Modeling and Simulation to Support Pediatric Clinical Trials

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Eli Lilly and Company

Acknowledgements

- PKPD – Xin (Cindy) Zhang
- PBPK – Maria Posada
- QSP – Jason Chan
- Statistics – Meg Gamalo
- Medical – Robert Hoffman, A.J. Allen, Mary Short

Outline

- Motivation
- Example
- Conclusions

Should we all be treated the same?

Should we all be treated the same?

Not pharmaceutically!

Motivation

- See back-ups
- It takes too long for information on treating pediatric populations to be available (~9 years on average)
- Many potentially effective products in pediatrics have no label information (~half)
- Many pediatric studies fail to demonstrate efficacy (42%)

Why is it so hard?

- Smaller population
- More mandated pediatric clinical trials
- Vulnerable population
- Unwillingness to expose to placebo or ineffective doses
- Access to treatments via approved adult indications

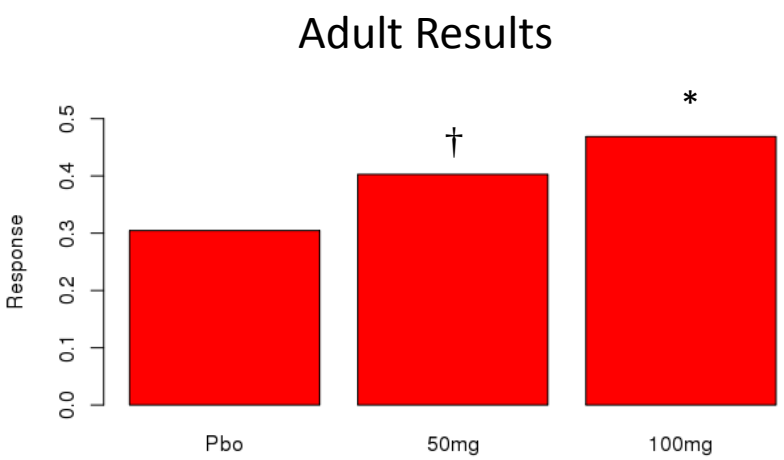
Example

- NME
- Adult Phase 3 is complete
- Pediatric patients tend to have more severe disease
- There is a biomarker that correlates well with the disease severity
- This biomarker is along the pathway of drug mechanism

Background

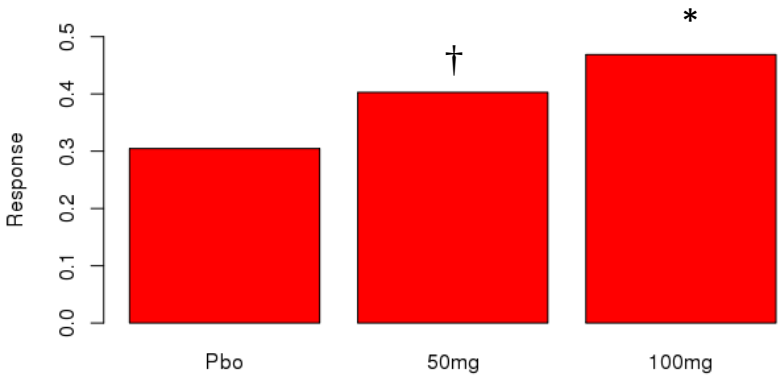
- Drug X: oral
- Pharmacokinetics:
  - 30% by kidney
  - 70% by liver metabolism (CYP3A4)
- Pharmacodynamics:
  - Biomarker of target engagement measurable in plasma
  - Biomarker of disease severity measurable in plasma
- Pediatric studies in this population have suffered from poor enrollment
- Disease and exposure-response may differ between adults and pediatrics
  - These can be modeled

What we can do



What we can do

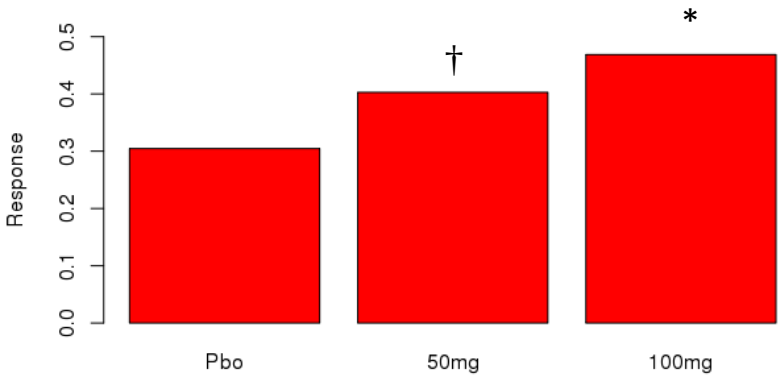
Adult Results



Pediatric Prior

What we can do

Adult Results



Different disease progression
Different exposure-response

Pediatric Prior

What we can do

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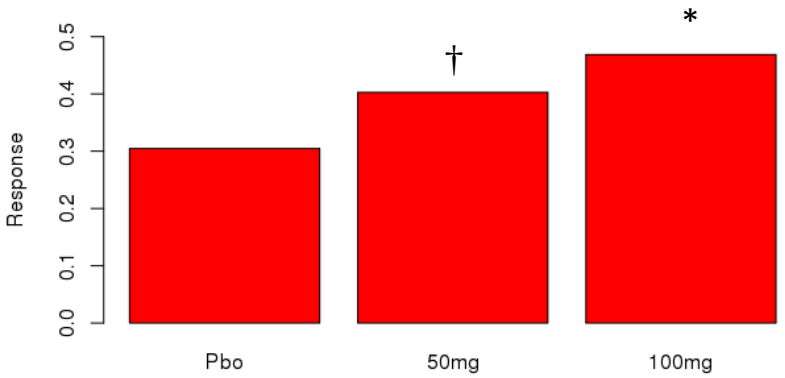

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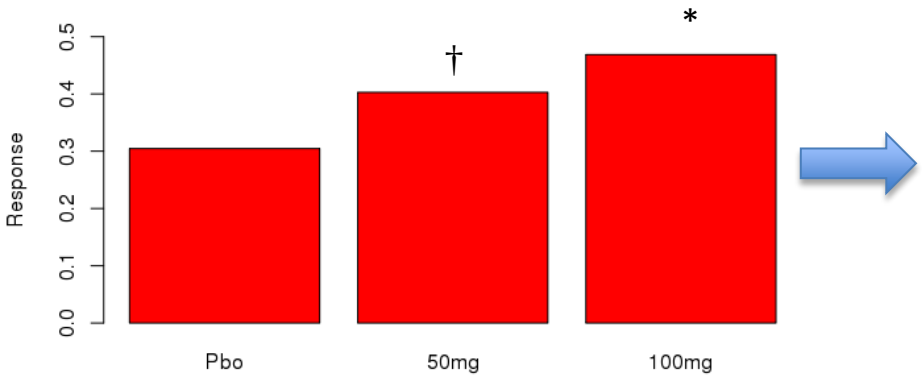
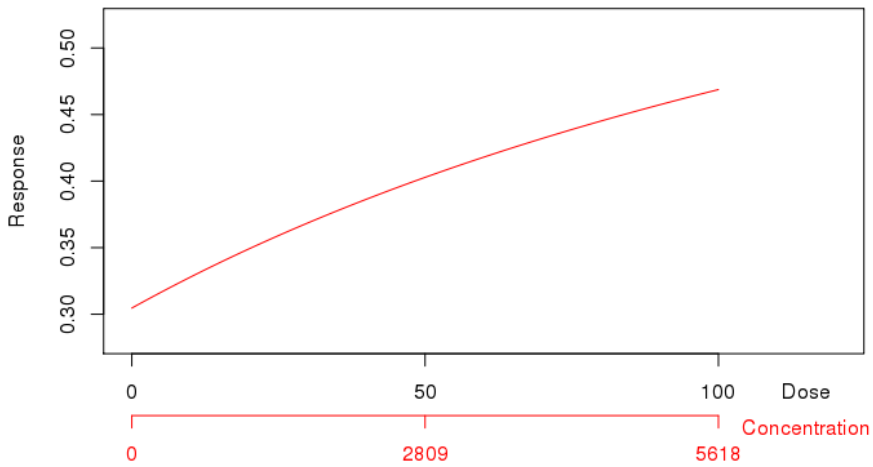


