

# Modeling and Simulation for Optimal Drug Development in Pediatric Populations

04 October 2008

Samer Mouksassi, PharmD  
Associate Scientist  
Reporting and Analysis Services  
[smouksassi@pharsight.com](mailto:smouksassi@pharsight.com)

JF Marier, PhD, FCP  
VP and Lead Scientist  
Reporting and Analysis Services  
[jfmarier@pharsight.com](mailto:jfmarier@pharsight.com)

# Pediatric Drug Development: Clinical Needs

- Clinical Needs:
  - To determine a safe and effective dose
  - A easy way to calculate individualized dose if needed
  - To understand the impact of developmental changes on PK/PD
- Current Status:
  - Drug dosing is highly empirical and based on trial and error
  - Linear extrapolation (mg/kg or mg/m<sup>2</sup>) may not be adequate
  - PK/PD relationship is unknown in pediatric patients

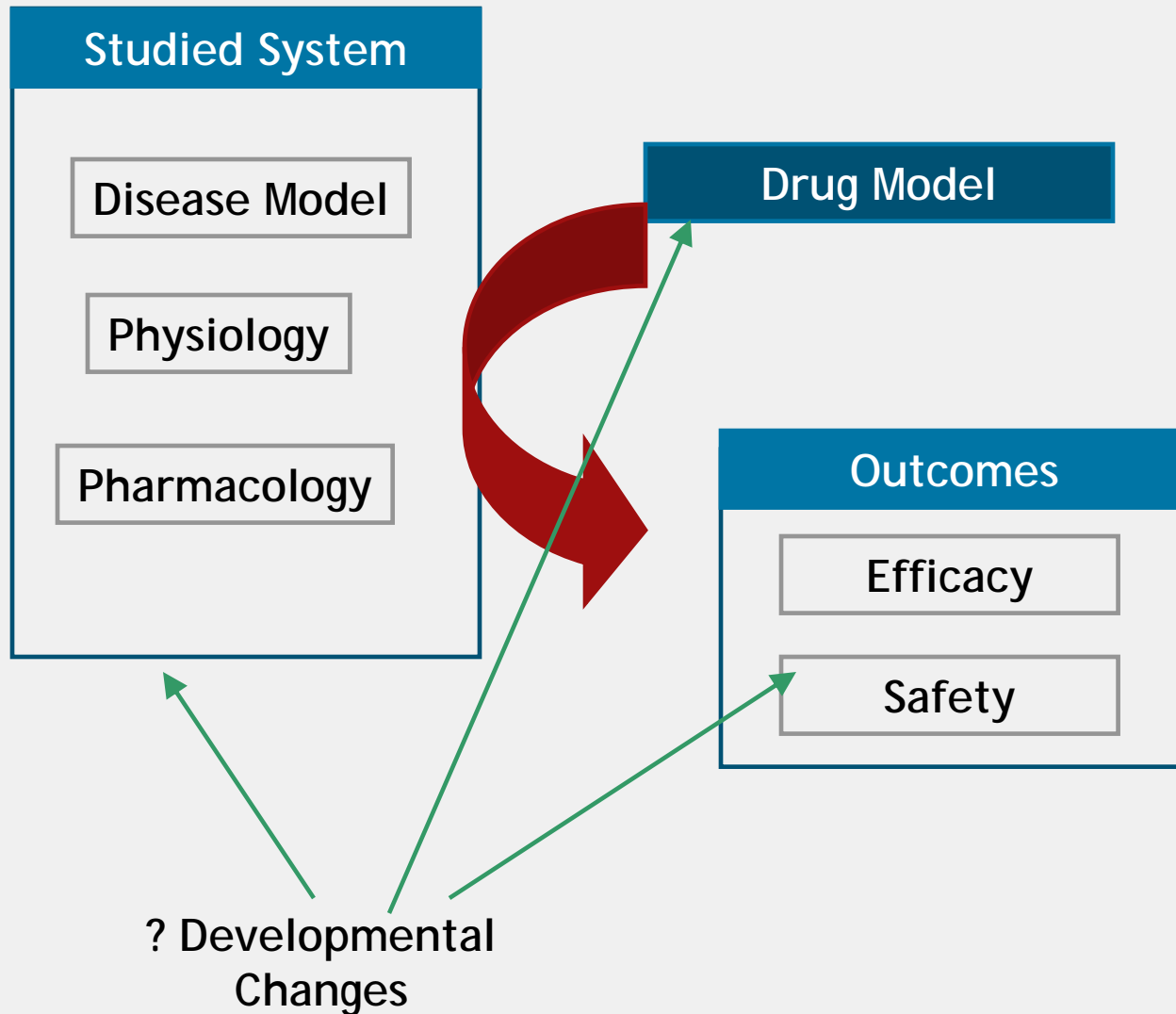
# Pediatric Drug Development: Challenges

- Data collection difficulties
  - Invasiveness
  - Limited sampling possibilities → sparse data
  - Recruiting and consent
- Costs/Ethical Issues

# Pediatric Drug Development: Opportunities

- Prior and current Knowledge
  - Extensive adult data available
  - Current understanding of physiology and pharmacology
  - Significant knowledge available in industry, academia and regulatory agency → need to share
- Non-linear mixed effects modeling and simulation
  - Can handle sparse and unbalanced data
  - Covariate analysis shed light on important determinants of exposure/safety/efficacy
  - Innovative models can reduce sampling ( e.g. Time-response or K-PD models)
- Allometry theory and developmental changes
- Optimal Pediatric studies
  - Clinical trial simulations to design successful trials
  - Population optimal design → limited sampling of high value
  - Adaptive Bayesian design to inform best the PK/PD relationship

# Pediatric Drug Development: Efficiency is the Key



Is a pediatric PK/PD and PK Safety required ?

