CERSI Workshop on the Use of Exposure Matching and Exposure Response for Extrapolation of Efficacy in Pediatric Drug Development. FDA White Oak Campus. Jan. 22, 2015

Methods for determining similarity of exposures between adult and pediatric patients and trial design considerations

Marc R. Gastonguay, Ph.D.

President & CEO, Metrum Research Group
Scientific Director, Metrum Institute
marcg@metrumrg.com

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Points for Discussion

- Need for a consistent approach to assessing similarity of exposures?
- Need for a priori determination of similarity versus a retrospective analysis?
  - Target exposure range and acceptance criteria
  - Basis for target criteria based on therapeutic range of the drug and risk benefit of the product for a given indication
- Trial designs
  - Cross study vs. within study
  - Adequate power, precision, and accuracy
  - Need for Bayesian approach to achieve target exposure
  - Simulations of doses when planning pediatric trials
- Need for statistical equivalence approach for assessing exposure similarity?
  - e.g. X% CI for ratio of exposure metric in pediatric vs adult within a predefined limit based on defined target criteria;
  - e.g. X% of population/concentrations within a predefined target exposure criteria)

Need for a Consistent Approach

- Consistency
  - Quality
  - Planning and pre-specification
  - Scope of the comparison (mean vs. mean and variability) and acceptance criteria
- Context-Specific Considerations
  - Specific exposure metric
  - Drug, mechanism
  - Disease
  - Age and weight range of intended treatment population
  - Route / formulation
  - Time dependency
  - Other covariate factors

A-Priori Specification of Metric

- Define metric for exposure-matching
  - Consider disease, treatment duration, formulation
  - For example:
    - Anti-infective, C_{min}, time above MIC
    - Chronic disease, controlled-release formulation, $C_{ss\ avg}$

A-Priori Specification of Target

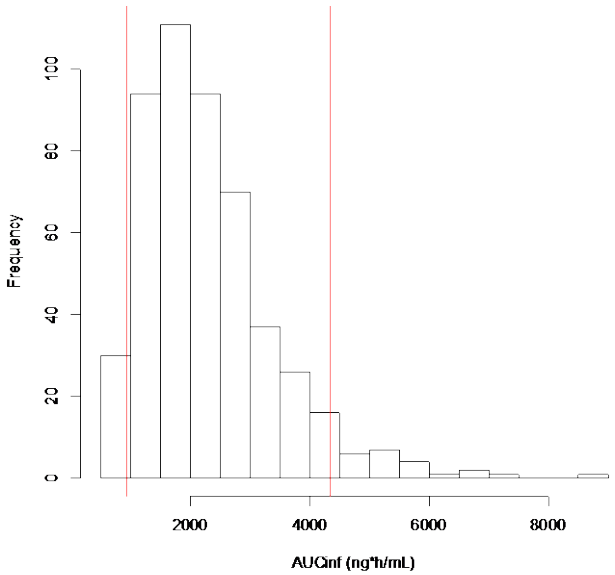
- Define pediatric target drug exposure based on adult data.
  - Exposure-response relationship has been quantified in adults
  - Exposure-response relationship quantified in pediatric population
  - No quantified exposure-response, but PK data available from adults. Safe, effective, doses have been defined.

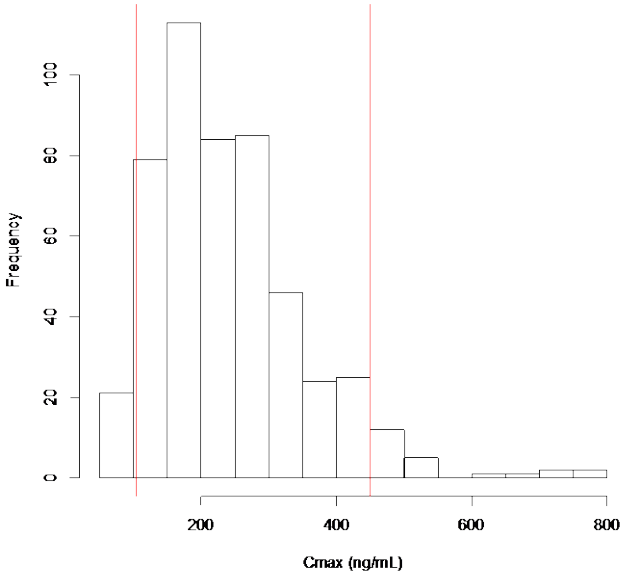
Target Range for Exposure Metrics

- Given adult data, obtain reference distributions of C_{max} , AUC_{inf}, or other metrics, mean and variability