Adult PKPD



Different disease progression
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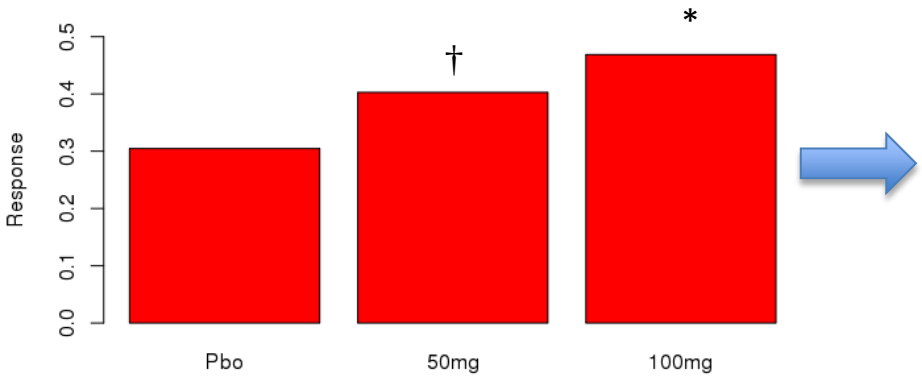
Pediatric Prior

Pediatric PKPD???

What we can do

Adult Results



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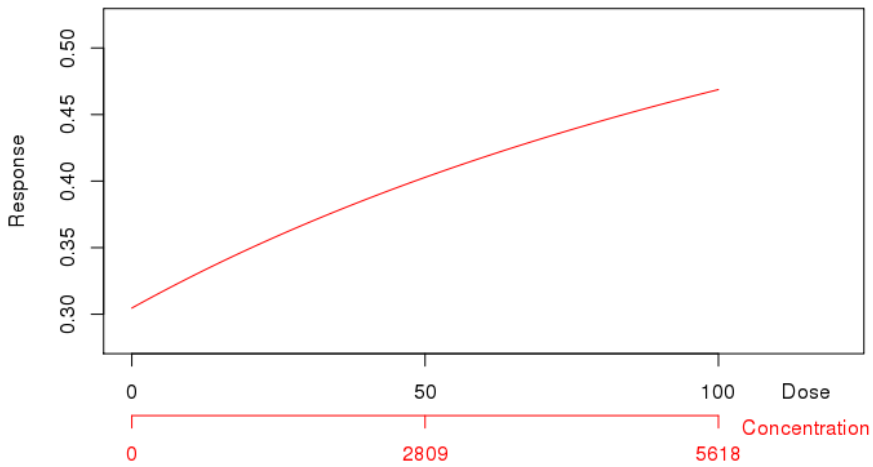

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Models!

What we can do

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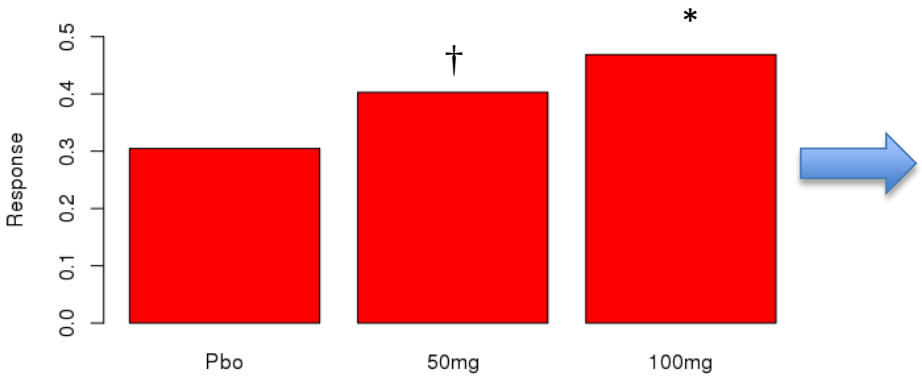

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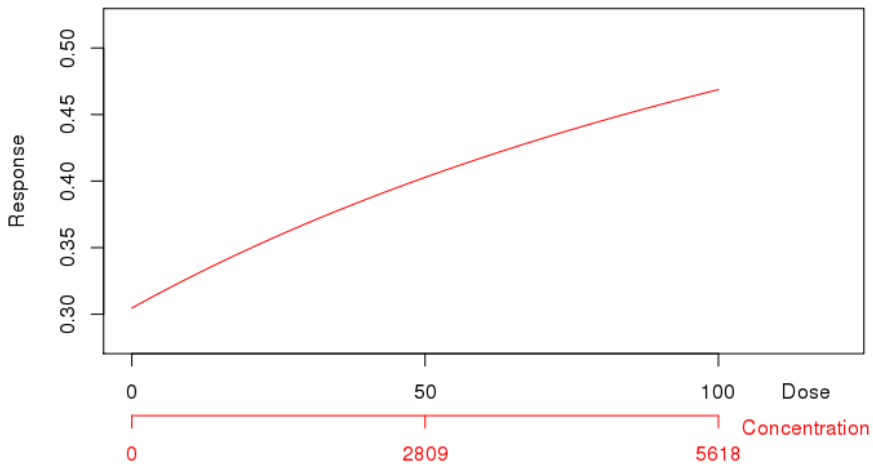


Different disease progression
Different exposure-response

Pediatric Prior

Pediatric PKPD???

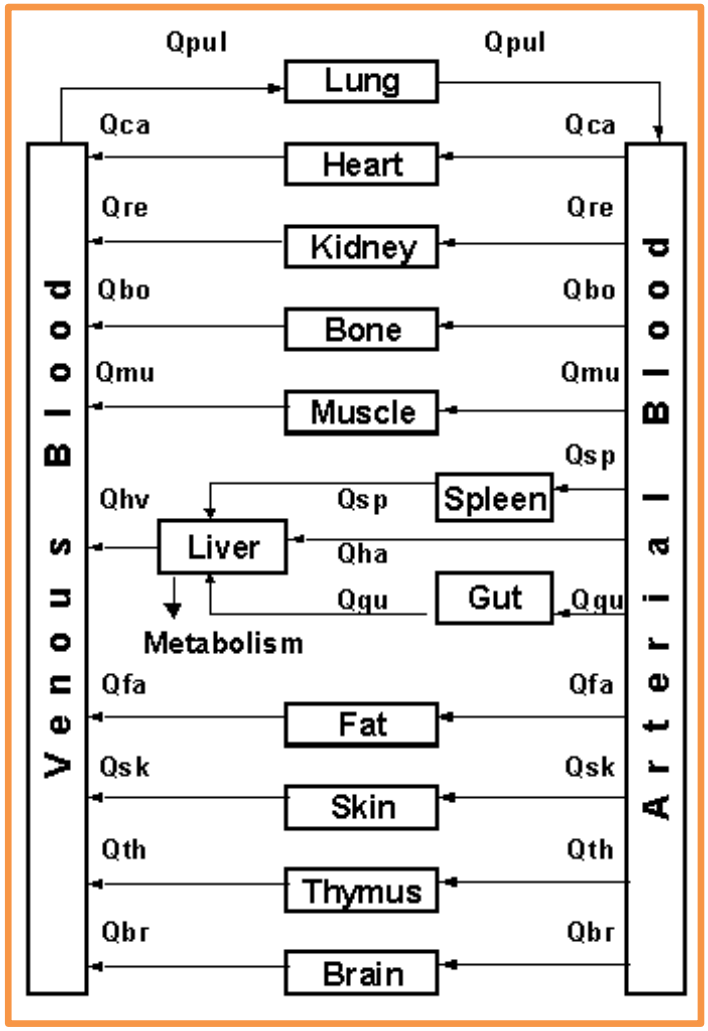
Simulate!

Models!