If yes what is the study design that best inform the decision ?

# Case Study I: Can we find a better initial dose, is TDM required ?

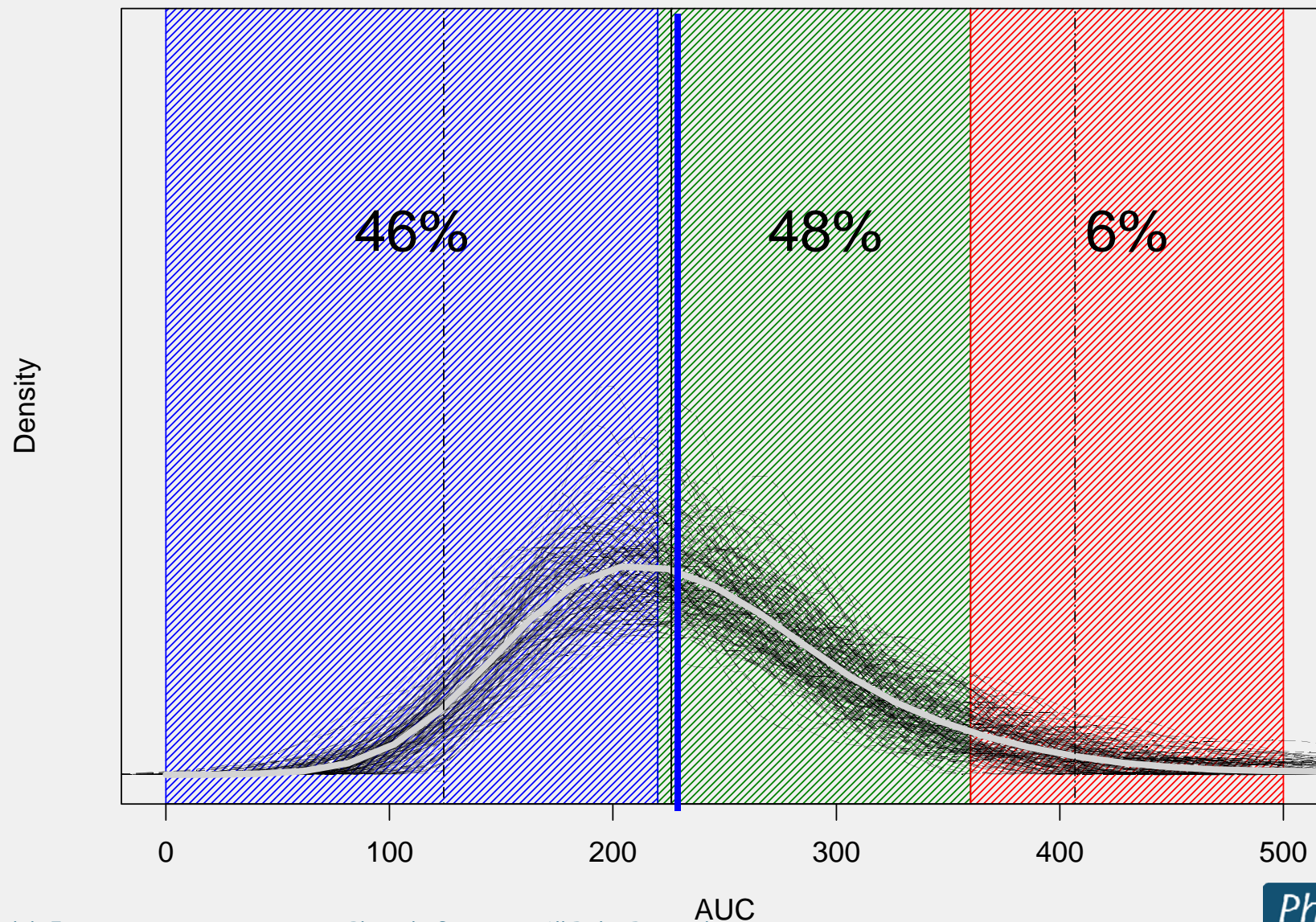
- Background:

- Narrow therapeutic window → AUC: 220 - 360 mg.h/L
- Population POP PK model

$$CL = TVCL \left( \frac{BSA}{1.1} \right)^{1.2} \quad BSV(AUC) = 38\%$$

- Current dosing strategy initial dose + TDM
  - 0.8 mg/m<sup>2</sup> if BSA < 1.2 m<sup>2</sup>
  - 1 mg/m<sup>2</sup> if BSA ≥ 1.2 m<sup>2</sup>
- Current outcome of the dosing strategy
  - Median AUC of 220 and 48 % of the patient are within the therapeutic range after the first dose.

# Original Dosing Regimen



## Model Based Optimal Dose: Current Status

# Population Pharmacokinetic–Based Dosing of Intravenous Busulfan in Pediatric Patients

*Brian P. Booth, PhD, Atiqur Rahman, PhD, Ramzi Dagher, MD, Donna Griebel, MD, Shari Lennon, David Fuller, MD, Chandra Sahajwalla, PhD, Mehul Mehta, PhD, and Jogarao V. S. Gobburu, PhD*

J Clin Pharmacol 2007;47:101-111

The authors tried several dosing strategies by simulation from 1 to 7 dosing steps according to empirical weight **cutoffs**.

Results showed that the optimal dose would be a two-step dosing approach according to weight.

