Scope**

- Methodology for characterizing uncertainty and variability in model predictions for risk assessment
  - Probabilistic vs. alternative methods.
  - Supplemental data *vis-à-vis* populations of interest
  - Uncertainty from alternative models (including “default” models)
- Statistical structure for parameter and prediction uncertainty and variability (overlap with Groups 1 and 2)
  - Intra- and inter- subject/experiment/group variability
  - Uncertainties carried over from calibration
  - Representation of biological and statistical interdependencies, correlations, and autocorrelations
- Feedback to data needs and experimental design

### **Key Issues**

- What changes to the PBPK and statistical models and parameters are needed for risk assessment prediction?
  - Alternatives to probabilistic methods?
  - How to incorporate supplemental data on populations of interest?
  - What sources of uncertainty/variability should/should not be carried over from specification and calibration steps?
  - Structural changes based on differences between available data and risk assessment needs?
- How to characterize uncertainty from alternative PBPK and statistical models?
- How to provide feedback to data needs and experimental design?

### **Cross-cutting issues (Addressed in multiple breakout groups)**

- Extrapolation to/among humans
  - Less data available as compared to laboratory animals
  - Overall population variability (vs. in a small number of healthy volunteers)
- Uncertainty in surrogate or “proxy” data
  - Rodent data as surrogate for humans (e.g., tissue-air partition coefficients; allometric scaling)
  - *In vitro* – *in vivo* extrapolation (e.g., microsomal metabolism)
- Availability/role of statistical models and methods
  - What level of rigor is necessary for different applications?
  - Sources of variability that are often ignored – among animals, intra-individual, inter-experimental?
- Model structure uncertainty