Pediatric Plan

- Use PBPK model to adjust for pediatric age-related renal and hepatic function differences
- Use QSP model to bridge pediatric exposure-response relationship from adult exposure-response relationship
- Simulate priors for Bayesian extrapolation from QSP model at doses yielding target exposures for pediatric patients

Physiologically-Based PK Modeling



Drug parameters:

- LogP, pKa, fraction unbound, B:P

Physiological parameters:

- Blood flows
- Organ weights and volumes
- Enzyme amounts
- Plasma protein concentrations
- Hematocrit
- Tissue compositions
- Lipids

Population parameters:

- Age, weight, gender, and enzyme phenotype.

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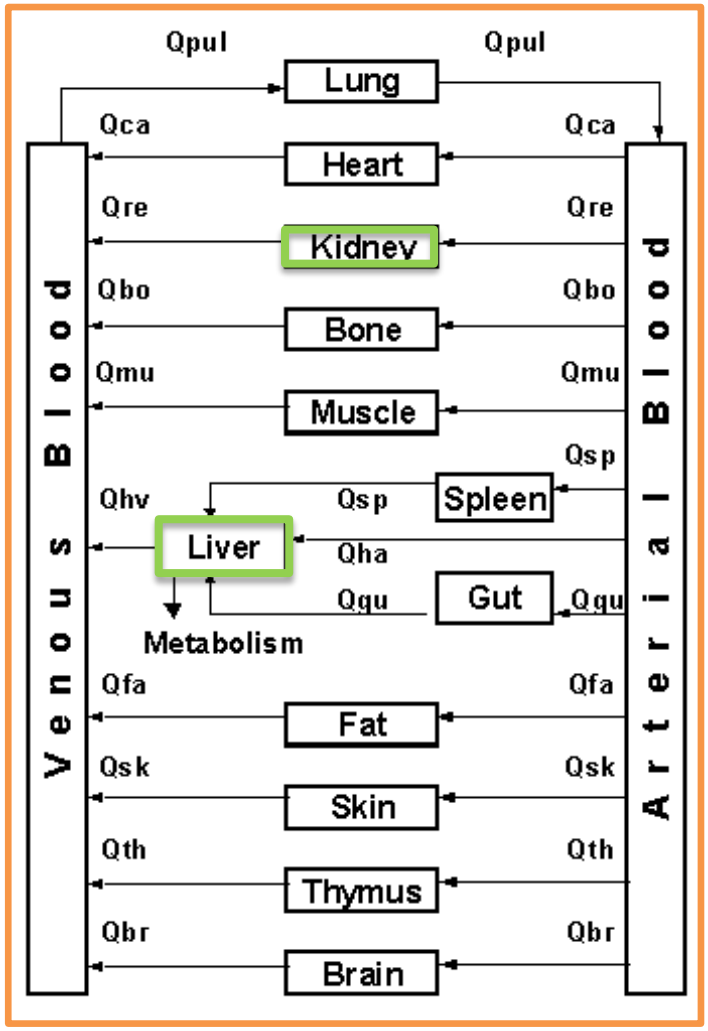

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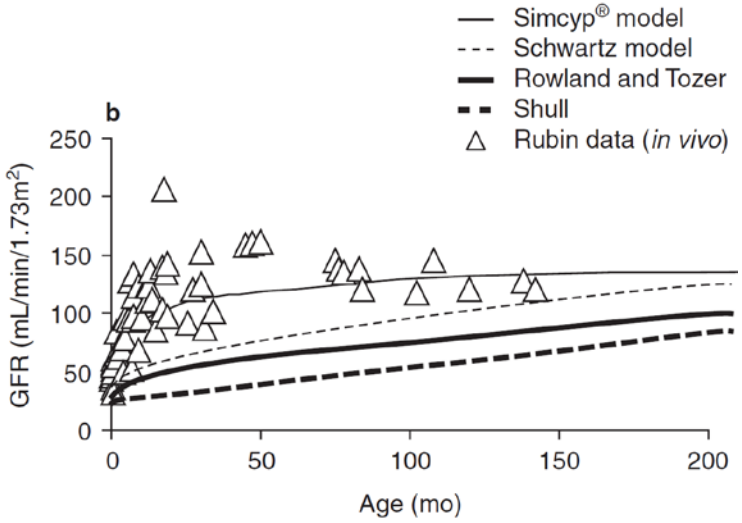
PBPK Model

- Model parameters can be interpreted physiologically
- Assumptions can be made about how parameters will change to predict PK in pediatric subjects
  - Renal clearance dependent on GFR
  - Hepatic CL dependent on CYP abundance and activity

Kidney

GFR vs. Age



Liver

Enzyme Maturation Function

$$CL_{NR,3A4} = \frac{CL_{NR,Adult} \times 0.76 \times Age^{0.83}}{0.31 \times Age^{0.83}}$$

$$CL_{NR,1A2} = \frac{CL_{NR,Adult} \times 0.16 \times Age^{1.41}}{1.13 + Age^{1.41}}$$

$$CL_{NR,2C9} = \left(CL_{NR,Adult} \times 0.06\right) \times \left[\frac{0.79 \times Age}{0.01 + Age} + 0.21\right]$$

Johnson et al. Clin Pharmacokinet 2006;45

Deriving Pediatric PK

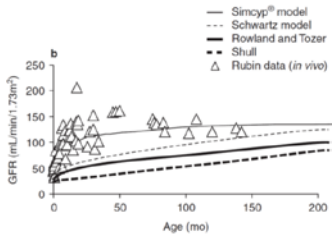
Drug parameters

Pediatric Population parameters

PBPK Model

Kidney

GFR vs. Age



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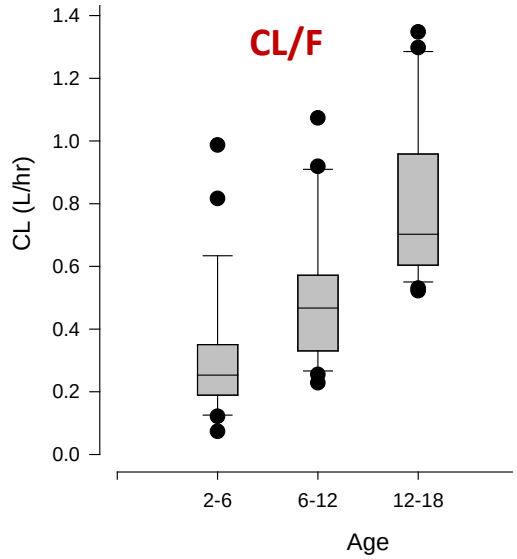
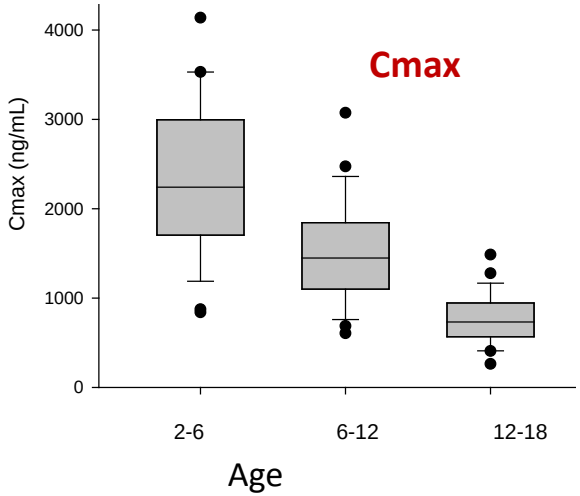
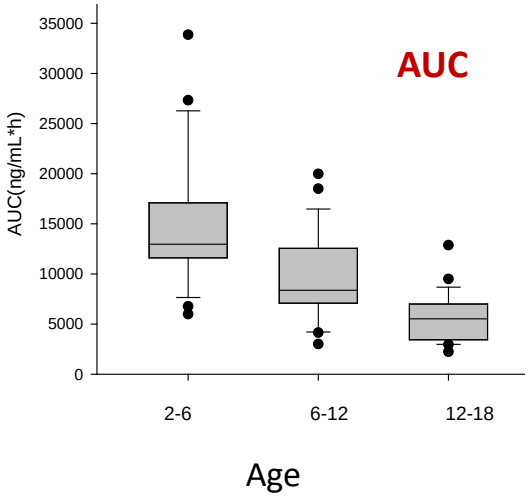
Physiological parameters