# Model Based Optimal Dose: Estimate the cutoff from the data

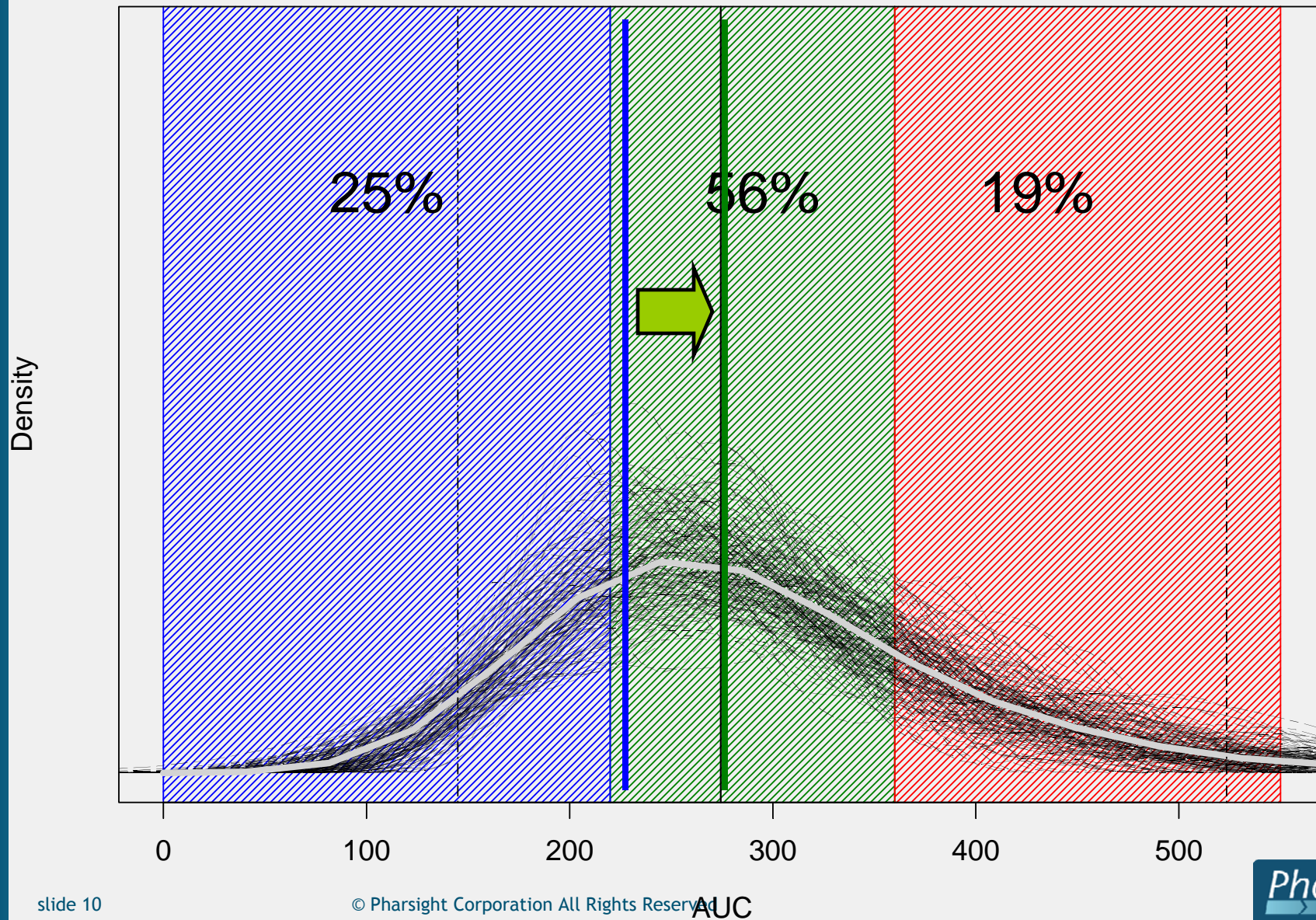
## A rational approach for selection of optimal covariate-based dosing strategies

