

Application of Model Informed Drug Development in Study Design and Analysis

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Disclaimer: My remarks today do not necessarily reflect the official views of the FDA

Outline

- **Relevance of model-informed drug development for pediatric research**
- **Case studies**
 - **Design**
 - **Analysis**
 - **Policy**
- **Summary**

FDA Pharmacometrics 2020

Strategic Goals

Train 20 Pharmacometricians

- Technical track
- Disease track
- Drug development track

International Harmonization

- Share expertise between global regulatory bodies

Implement 15 Standard Templates

- Develop disease specific data, analysis standards
- Expect industry to follow

Integrated Quantitative CP Summary

- All NDAs should have exposure-response analyses

Develop 5 Disease Models

- Create public disease model library

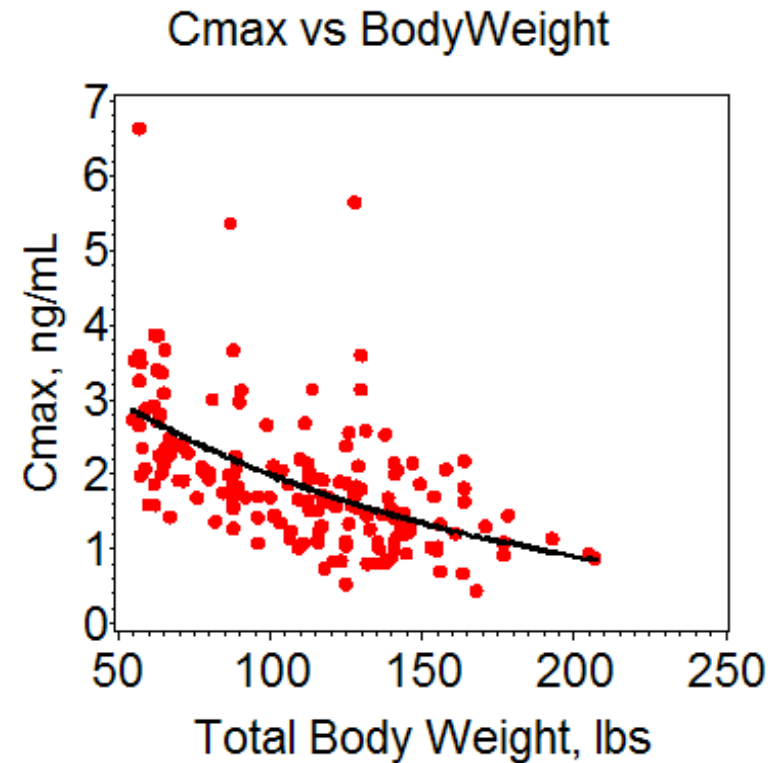
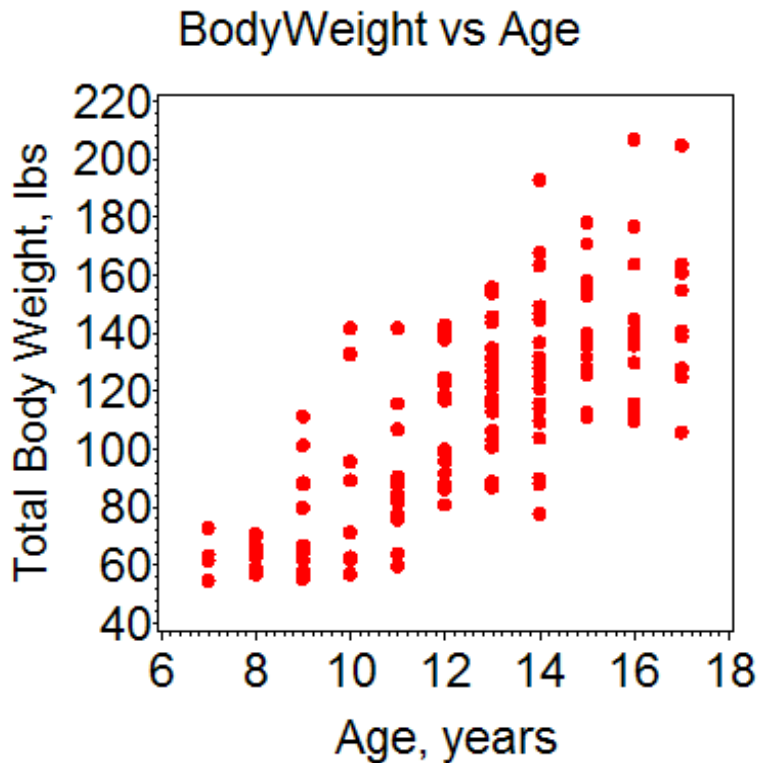
Design by Simulation: 100% Pediatric trials