Pediatric PK

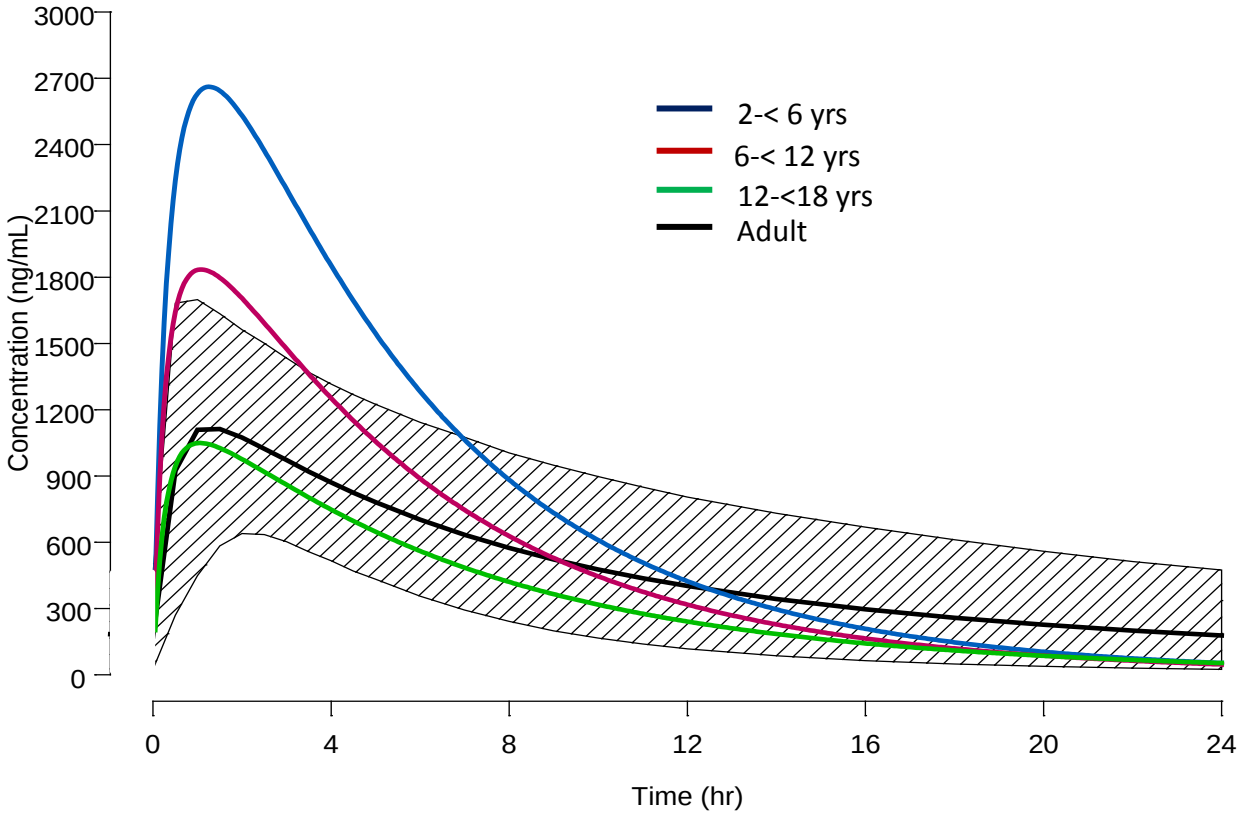
Predicted PK Parameters



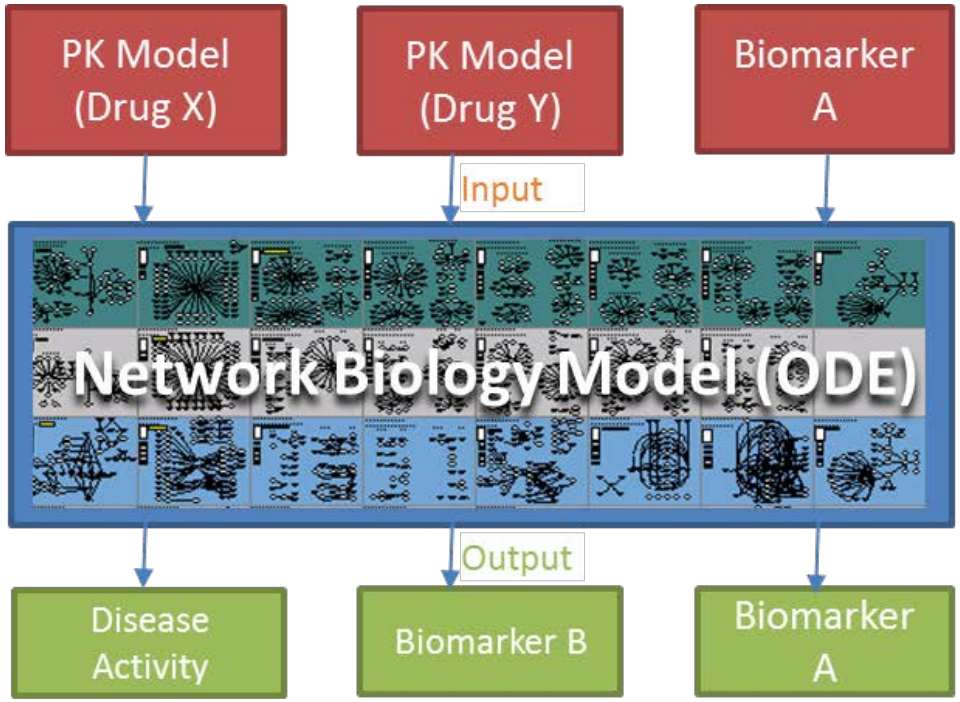




Predicted PK Profiles in Children Compared to Adult

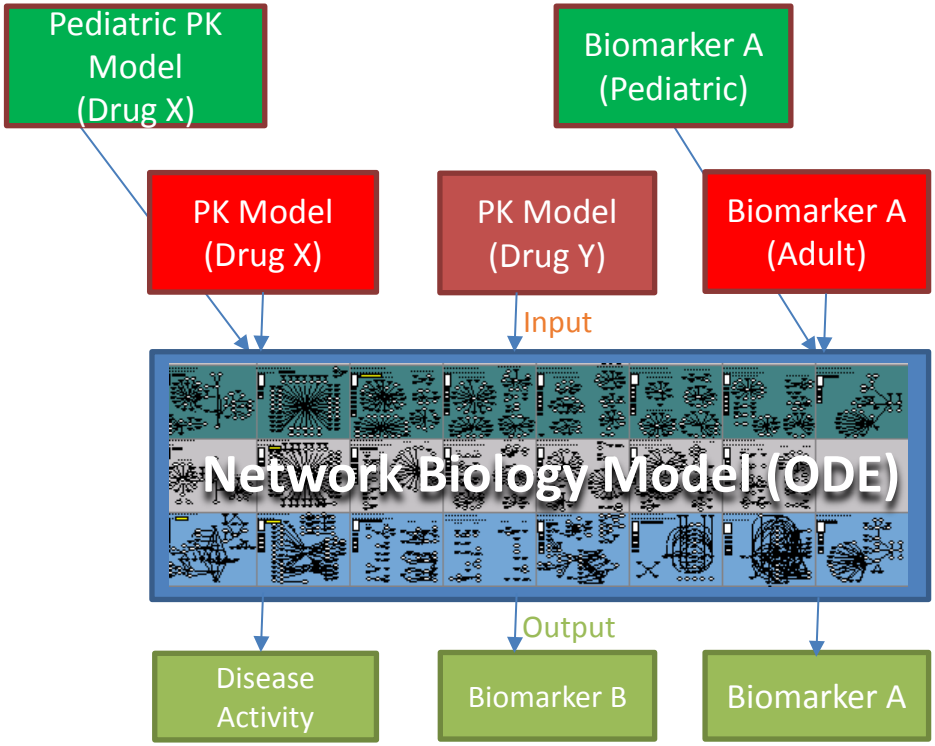


Quantitative Systems Pharmacology

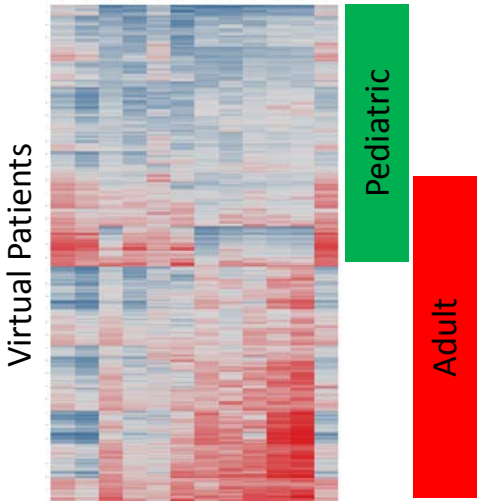


A mathematical representation of biology, including disease states, that incorporates various data types (preclinical, clinical, PK/PD) into a common dynamic framework and is used to understand the impact of perturbation via drugs or other interventions

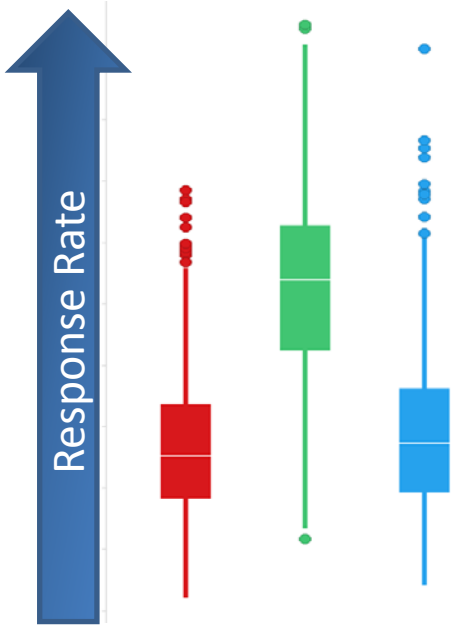
QSP model used to estimate effect of differences in pathophysiology



Patients can be stratified to adult and pediatric populations based on known differences in biology