Siv Jönsson, MSc, and Mats O. Karlsson, PhD *Uppsala, Sweden*

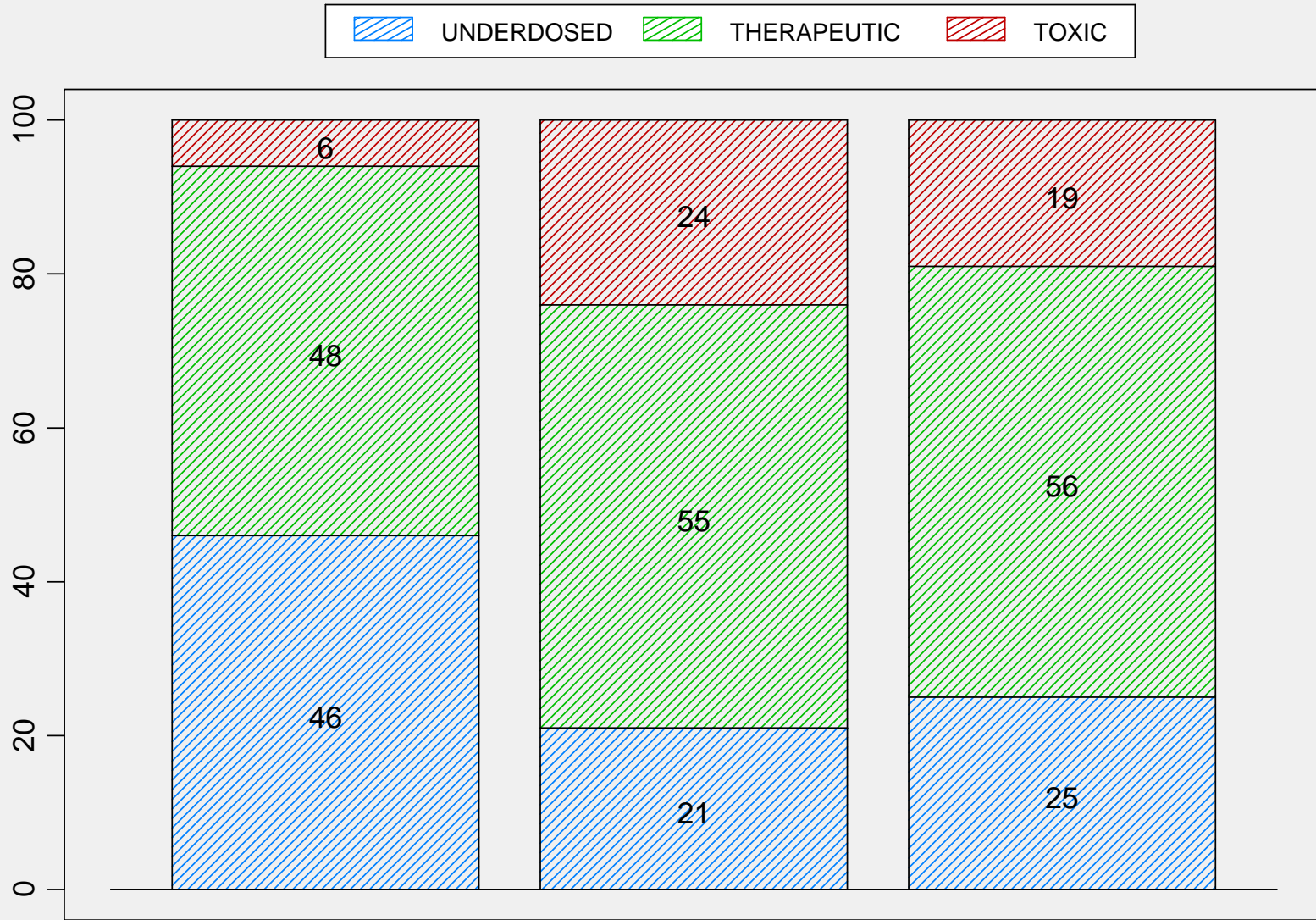
CLINICAL PHARMACOLOGY & THERAPEUTICS  
JANUARY 2003

- Can a more rational approach improve the dosing strategy ?
- This method was tested to estimate the optimal cutoff of covariate and dose that maximizes the percent of therapeutic patients after the first dose.

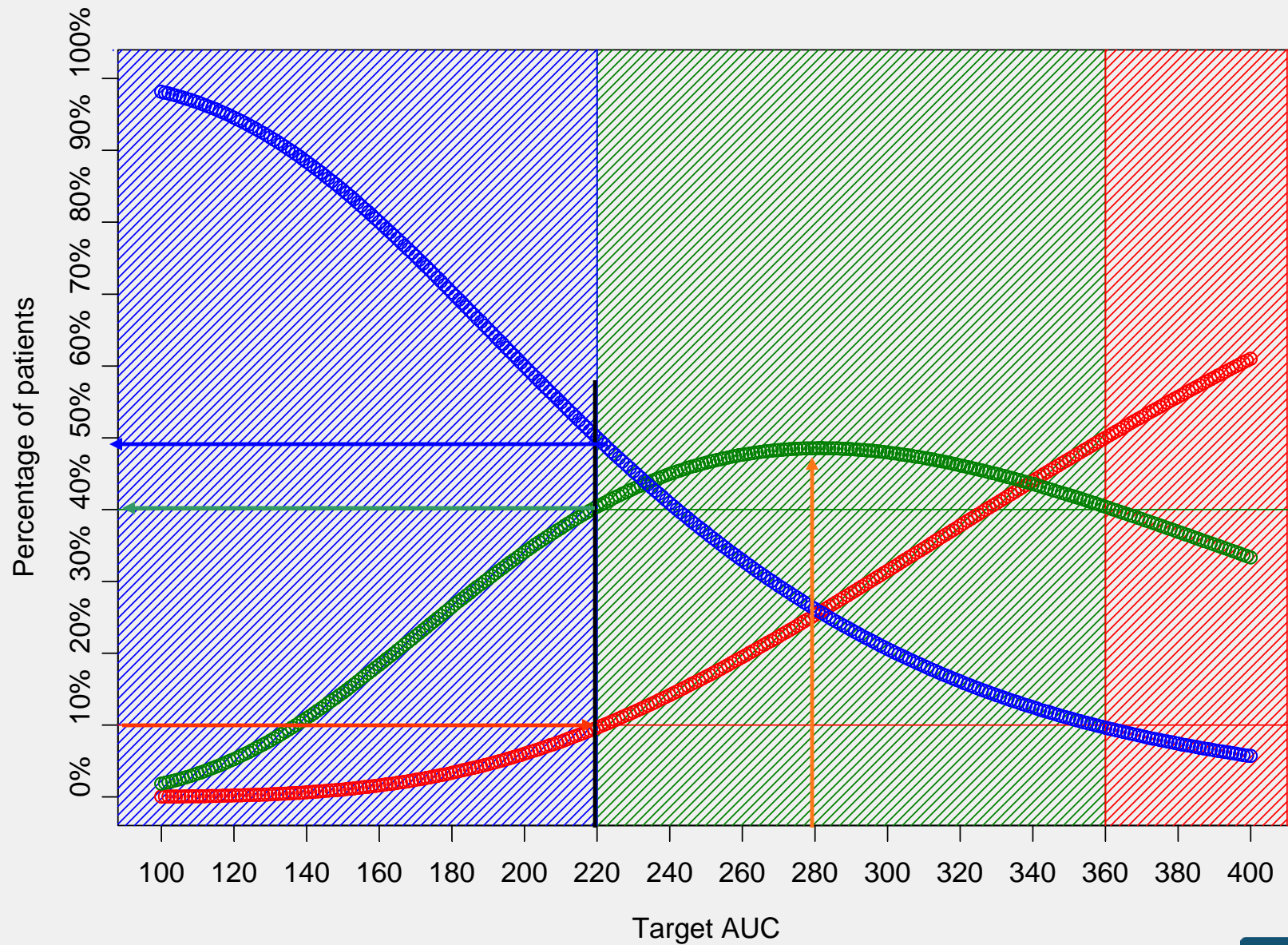
# Best Dosing Regimen With 5 Dosing Steps