- Leverage prior knowledge to design Pediatrics Written Request trials

Case 1: Guanfacine

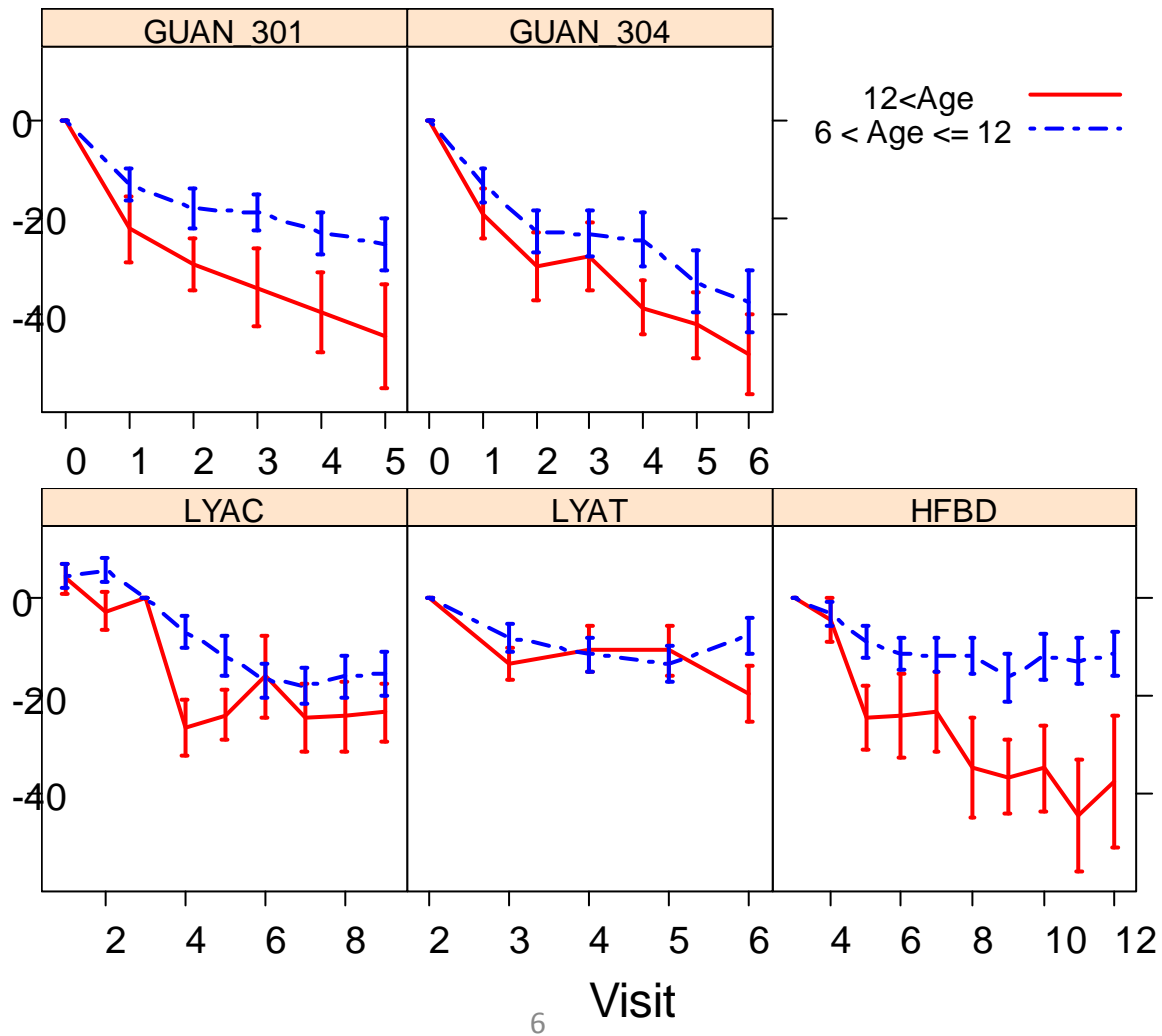
- **Intuniv™ (extended-release guanfacine, SPD503), approved for QD administration for the treatment of ADHD in children and adolescents age 6–17 years old.**
- **Initially approved dose in 2009: 1 to 4 mg**
- **Subgroup analyses suggested a lack of efficacy for adolescents (13-17)**
- **PMR study for adolescents (13-17)**