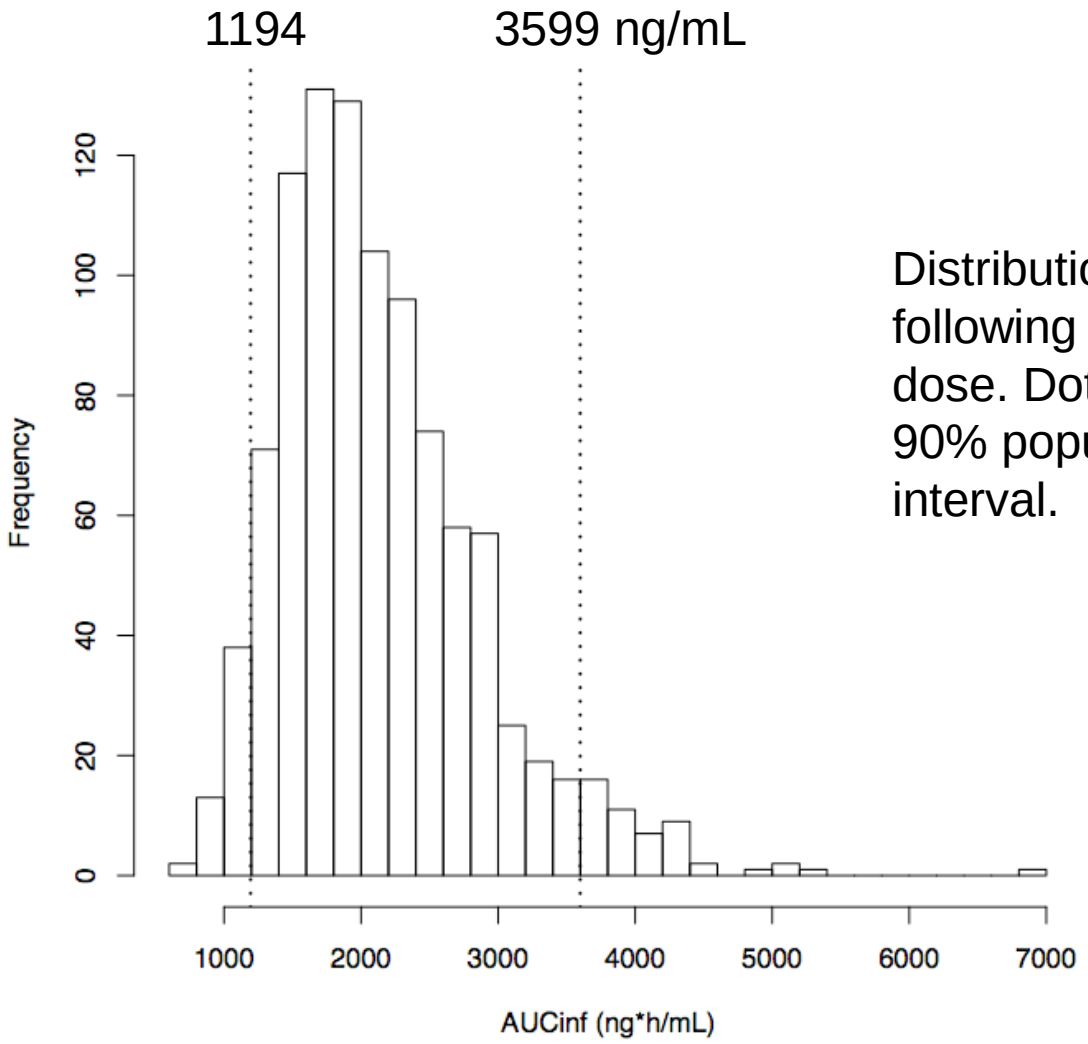
- Target range defined as 90% population prediction interval

		5%	95%
AUC_{inf} (ng*h/mL)		943	4340
C_{max} (ng/mL)	103	449	





Adult Target Exposure of PSE



Distribution of Adult AUC_{inf} following a single 60 mg PSE dose. Dotted lines represent the 90% population prediction interval.