# Summary of Different Dosing Strategies



# A Simple Visual Method to Detect the Clinical Target



## Case Study I: Conclusion

- A simple method was developed to quickly identify whether a better dosing strategy is feasible
- Current Dosing Strategy cannot be improved due to high variability
- TDM is required

# Case Study II: Supporting Pediatric Dose Selection

## Background

- Biologic drug X approved in adults
- PK model one-compartment, the drug is excreted by receptor mediated mechanisms
- PD model steep direct Emax (on-off) model, need to keep concentration above a threshold.
- Disease progression is not likely to be different in pediatric patients
- Limited prior experience demonstrated that the EC50 is similar in pediatric patients
- Allometry theory can be used to predict pediatric clearance

## • Objectives

- To design an optimal sampling strategy for PK/PD determination in pediatric patients
- To design a dosing strategy for a pediatric trial that will ensure adequate PD response (> 95% above threshold).

## • Tools

- Optimal design based on the population fisher information matrix and partial derivatives.
- Various clinically feasible dosing scenarios were tested to find the dosing strategy that has the minimum likelihood of PD response breakthrough.

# Scaling from Adults to Pediatrics: Predicting PK

$$CL = TVCL \left( \frac{Weight}{70} \right)^{0.75} \cdot (Maturation(age))$$

Drug X is cleared by receptor mediated mechanisms

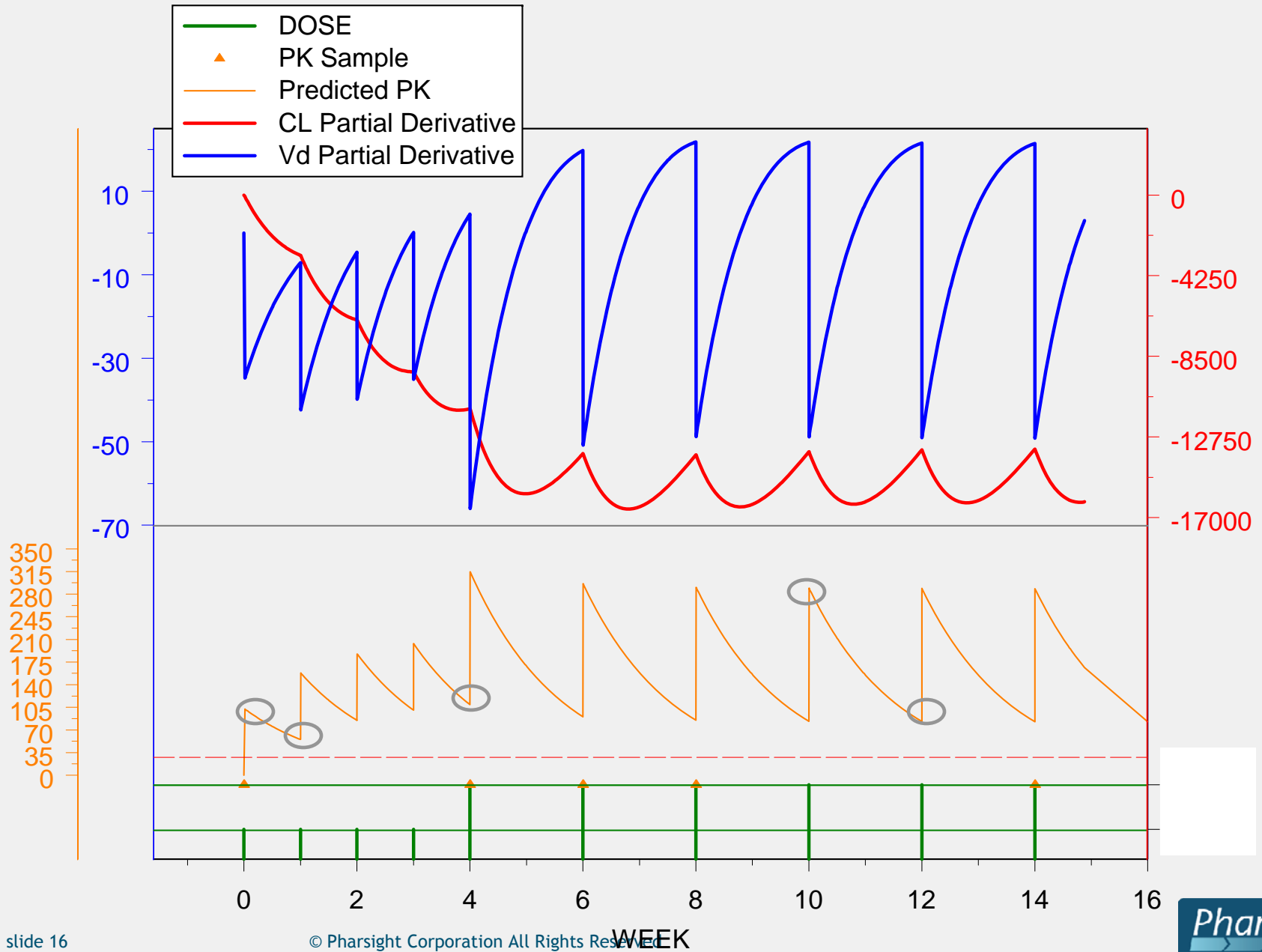
No correlation with renal function.