Drug Concentrations Are Lower for Adolescents

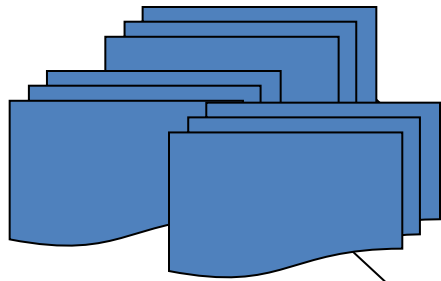


Placebo Effects Are Larger for Adolescents

% Change From Baseline



Clinical Trial Simulation

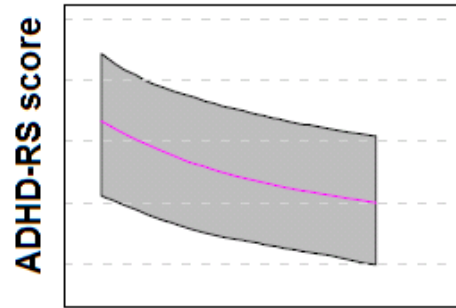


*Prior information
(data from 9 trials)*

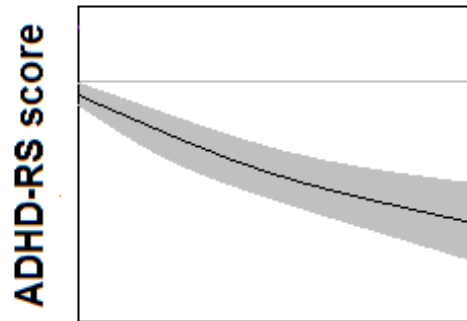
Pediatrics (6-17)

5 trials - placebo
and active SPD503

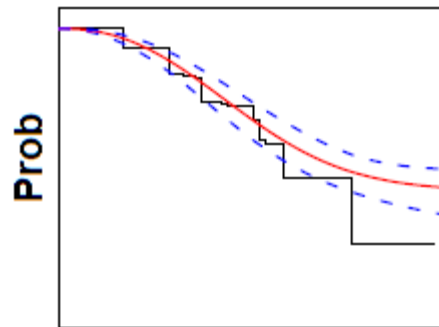
4 trials - placebo
arms from different
programs



Exposure-response
model



Placebo
model



Dropout
model

*Simulate
experimental design*

- 312 Protocol

**Probability of
Success
97%**

| STUDY | 301 | 304 |
|-----------------------------|------------------------------|----------------------------------|
| <i>Age range</i> | 6 – 17 | 6 – 17 |
| <i># subjects</i> | 345 (~ 86 per group) | 324 (~65 per group) |
| <i>Titration</i> | Forced | Forced |
| <i>Target Doses</i> | Placebo, 2, 3 or 4 mg/day | Placebo, 1, 2, 3, or 4 mg/day |
| <i>Duration (weeks)</i> | 8 | 9 |
| <i>Titration</i> | 5 | 3 |
| <i>Maintenance</i> | 0 | 3 |
| <i>Tapering</i> | 3 | 3 |
| <i>Notes:</i> | | |

| 312 |
|--|
| 13 – 17 |
| 280 (140 per group) |
| Flexible |
| Placebo, Based on weight, maximum 4-7 mg/day |
| 15 |
| 7 (optimization) |
| 6 |
| 2 |
| Min ADHD-RS IV of 32 at baseline |