Gastonguay et al. Evaluation of the Performance of Pediatric OTC Monograph Dosing Guidance for Pseudoephedrine via Population Pharmacokinetic Modeling and Simulation. CP&T. Suppl. 2011

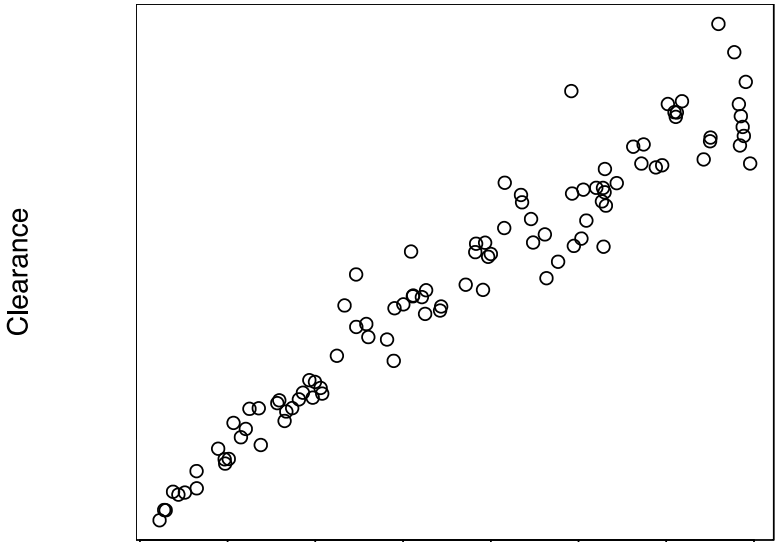
Trial Design and Analysis

- Empirical Comparison
  - Exposure matching acceptance based on comparison of observed adult and pediatric exposure data in a prospectively designed trial
  - Within-study comparison
  - Simulation-guided trial design

- Model-Based Comparison
  - Given existing adult exposure data and target range, design a new pediatric PK trial
  - Simulation-guided trial design
  - Develop a mathematical model and explore a variety of pediatric dosing strategies via computer simulation
  - More useful if comparison must be made across studies
  - Model-based evaluation of uncertainties
  - Requires rigorous model checking

Simulation-Guided Trial Design

- Based on adult data and prior knowledge
- Covariate effects
  - Body size: function of body weight (allometric)
  - Formulation
  - Disease or co-med
  - Age effects (usually if less than 1-2 yrs old)



*CL in arbitrary units

Simulation-Guided Design: Dosing Strategy

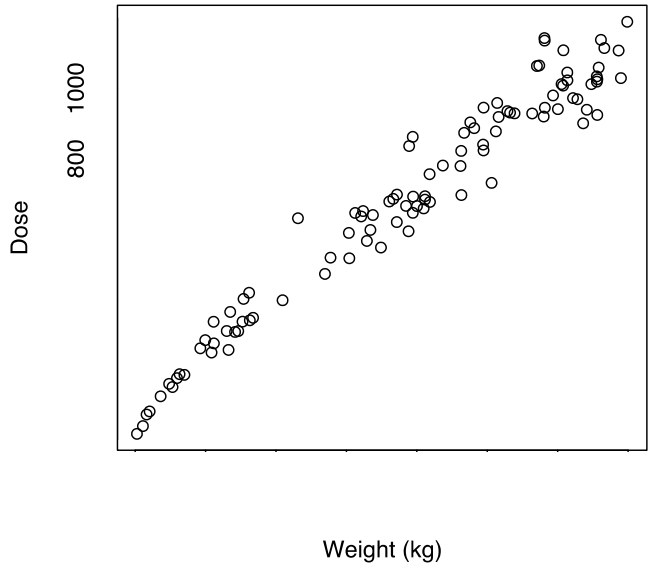
Given:

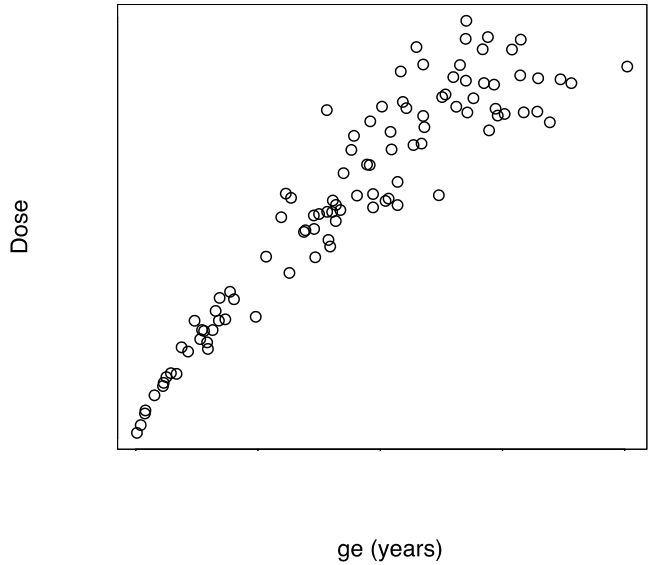
- Target exposure range
- Simulation PK model