Maturation can reflect receptor density or disease interaction with age. No maturation function was incorporated in this CTS exercise

The allometric model was also used for volume of distribution

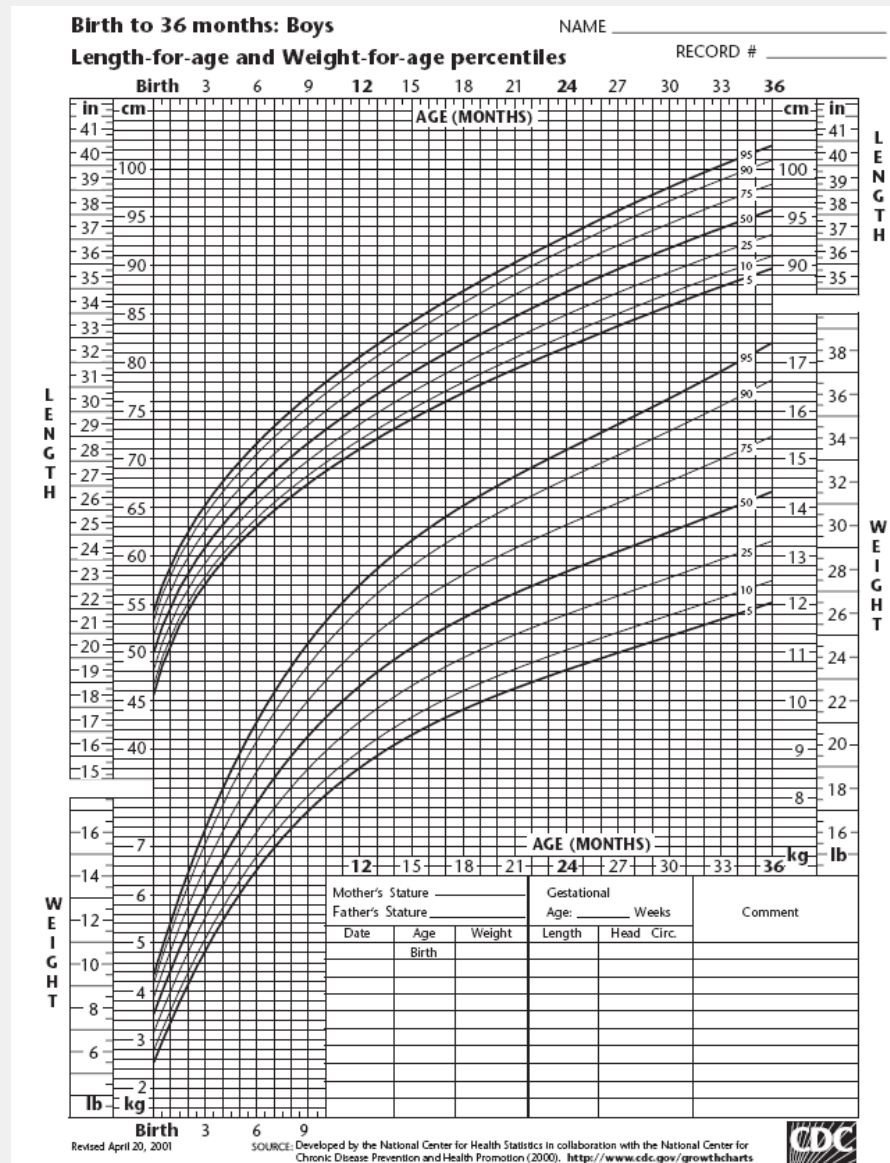
$$Vc = TVVc \left( \frac{Weight}{70} \right)^1$$