Successful Study 312

Table 1: Summary of MMRM Analysis of ADHD-RS-IV Total Score and Change from Baseline in ADHD-RS-IV Total Score at Week 13 (FAS) - Study SPD503-312

| | Placebo (N=155) | SPD503 (N=157) |
|------------------------------------|--------------------|-------------------|
| Baseline | | |
| N | 155 | 157 |
| Mean (SD) | 40.0 (6.11) | 39.9 (5.57) |
| Visit 13 | | |
| N | 106 | 109 |
| Mean (SD) | 20.3 (13.35) | 14.1 (9.38) |
| Change from baseline | | |
| Mean (SD) | -19.5 (12.63) | -25.7 (10.09) |
| Comparison to placebo ^a | | |
| LS mean | -18.527 | -24.552 |
| Difference in LS means | NA | -6.026 |
| (95% CI) | NA | -8.865, -3.187 |
| Effect Size | NA | 0.52 |
| p-value | | <0.001 |

Summary of Case 1

- **Clinical pharmacology principles to support subgroup analysis results**
- **Quantitative models built from existing data**
- **Extensive clinical trial simulation optimized key design features of the new study**
- **Clinical trial simulation should be conducted routinely to maximize the success chance of any pediatric study**

Case 2: Raxibacumab

- **Indication: treatment of inhalational anthrax due to Bacillus anthracis in combination with appropriate antibacterial drugs**
- **Proposed adult dose: 40 mg/kg single dose (effective in rabbit and monkey models of inhalational anthrax)**
- **The effectiveness of raxibacumab is based solely on efficacy studies in animal models of inhalational anthrax¹ (animal rule)**
- **What should be the pediatric dose?**

1. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125349s000lbl.pdf

Assumptions

- **40 mg/kg dosing regimen may provide an acceptable benefit/risk profile for adult patients**
- **Adult and pediatric patients are similar in terms of:**
 - **Disease progression**
 - **Response to the treatment**
 - **Exposure-response (E-R) relationship**

Determine the Pediatric Dose

- **Learn** from adult population PK analysis
 - The relationship between PK parameters vs body weight
 - Inter-subject variability
 - Residual variability