Prospectively assess:

- Optimal dose to achieve midpoint of exposure target across WEIGHT and/or AGE range

Develop simplified dosing strategy to evaluate in new trial

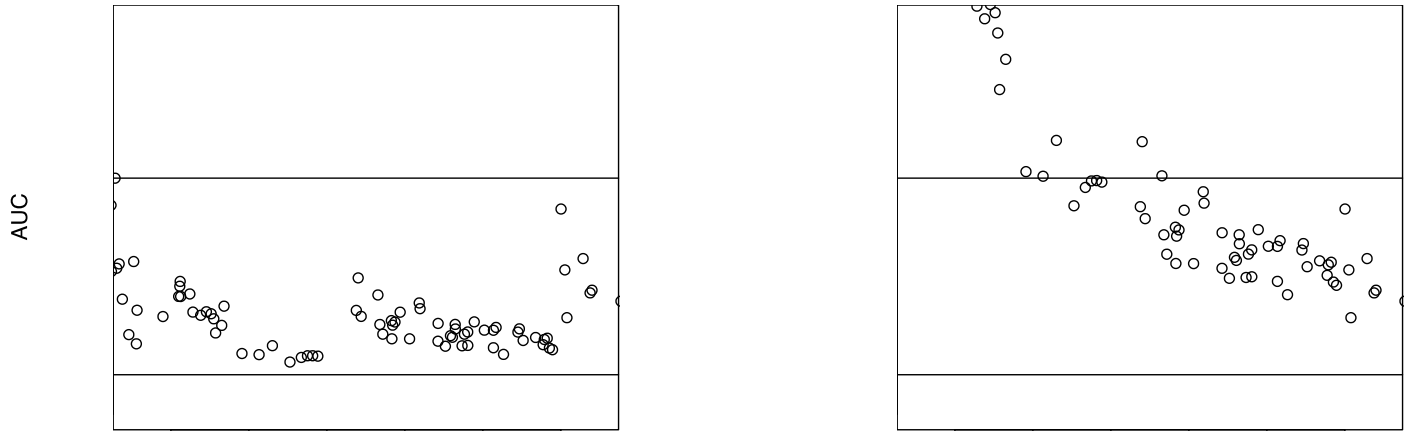




*Dose in arbitrary units

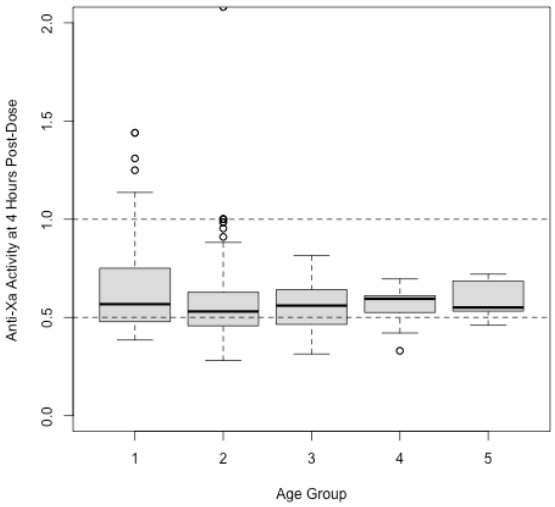
Assess Empirical Data Across Age/Weight Range

- Visual inspection
- Quantify % individuals within target range
- Across age/weight ranges
- Not just a simple BE-like comparison of population means within specified precision