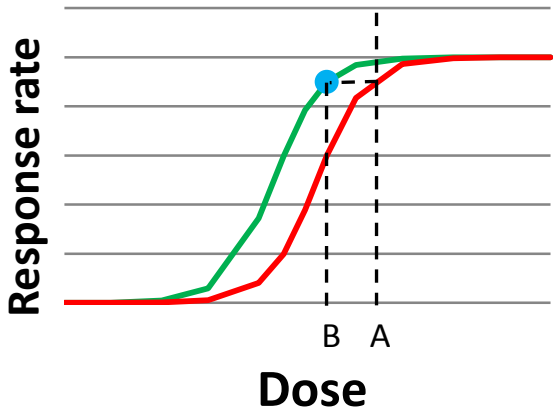


QSP model can be used to adjust pediatric dosing

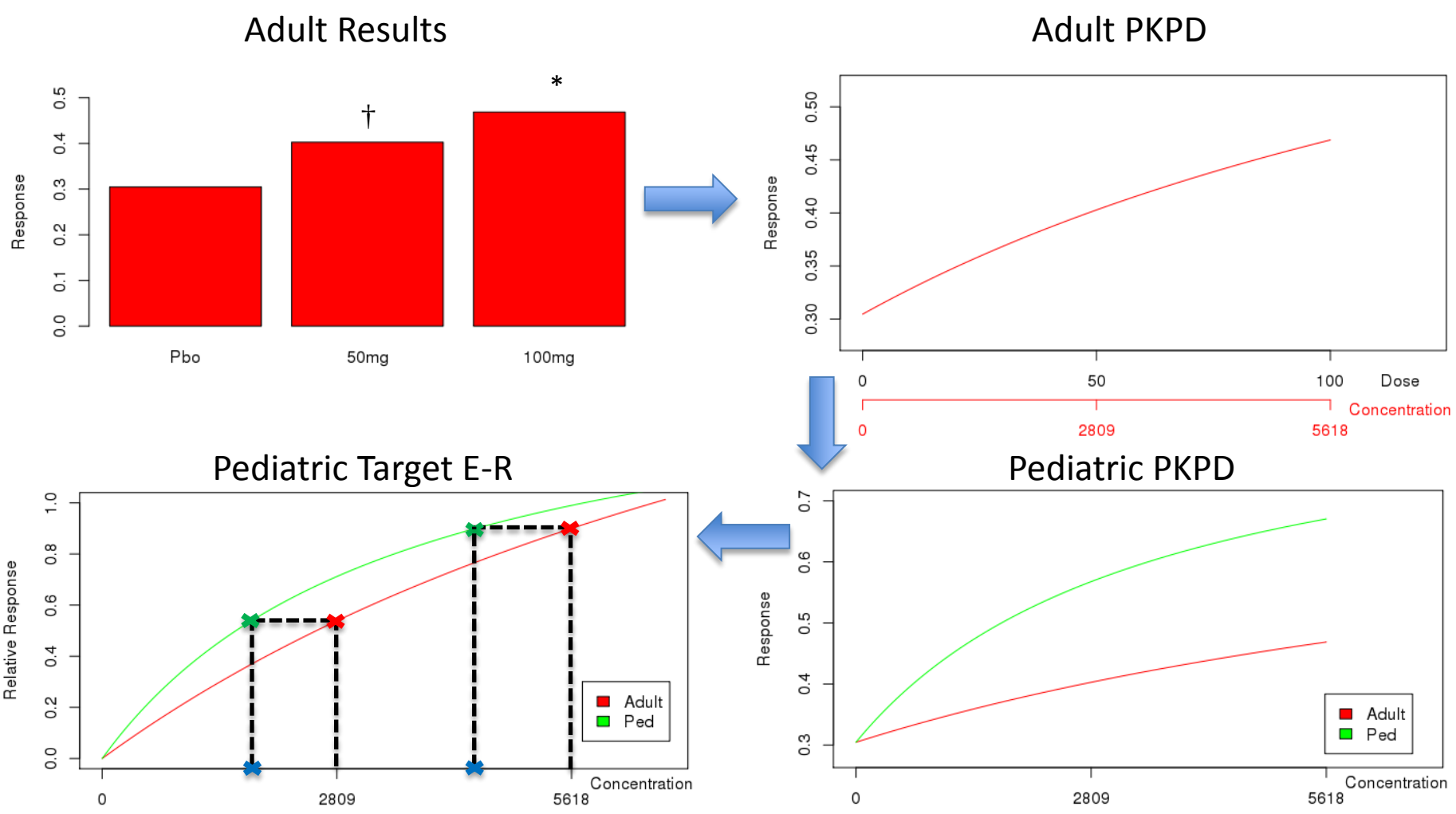


Dose	A	A	B
PK	Adult	Pediatric	Pediatric
Biomarker	Adult	Pediatric	Pediatric

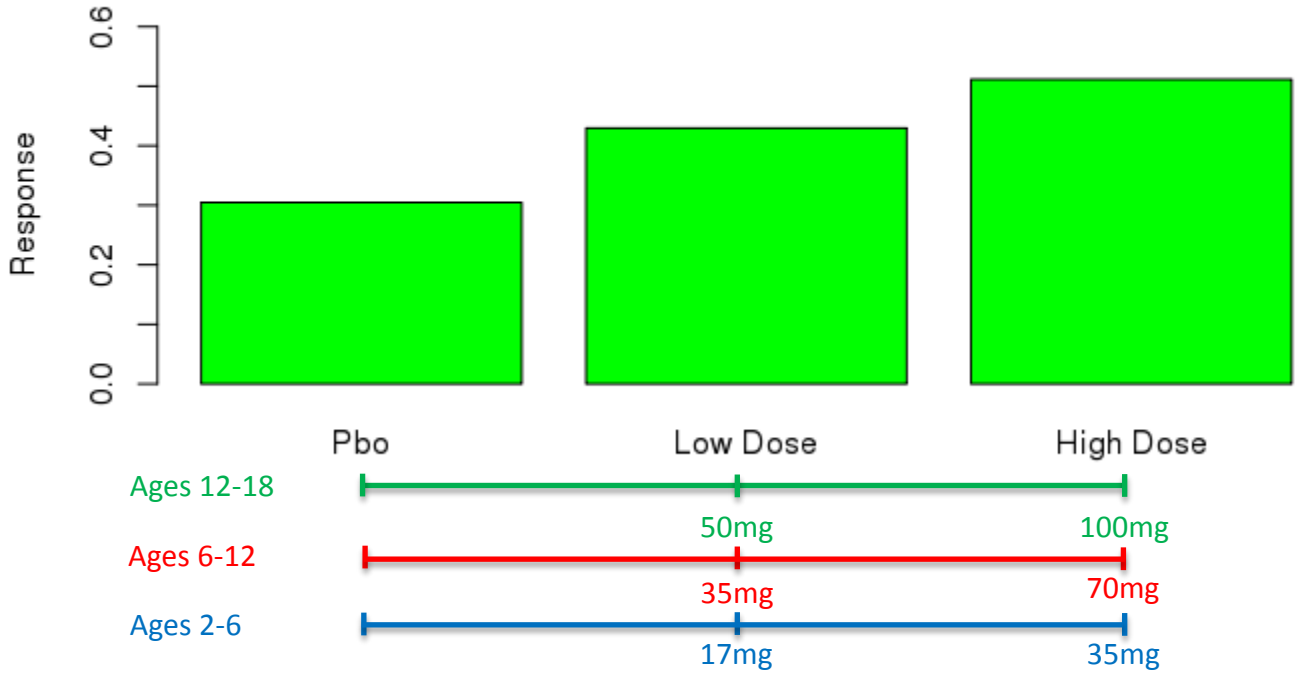
QSP model integrates differences in PK and underlying physiology between adult and pediatric populations to estimate dose/response relationship in pediatric population



Results of Modeling



Simulated Pediatric Study



Bayesian Sample Size

- Borrow information from other data sources (e.g. adult studies) – “prior”