# Optimal Design Points Based on Partial Derivatives



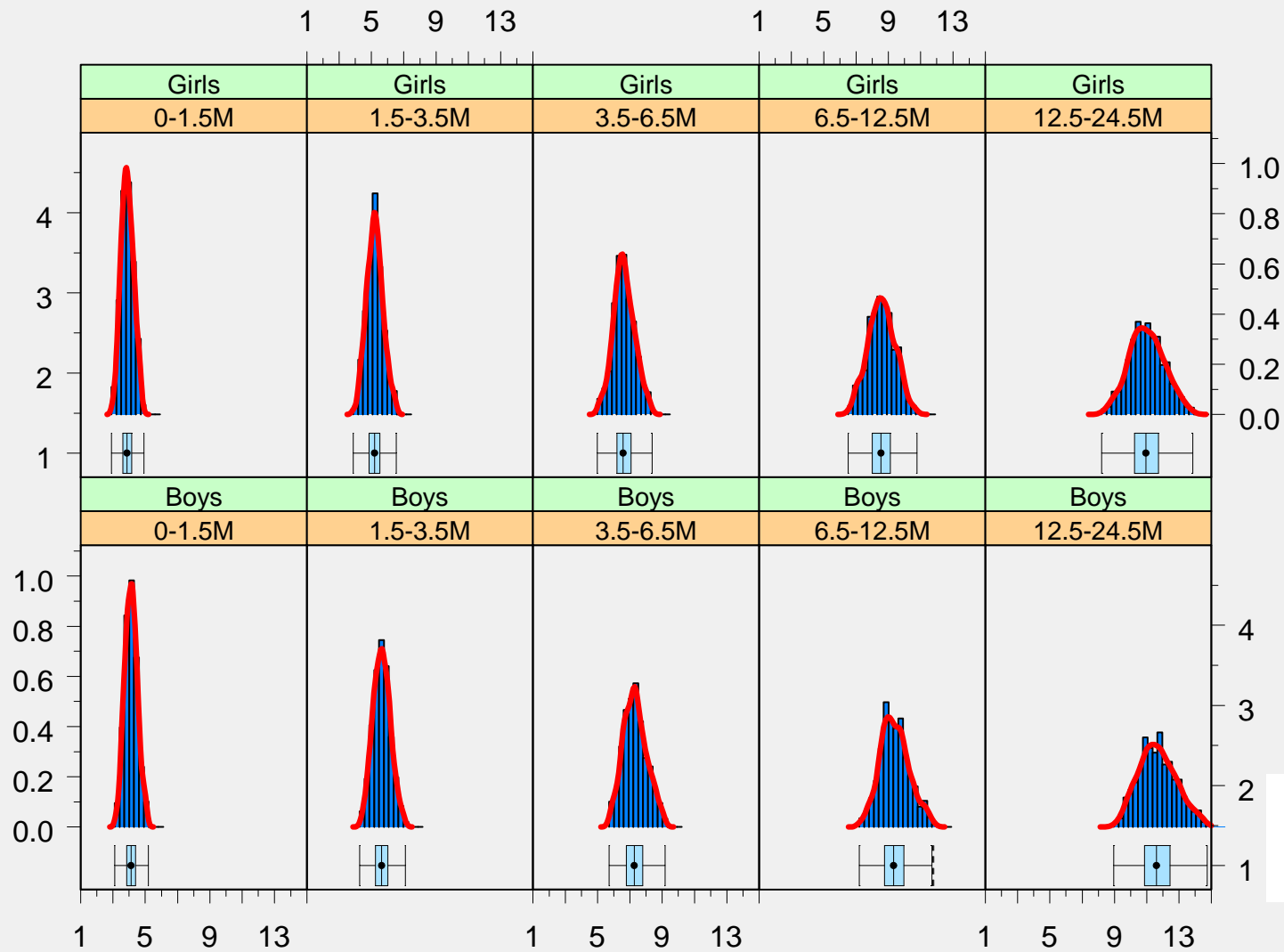
# Clinical Trial Simulations

## Covariate Distribution Model



# Clinical Trial Simulations

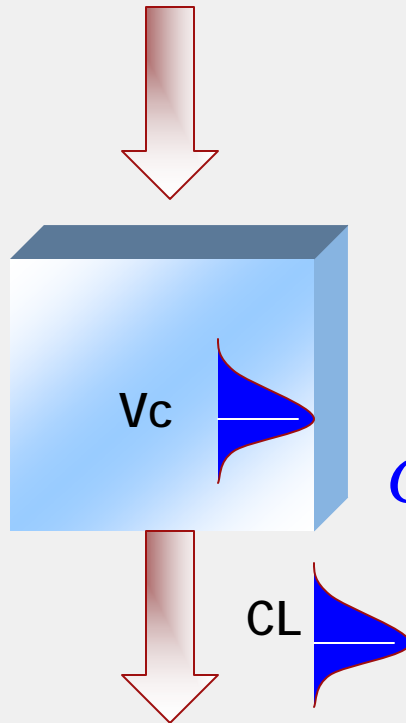
## Covariate Distribution Model



# Clinical Trial Simulations

## PK/PD Model

Zero Order Infusion  
over 30 minutes



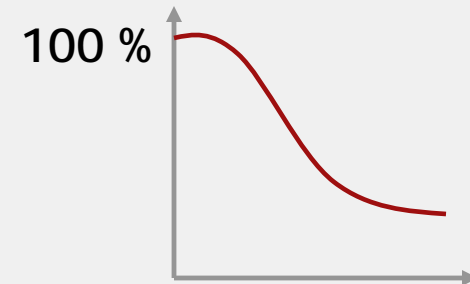
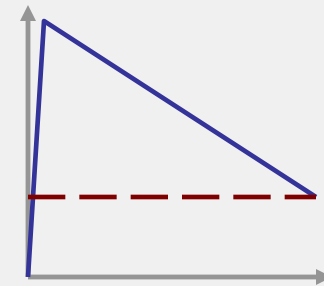
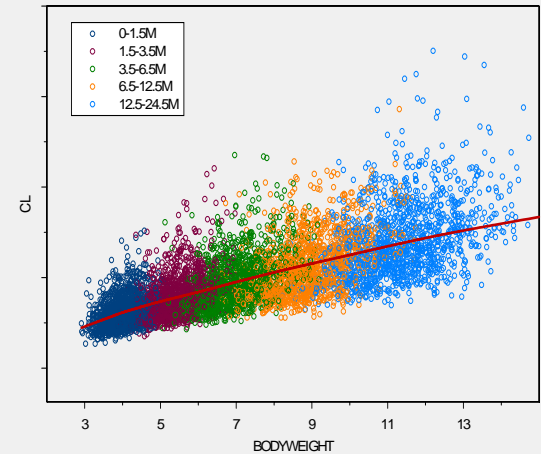
$$PD = 100 \left[ 1 - \left( \frac{E_{max} \cdot Conc^{\gamma}}{EC50^{\gamma} + Conc^{\gamma}} \right) \right]$$