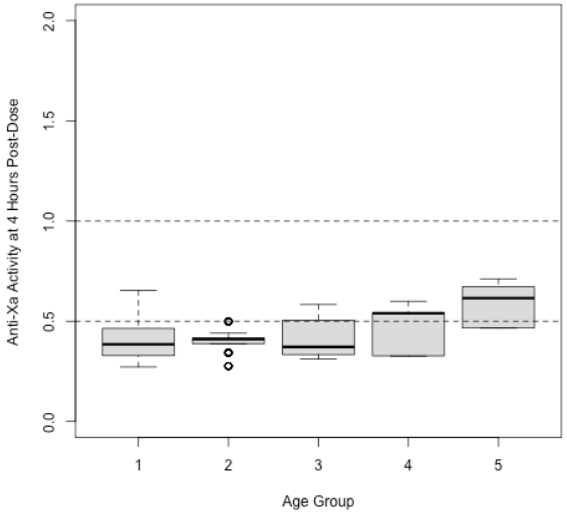


*AUC in arbitrary units

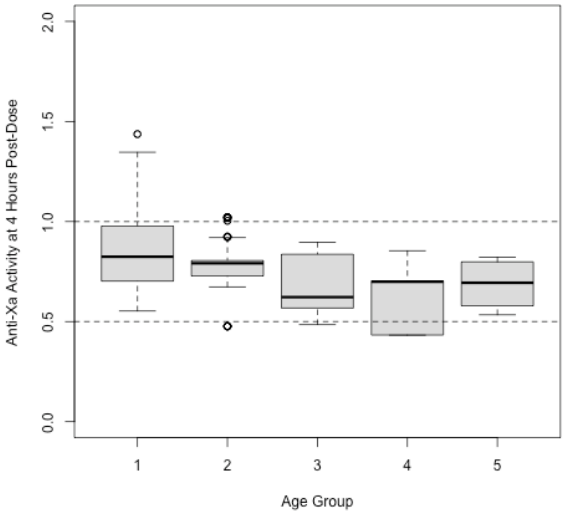
Model-Based Comparisons (After New Trial)



Actual dosing and observed exposure



Per-protocol dosing (IU/kg)



Allometric dosing

Gastonguay et al. Optimizing a Bayesian dose-adjustment scheme for a pediatric trial: A simulation study. in *Simulation for designing clinical trials: A pharmacokinetic-pharmacodynamic modeling perspective*. Marcel Dekker, NY, 2003.

Acceptance Across Range of Age / Weight

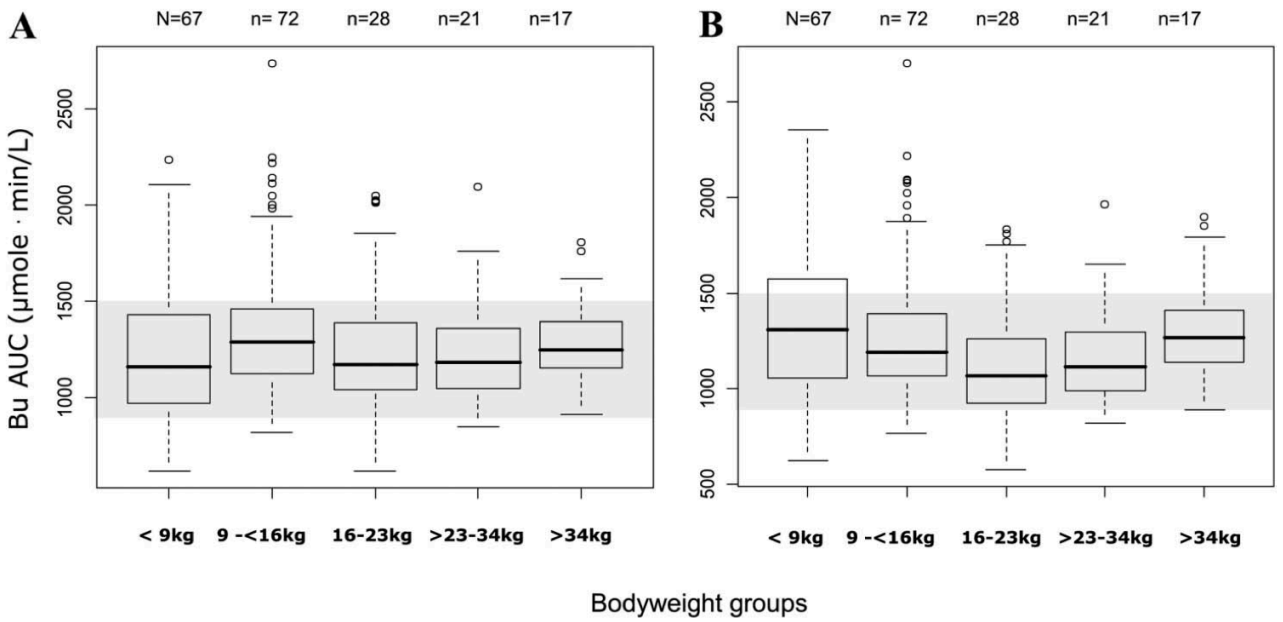


FIGURE 5. Comparison of dosing strategy between model-based and EU labeled dosing. A, Bu AUC distribution using approved EU labeling dosing. B, Bu AUC distribution using model-based dosing.