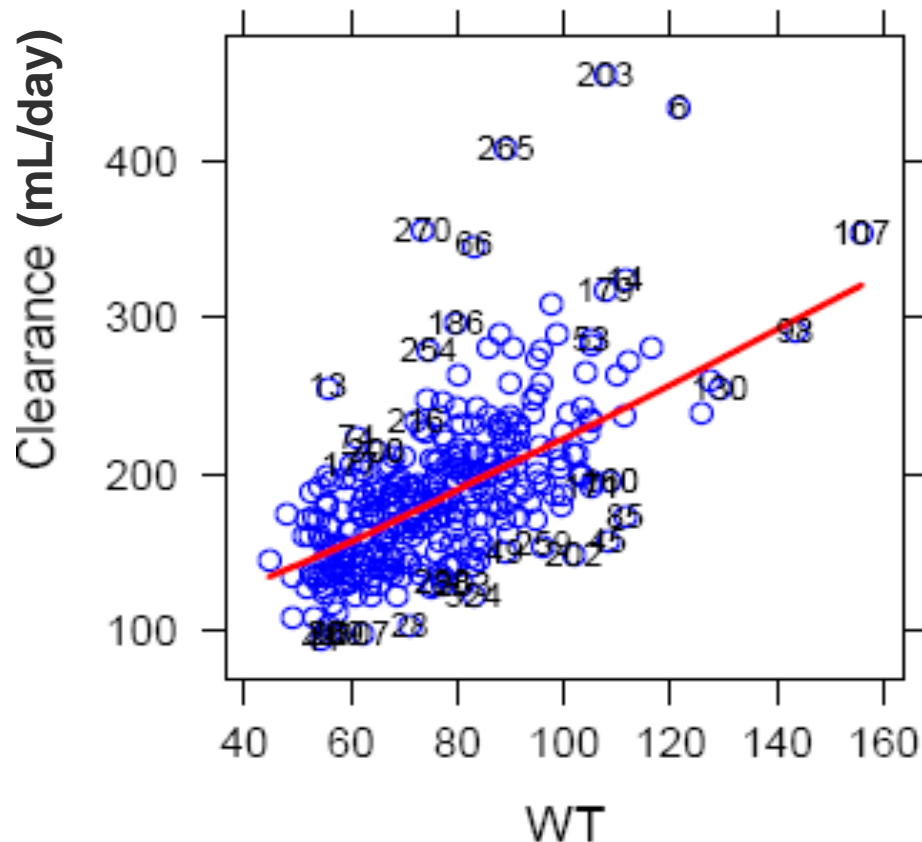
- **Simulate** pediatric PK profiles using different dosing regimens
 - Various combinations of dose and body weight band

- **Select** a pediatric dosing regimen
 - Match the exposure (e.g., AUC*) observed in adults at 40 mg/kg
 - Simple to implement

* AUC: Area under the concentration-time curve

Raxibacumab Clearance vs Body Weight in Adults

Healthy adult PK @ 40 mg/kg

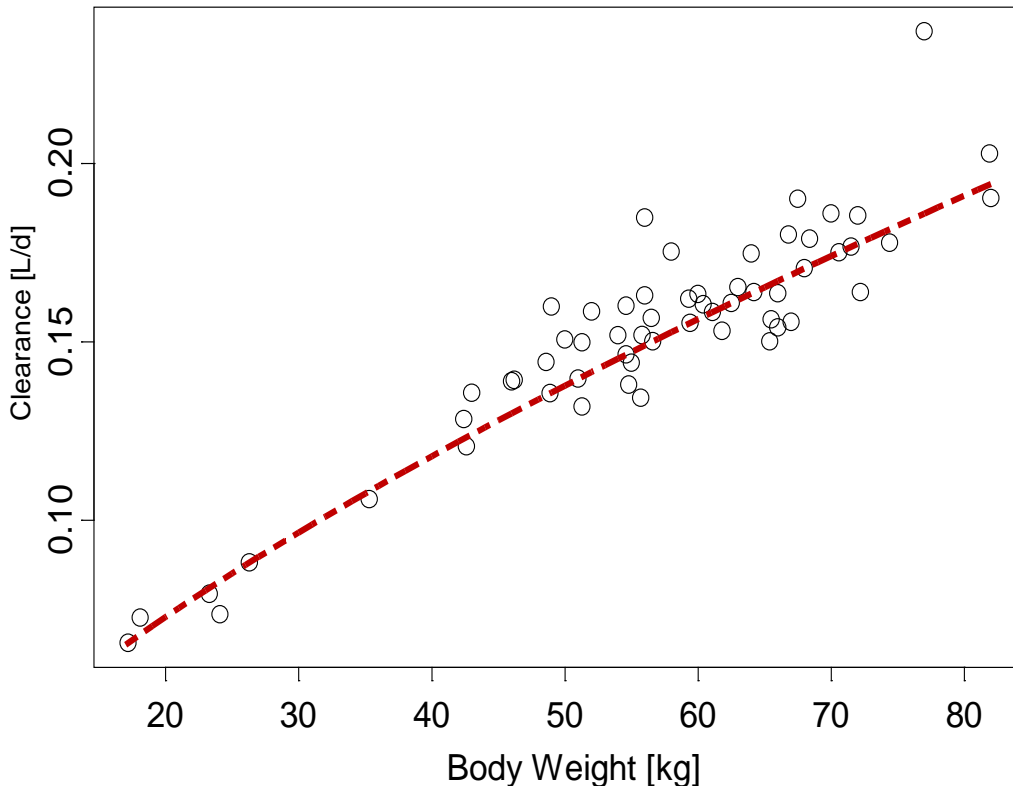


Assuming the observed relationship between PK and body weight in adults is applicable to the pediatric population