## Covariate Model

Scaling Model

$$V_c = TVV_c \left[ \frac{Weight}{70} \right]^1$$

$$CL = TVCL \left[ \frac{Weight}{70} \right]^{0.75}$$



# Clinical Trial Simulations

## Dosing Scenarios

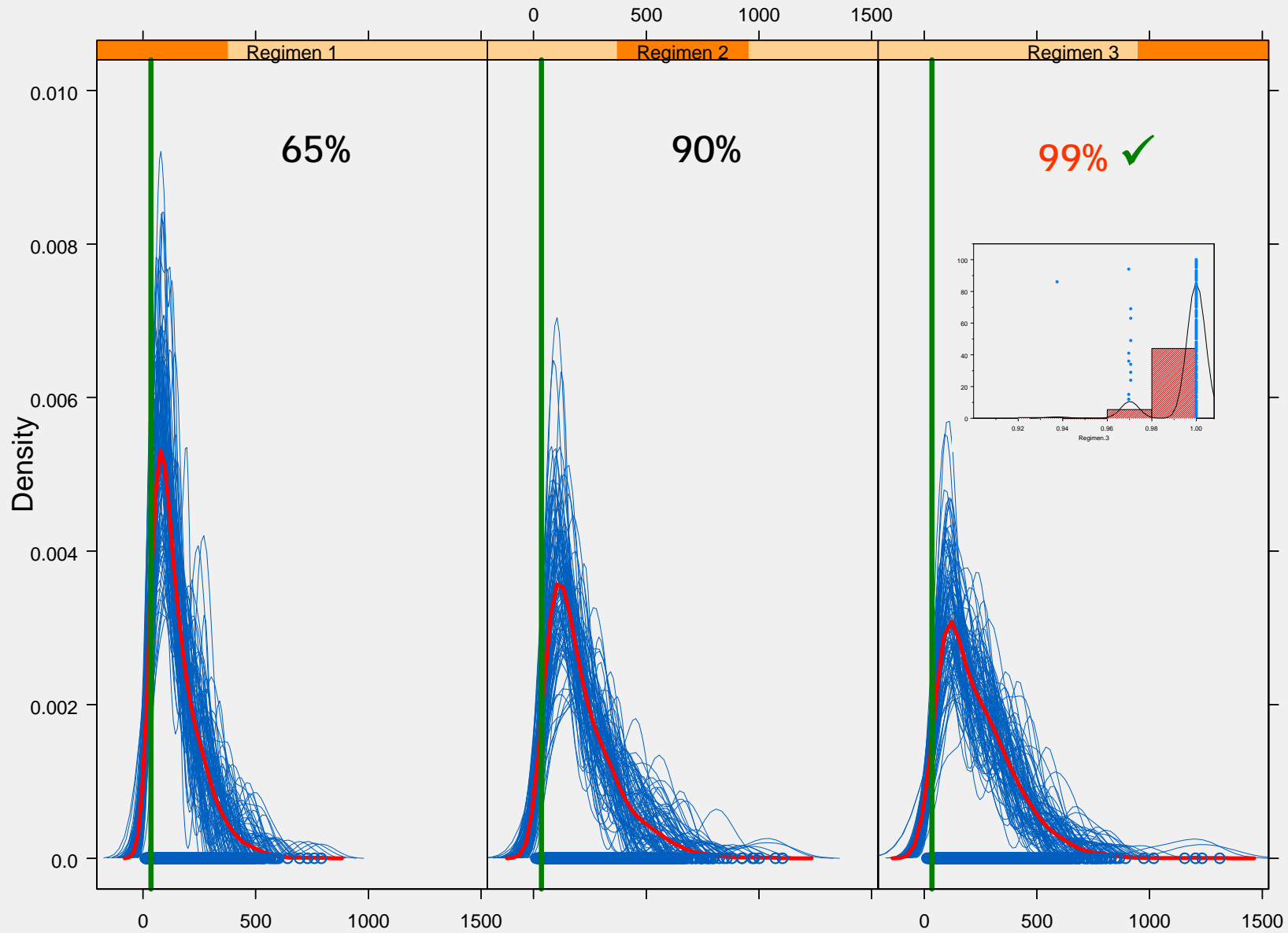
### Goal

Find the dosing regimen that has the highest likelihood to keep 95% of the patients concentrations above a critical threshold.

### Constraints

Dose should be a multiple of the one available strength  
Dosing may be every two weeks or less

# Success Rates (>95% above threshold) of Different Regimens



# Case Study II: Conclusion

Combining Modeling and Simulation tools:

- Understanding of the underlying disease and adult/pediatric differences
- Allometric Scaling
- Optimal design
- Clinical Trial Simulation incorporating variability and uncertainty
- Testing multiple what if Scenarios of dosing Regimens

Made possible to find an effective dose and an optimal design for a prospected pediatric study.

Early clinical findings from the actual trial are confirming the proposed dosing regimen that was based on a computer-assisted trial design.

# Acknowledgements

## CASE STUDY I

Nastya Kassir  
(University of Montreal and Pharsight Reporting and Analysis Services)

## CASE STUDY II

Chun Lin Chen  
(Pharsight Reporting and Analysis Services)

Anonymous Sponsor

Thank you !

Questions

?