- Can lead to more efficient study
- Depends on consistency between prior and new data
- Amount of borrowing should be based on biology and pharmacology - not just how similar the data looks

Bayesian Approach

Prior = ϵ*(Informative Prior)+(1-ϵ)*(Non-informative Prior)

Use the prior data

Let new data speak for itself

Bayesian Approach

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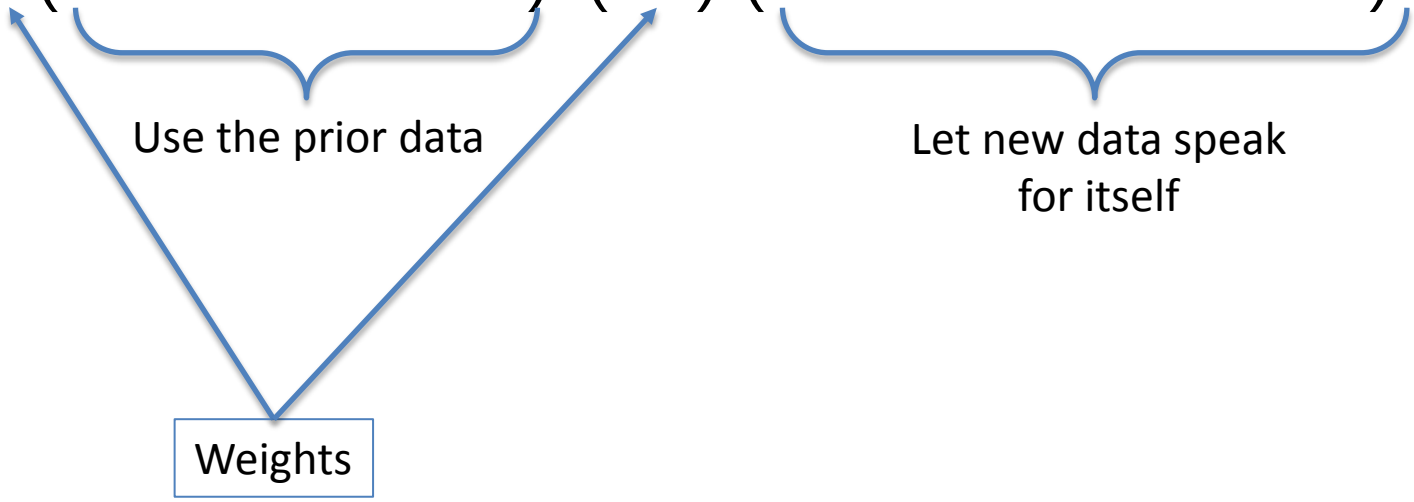

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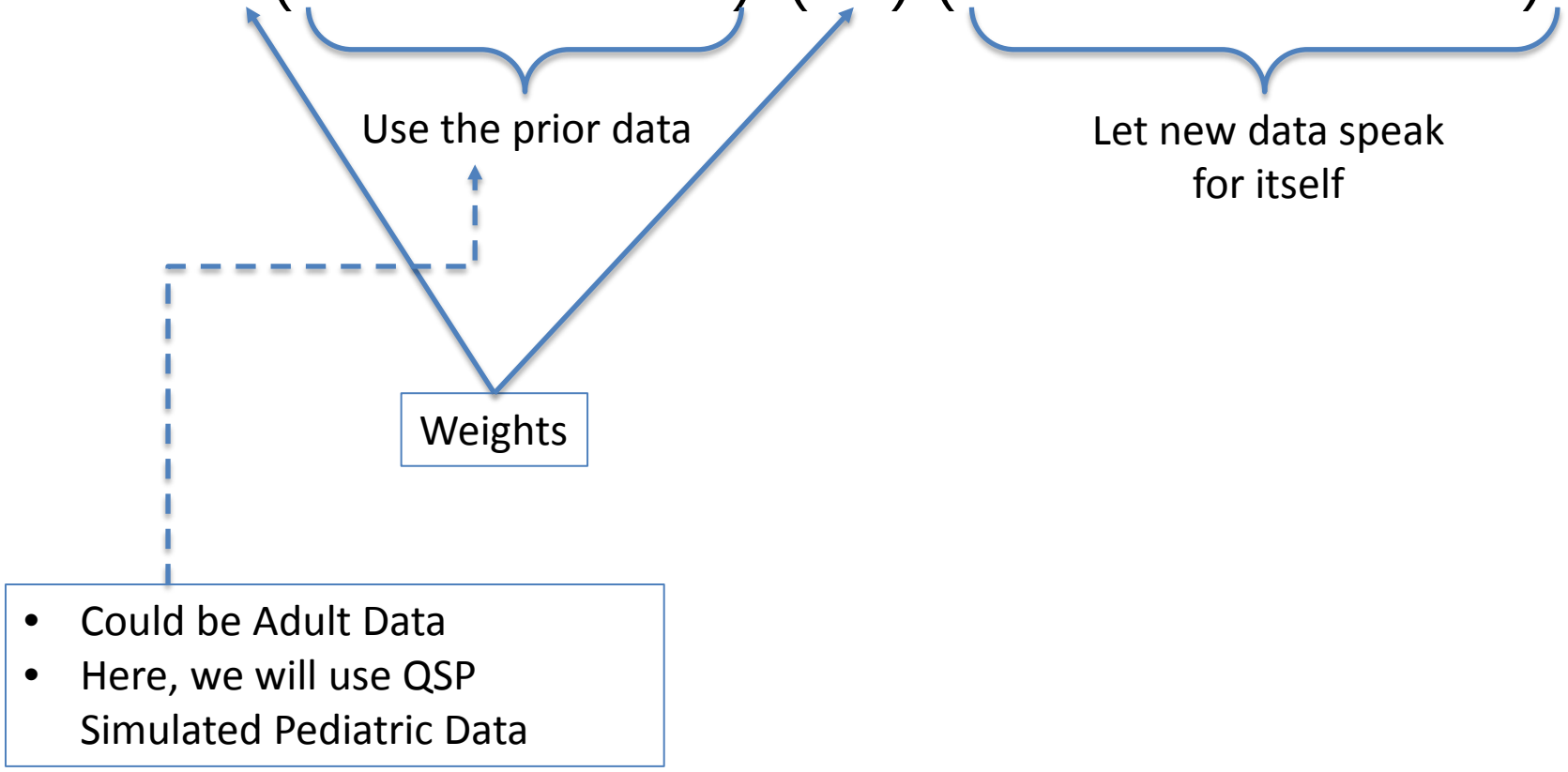