- Mainly eliminated by non-specific proteolysis
- Very unlikely to be eliminated by kidney due to its large size
 - Renal maturation for <2 yrs should have minimal effect on PK

Clearance vs Body Weight for Other Monoclonal Antibodies (In Adults and Pediatrics)

Canakinumab*



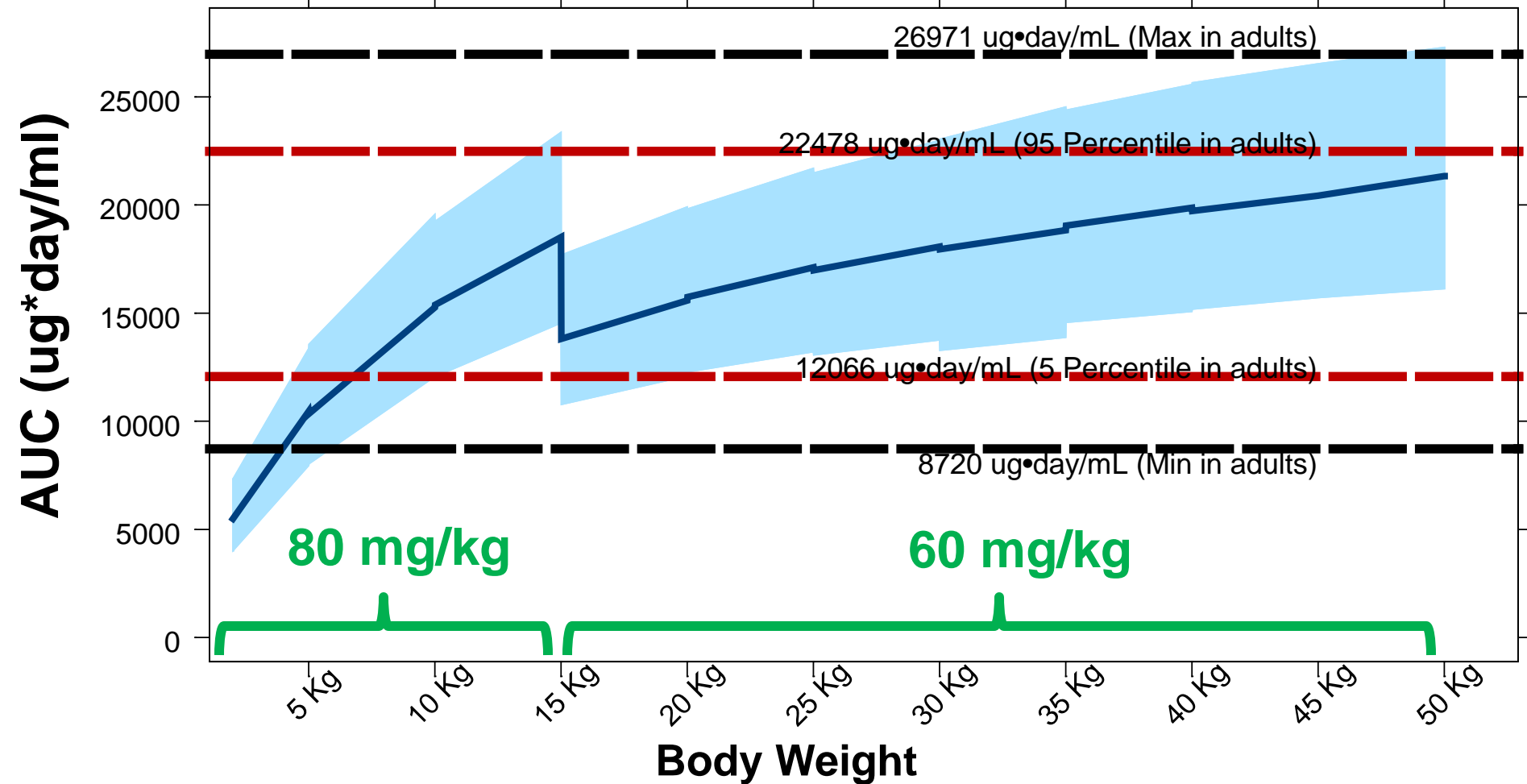
Other monoclonal antibodies with similar relationship:

- **Infliximab**
- **Certolizumab**
- **Basiliximab**

Proposed Pediatric Dosing

| Body Weight | Pediatric Dose |
|--|-----------------------|
| >50 kg | 40 mg/kg |
| > 15 kg to \leq 50 kg | 60 mg/kg |
| \leq 15 kg | 80 mg/kg |

Simulated AUC in Pediatrics Following the Proposed Dosing Regimen



Summary of Case 2

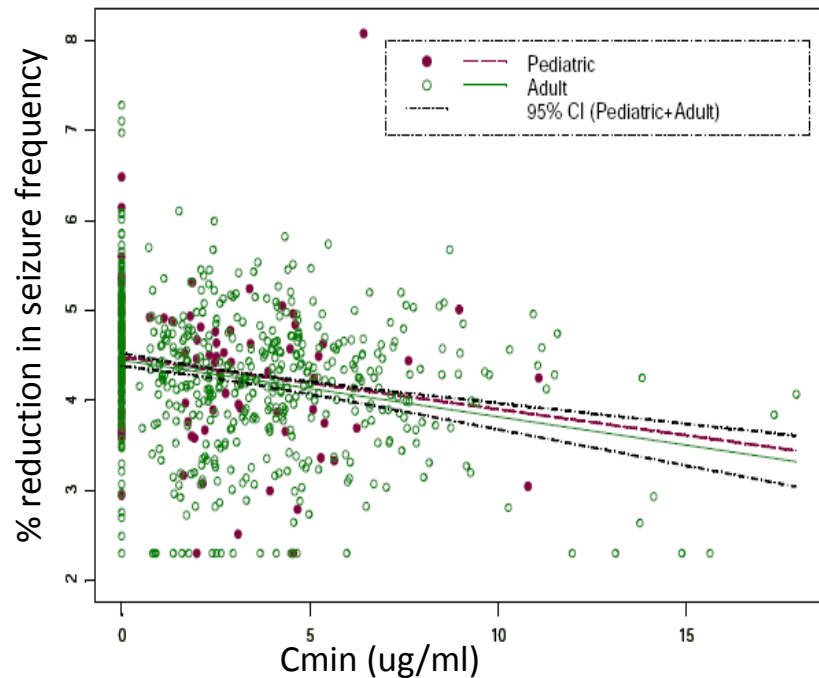
- **Assumptions**
 - 40 mg/kg may be safe and efficacious in adult patients
 - Extrapolation from adults to pediatrics
 - Disease, exposure-response, PK variability
 - Relationship between PK parameters and body weight
- **Criteria**
 - Match the observed exposure in adults at 40 mg/kg
 - Simple to implement in clinical practice
- **Proposed pediatric dosing regimen was discussed at the advisory committee meeting and approved**
- **“There have been no studies of raxibacumab in the pediatric population. Dosing in pediatric patients was derived using a population PK approach”¹**

1. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125349s000lbl.pdf

Case 3: Extrapolation of Anti-Epilepsy Drugs (AED) Efficacy from Adult to Pediatric Patients

- **Collaboration among Pediatric Epilepsy Academic Consortium on Extrapolation (PEACE), University of Maryland and FDA**
- **Efforts to make pediatric drug development more efficient**
- **Full extrapolation already applied for monotherapy of partial onset seizures (POS)**
- **To support full extrapolation for adjunctive therapy of POS**
 - **Analysis of existing data (7 drugs) to demonstrate similar exposure-response relationship between adult and pediatric patients**