Paci et al. Pharmacokinetic Behavior and Appraisal of Intravenous Busulfan Dosing in Infants and Older Children: The Results of a Population Pharmacokinetic Study From a Large Pediatric Cohort Undergoing Hematopoietic Stem-Cell Transplantation. Ther Drug Monit 2012;34:198–208.

Evaluate Multiple Dosing Strategies via Simulation

Scenario 1	**weight-based dose**
	1.2 mg/kg
Scenario 2	**lowest fixed and weight-based dose**
	1.25 mg in preterm infants (granules) 2.5 mg (2.5 to < 7kg) or 5 mg (>=7 to <= 15 kg) in 1 to < 12 month old (granules) 5 mg (<=12.5kg), 10 mg (>12.5 - <25 kg), or 20 mg (>=25 kg) in 1 to < 12 year old (spheroid in < 6 years old and tablets in >= 6 years old) 20 mg in 12 – 16 years old (tablet)
Scenario 3	**highest fixed weight and dose**
	2.5 mg in preterm infants (granules) 5 mg (2.5 to < 7kg) or 10 mg (>=7 to <= 15 kg) in 1 to <12 month old (granules) 15 mg (<=12.5kg), 20 mg (>12.5 - <25 kg), or 40 mg (>=25 kg) in 1 to < 12 year old (granules in < 6 years old and tablets in >= 6 years old) 40 mg in 12 – 16 years old (tablet)