Bayesian Approach

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Use the prior data

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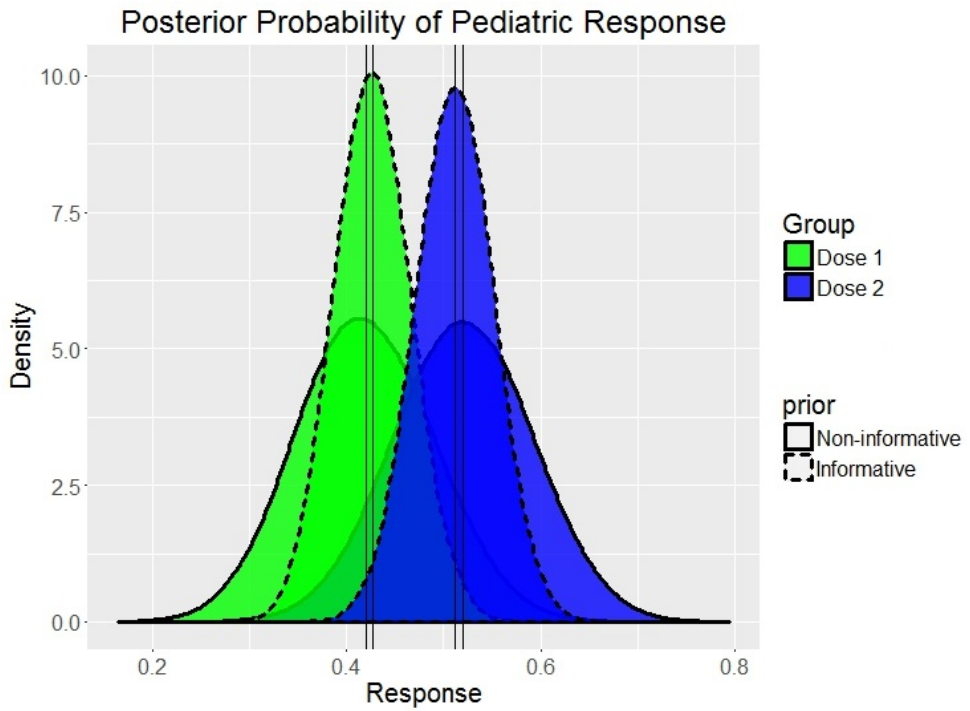
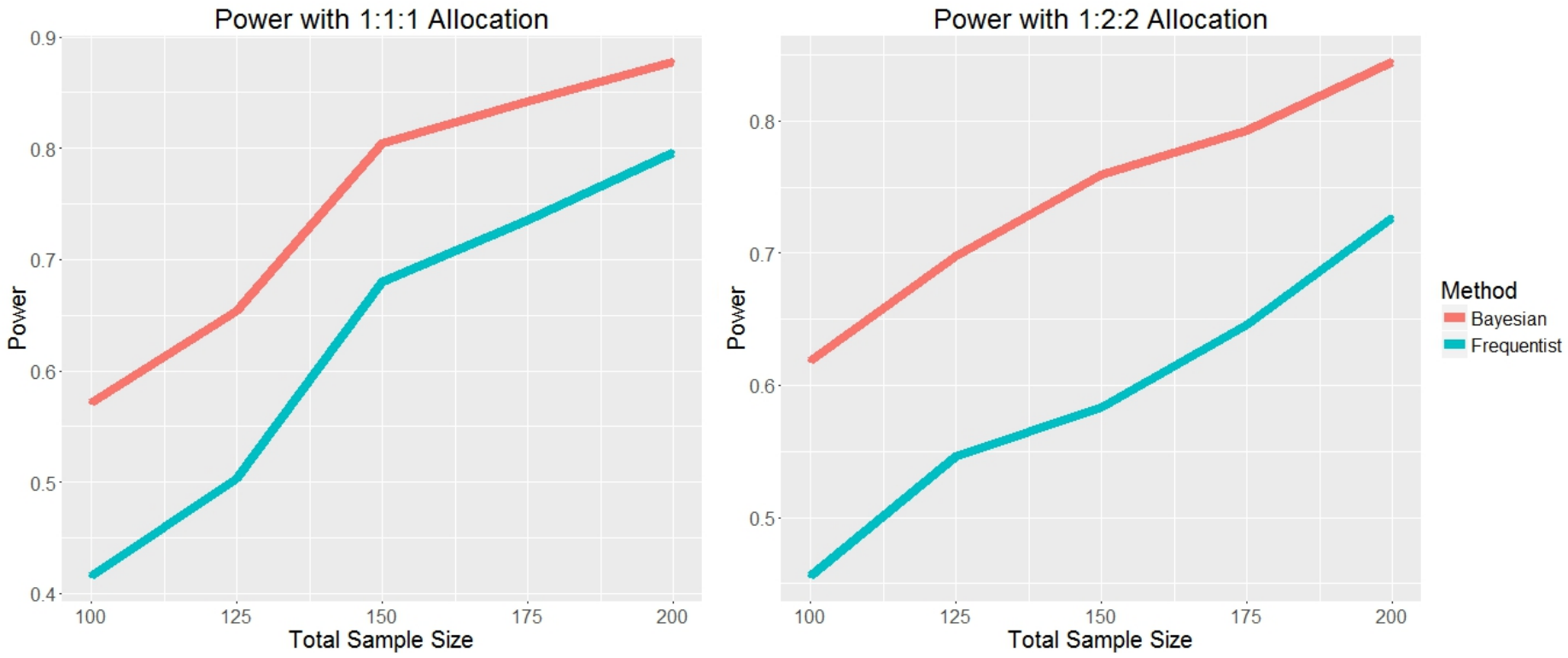
Weights

- Could be Adult Data
- Here, we will use QSP Simulated Pediatric Data



Power and Sample Size



Use of “Prior” QSP Model results in a more efficient study

Gives feasible options for study designs

Conclusions

- Due to ethical, feasibility, and scientific challenges, extrapolation is often necessary to guide pediatric treatments
- Even when disease progression or exposure-response are expected to differ between adults and pediatrics, modeling and simulation can be used to bridge data gaps
- Efficient clinical studies should be run when possible to confirm models

Thank you!