Topiramate: Similar Exposure-Response Relationship between Adult and Pediatric Patients



| Parameter | Estimate \pm SE | |
|------------------|----------------------|----------------------|
| | Adults (n=663) | Pediatrics (n=115) |
| Intercept | 4.4469 \pm 0.0313 | 4.4830 \pm 0.0916 |
| Slope | -0.0627 \pm 0.0097 | -0.0579 \pm 0.0305 |

Policy Letter

This letter is to inform you that the Division of Neurology Products has determined that it is acceptable to extrapolate to pediatric patients 4 years of age and older the effectiveness of drugs approved for the treatment of partial onset seizures (POS) in adults. This determination was based on the similarity of POS in pediatric patients 4 years of age and older and adults and on an analysis of multiple antiepileptic drugs, conducted by the FDA, that demonstrated a similar exposure-response relationship in pediatric and adult patients with POS. Extrapolation based on this analysis applies only to POS in pediatric patients 4 years of age and older, and not to POS in pediatric patients 1 month of age to less than 4 years of age or to other forms of epilepsy.

If you have already submitted an initial Pediatric Study Plan (iPSP), a Pediatric Study Plan (PSP), or a Proposed Pediatric Study Request (PPSR) that includes studies intended to independently provide evidence of effectiveness in POS patients 4 years of age and older, you may amend these to reflect the acceptability of extrapolation.

Policy Letter

- **Required information to support an indication for the treatment of POS in patients 4 years and older that relies upon extrapolation:**
 - Approved indication for the treatment of POS in adults.
 - A pharmacokinetic analysis to determine a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric patients 4 years of age and older and in adult patients with POS. This analysis will require pharmacokinetic data from both the adult and pediatric (4 years of age and older) populations.
 - Long-term open-label safety study(ies) in pediatric patients 4 years of age and older.

Summary of Case 3



FDA Conducts Analysis to Assess Acceptability of Extrapolation of Antiepileptic Drug (AED) Effectiveness in Adults to Children Four Years of Age and Older with Partial Onset Seizures (POS)

A collaborative research project led by FDA (Division of Clinical Pharmacology [DCP] and Division of Pharmacometrics [DPM] in the Office of Clinical Pharmacology [OCP], and Division of Neurology Products [DNP] in the Office of New Drugs [OND]), and supported by the Pediatric Epilepsy Academic Consortium for Extrapolation (PEACE) and the Center for Translational Medicine (CTM) at the University of Maryland, Baltimore (UMB) School of Pharmacy, has resulted in a conclusion that extrapolation of the efficacy results from adults to children 4 years of age and older with POS is acceptable and that independent clinical efficacy trials in these children will not be needed.

Blog from FDA Commissioner

- **Dr. Scott Gottlieb – July 7th, 2017**
 - **How FDA Plans to Help Consumers Capitalize on Advances in Science**
 - ***“I want to highlight one example of these steps, which we’re investing in, and will be expanding on, as part of our broader Innovation Initiative. It’s the use of in silico tools in clinical trials for improving drug development and making regulation more efficient.”***
 - ***“Modeling and simulation play a critical role in organizing diverse data sets and exploring alternate study designs. This enables safe and effective new therapeutics to advance more efficiently through the different stages of clinical trials. ”***
 - ***“FDA’s Center for Drug Evaluation and Research (CDER) is currently using modeling and simulation to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms.”***
 - ***“...uses these same strategies in the review of Investigational New Drugs Applications (INDs) and New Drug Applications (NDAs)”***
 - ***“An important objective of modeling and simulation is to better evaluate the behavior of new treatments in rare disease populations that are inherently hard to study due to their small size.”***

Acknowledgements

- **Division of Pharmacometrics**
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- **Office of New Drugs**
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- **PEACE**
- **University of Maryland**