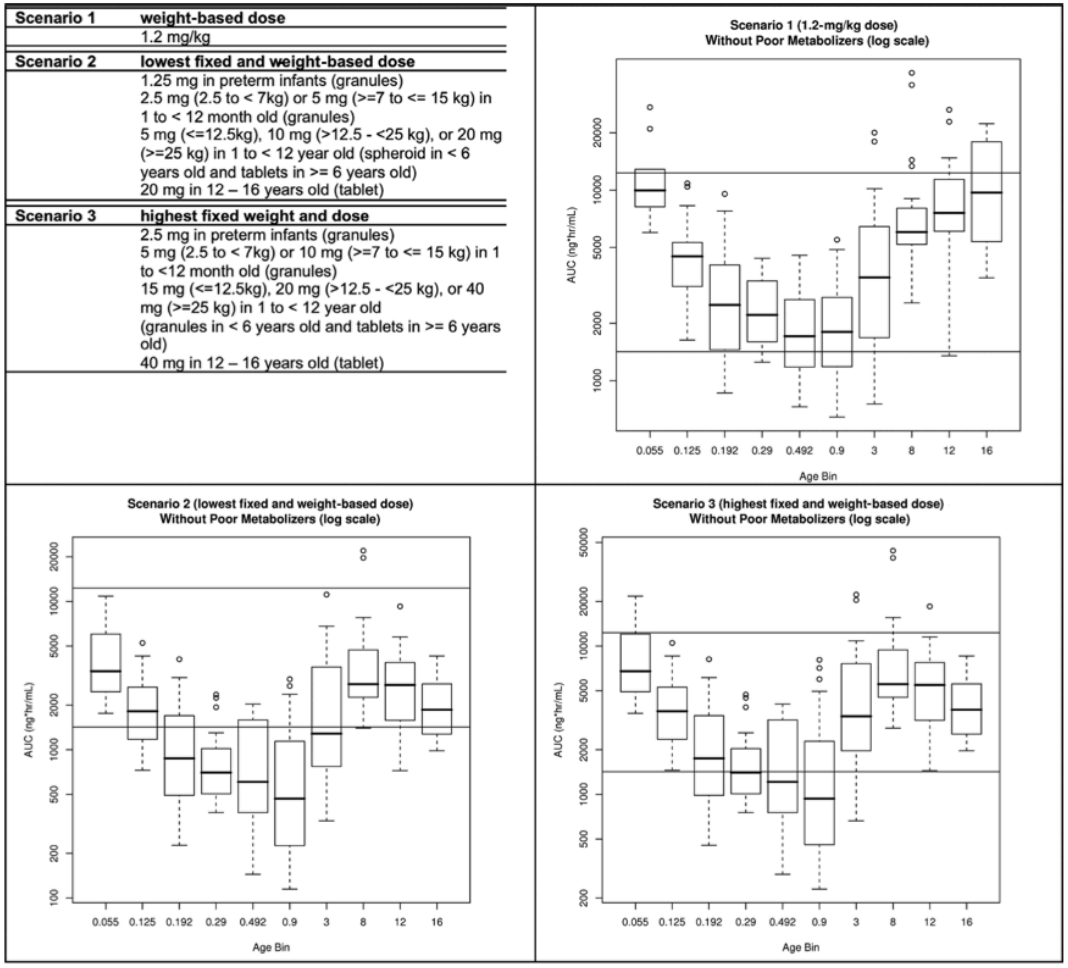


*Figure 6. Image shows simulated AUC_{ss} for 3 dosing scenarios. Final model simulated AUC_{ss} for the 1.2-mg/kg, lowest fixed and weight-based, and highest fixed and weight-based dose groups is plotted by age group using box and whisker plots. Median values of AUC_{ss} are designated by a black line in the center of the box. Boxes indicate the interquartile range (IQR). Whiskers represent 1.5*IQR. Outliers are marked outside of the whiskers by open circles. Solid black lines represent the range of data from 40 mg in adult extensive metabolizers. The top left shows simulation scenarios, the top right shows 1.2 mg/kg, the bottom left shows lowest fixed and weight based, and the bottom right shows highest fixed and weight based.*

Pediatric dosing strategies for pantoprazole. Knebel et al. *J Clin Pharmacol. 2011 Mar;51(3):333-45. Epub 2010 May 19.*

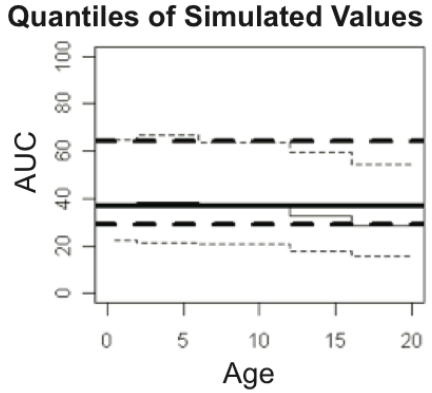
Simulation-Based Evaluation

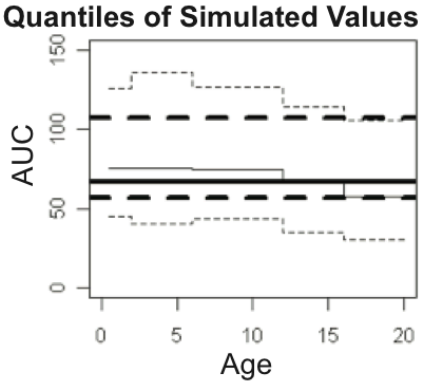
Figure 4: Simulation of Dosing Regimens Targeting Mean Adult AUC(0-τ).

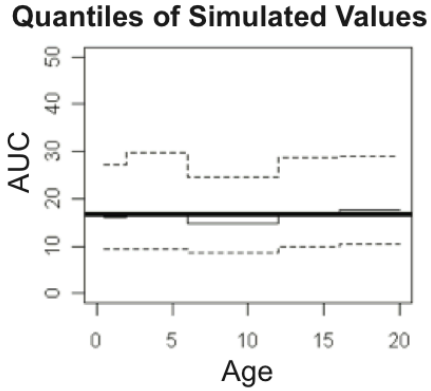
BID RTV+; AGE<2: 36mg; AGE 2-6: 23mg/kg; AGE> 6: 18mg/kg; Max 700 mg

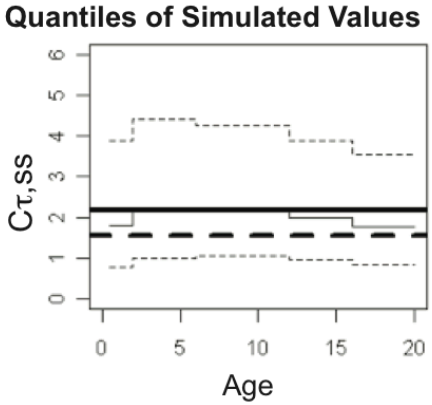
QD RTV+; AGE <2: 72mg/kg; AGE 2-6: 46 mg/kg: AGE >6: 36 mg/kg; Max 1400 mg

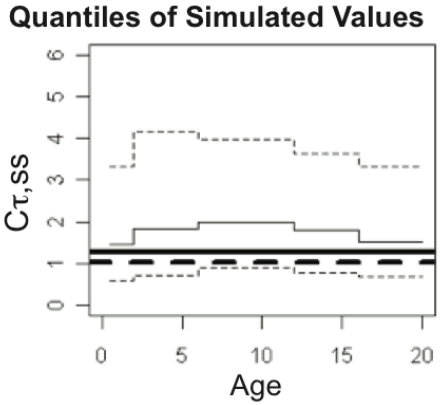
BID RTV-; AGE <2: 38 mg/kg: AGE 2-6: 25 mg/kg: AGE >6: 17 mg/kg; Max 1400 mg