Back-ups

Time Lapse: Adult NDA Date to First Ped Label

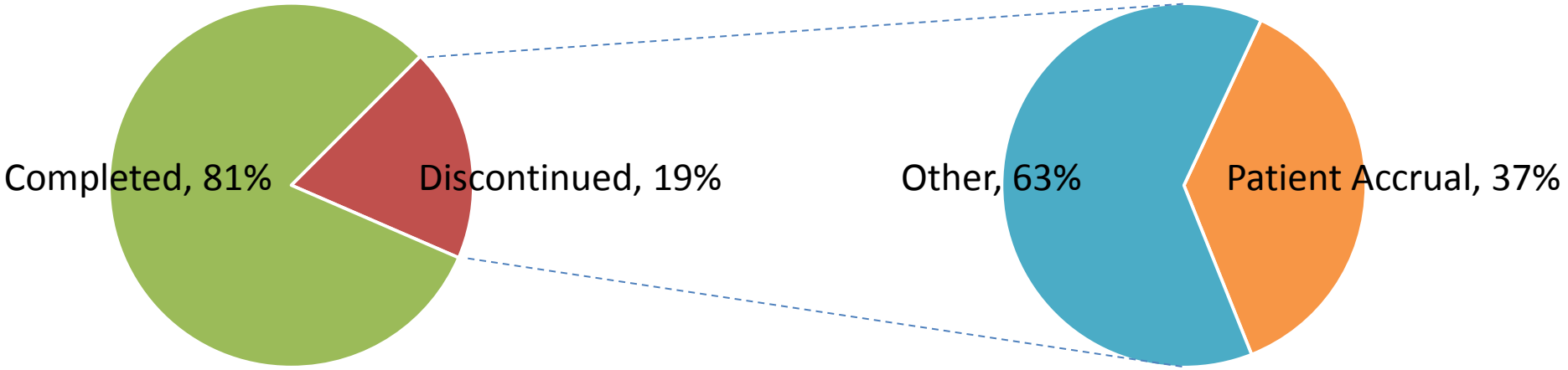
Average Time Lapse (in years)			
Difference between Adult NDA Date and First Pediatric Label Date			
2001 & Earlier	**2002–2006**	**2007–2011**	**2012–2016**
7.03	**9.84**	**7.06**	**9.68**
N=17	*N=35*	*N=34*	*N=28*

Source: Simpkins, P.L., 2017. Analysis was completed using data from Evaluate Pharma, Drugs@FDA.gov (label) and FDA New Pediatric Labeling Information Database (pediatric label changes). Accessed February 2017. Sample size N = 114 pediatric labels. Rx products only (excludes OTC products).

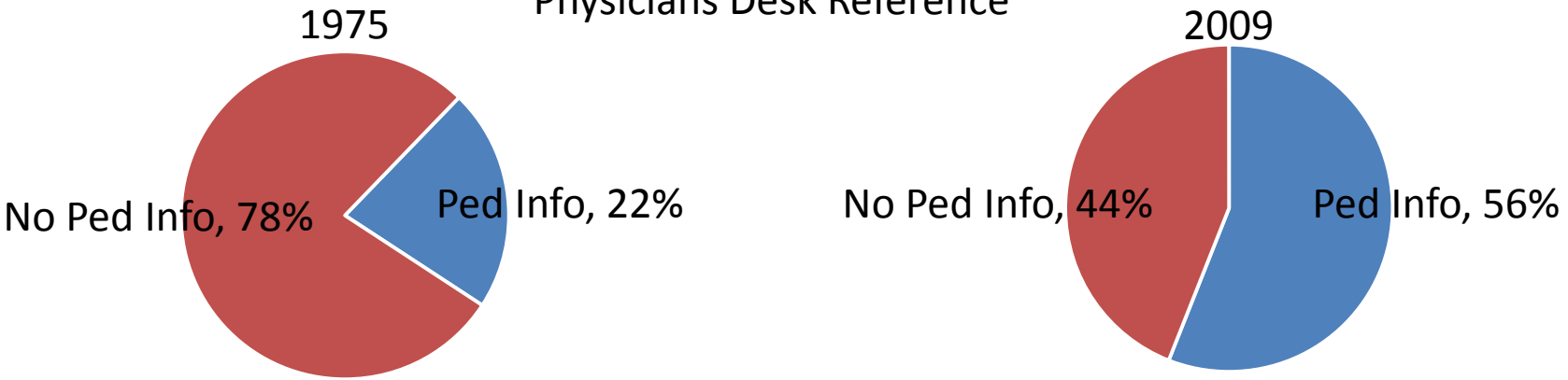
- On average, it takes 9 years from the time of a product's approval for use in adults until the label is updated to include pediatric data.
- Off-label use occurs during this time period.

Pediatric Information

Pediatric RCTs, 2008-2010, ClinicalTrials.gov[1]



Physicians Desk Reference[2]

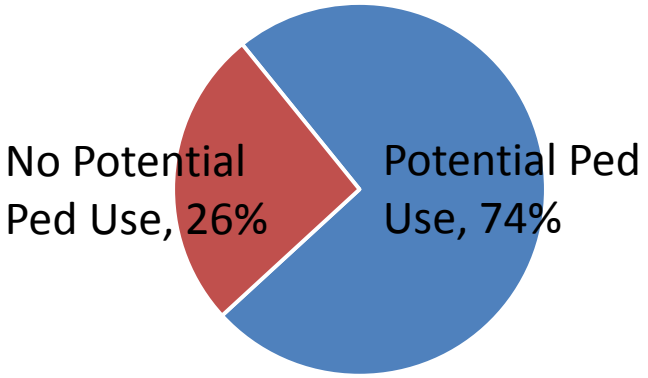


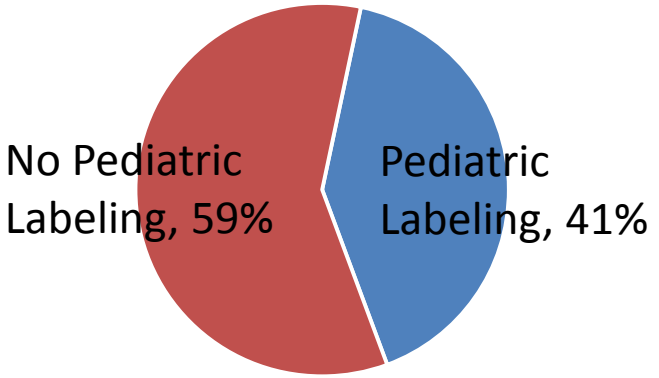
[1]Pica N. and Bourgeois F., **Discontinuation and Nonpublication of Randomized Clinical Trials Conducted in Children**, *Pediatrics*, on-line, Aug. 4, 2016

[2]FDA OPT and Pediatric and Maternal Health Staff, **More drug labels include pediatric information, but work remains**, *AAP News* 2012;33;12

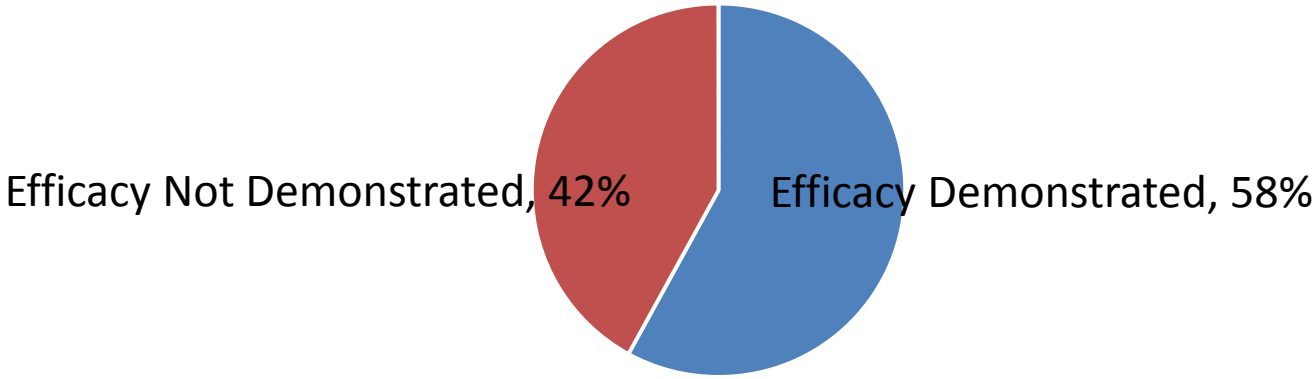
Pediatric Labeling

US NMEs, 2002-2008[1]





Written Requests, 1998-2012[2]



[1]FDA OPT and Pediatric and Maternal Health Staff, **More drug labels include pediatric information, but work remains**, *AAP News* 2012;33;12
[2]Wharton G. et al., **Impact of Pediatric Exclusivity on Drug Labeling and Demonstrations of Efficacy**, *Pediatrics*, 2014;134;e512