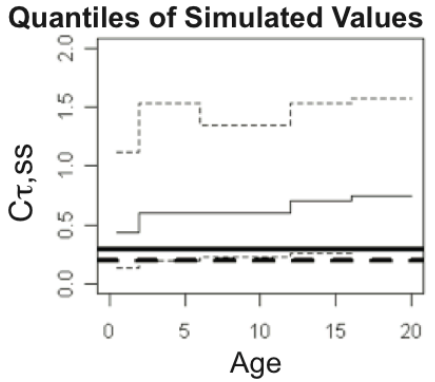












The thin solid line indicates geometric mean (by age group) of the simulated PK values while thin dashed lines show 5th and 95th percentiles of the simulated values. The bold lines indicate targets: geometric mean (bold solid), 25th percentile and 95th percentiles (bold dashed lines) of the AUC values observed in the adult population. Top row: AUC. Bottom row: Cτ,ss.

Fisher et al. Population Pharmacokinetic Modeling of Fosamprenavir in Pediatric HIV- Infected Patients. ACOP 2008.

Assessment Based on % Individuals Within Target

Percent of Pediatric Subjects with AUC_{inf} Below and Above Target Exposure Bounds Following Monograph Dosing by Age. 95% CI based on 1000 simulated trials with 1821 subjects/trial (amplified from CDC age-weight database).

	Below Target			Above Target			
		95% CI			95% CI		
Age Group (yr)	Median	2.5^{th}	97.5^{th}	Median	2.5^{th}	97.5^{th}	Dose (mg)
2	18.20	12.300	25.10	0.000	0	0.535	15
3	31.20	22.900	40.00	0.000	0	0.000	15
4	46.60	37.400	54.60	0.000	0	0.000	15
5	59.80	51.700	69.00	0.000	0	0.000	15
6	2.21	0.552	4.97	1.660	0	3.870	30
7	4.44	1.670	8.33	0.556	0	2.220	30
8	9.39	4.970	14.90	0.000	0	1.100	30
9	16.80	10.800	22.70	0.000	0	0.541	30
10	26.90	20.300	34.60	0.000	0	0.549	30
11	37.70	30.600	44.80	0.000	0	0.000	30

Gastonguay et al. Evaluation of the Performance of Pediatric OTC Monograph Dosing Guidance for Pseudoephedrine via Population Pharmacokinetic Modeling and Simulation. CP&T. Suppl. 2011

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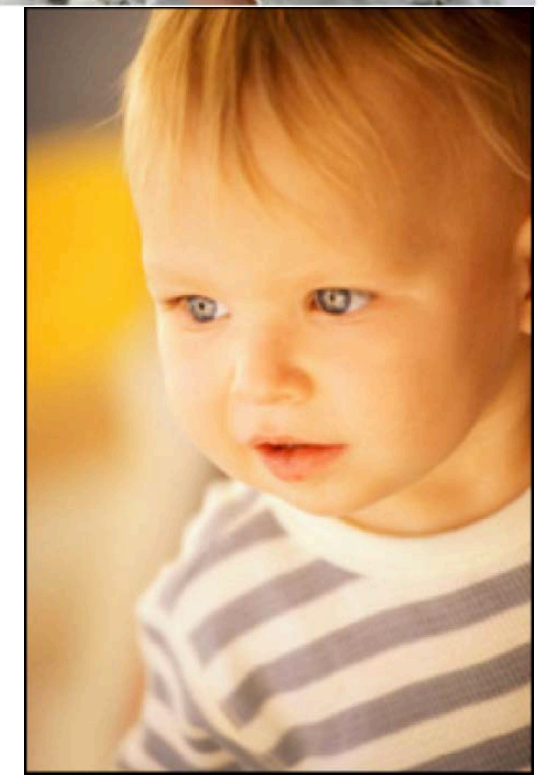
Summary



- Consider context of exposure-matching
- Simulation to guide design
- Assess performance across age and weight range
- Mean and variability (e.g. % of individuals within target)
- Empirical data comparison within study
- Simulation to explore alternative dosing strategies

Acknowledgements

Metrum Research Group Scientists

Industry Collaborators

CERSI Workshop Panel and Organizers