Leveraging Prior Knowledge in Guiding Pediatric Drug Development

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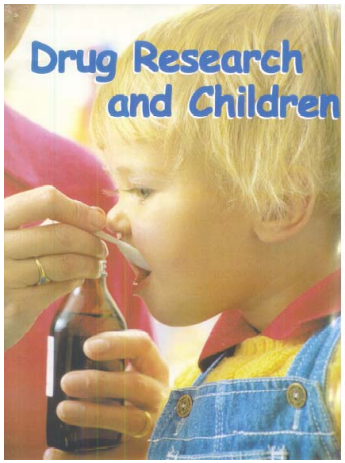
The views expressed in this presentation do not necessarily reflect the agency position

Agenda

1. History of Legislation
2. Retrospective Analysis
3. Impetus
4. CTS Framework
5. Results
6. Conclusions

Legislation History

Active history to obtain good quality pediatric data



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- 1994 Pediatric Labeling Rule
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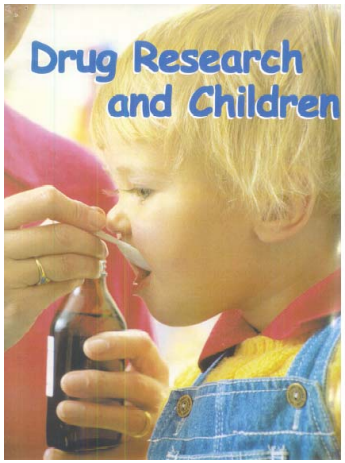

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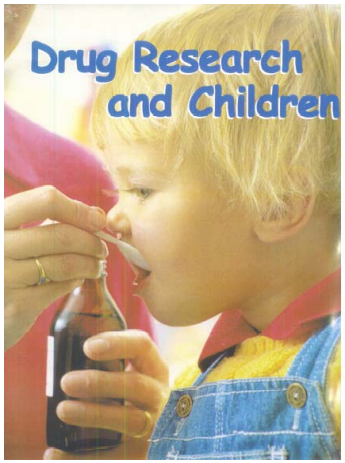

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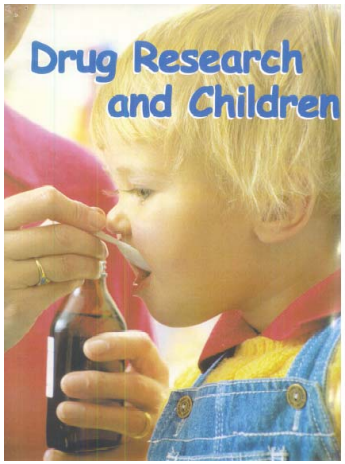
Improved Labeling Information for Pediatrics

A central goal of pediatric exclusivity program



- **General principles** [a]
  - Pediatric patients should be given medicines that have been appropriately evaluated for their use in those populations
  - Product development programs should include pediatric studies when pediatric use is anticipated
  - Shared responsibility among companies, regulatory authorities, health professionals, and society as a whole

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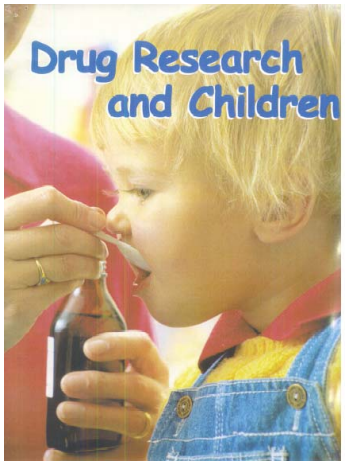

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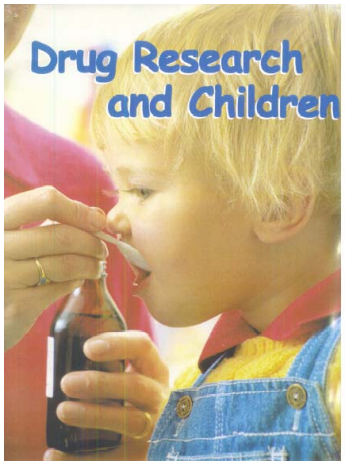

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Improving Pediatric Dosing through Pediatric Initiatives

What we have learned

- Substantive differences in dosing, safety, or efficacy in children [1] compared with adults for at least half of the products studied
- Twenty nine of 131 drugs were concluded to be ineffective
- Several oral antihypertensive products that were approved in adults did not seem to work in children
- With rising obesity in children and adolescents, failed trials for antihypertensive products have significant public health implications

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Antihypertensive Trial Failures

Analysis of 6 type C study designs

- Six dose-ranging antihypertensive efficacy trials completed for pediatric exclusivity from 1998 to 2005 were reviewed [a]
- Three failed and Three succeeded to demonstrate dose response as a primary endpoint
  - Failed trials included 2-9 fold and Successful trials included 20-32 fold dose range
  - Two failed drugs were significantly different compared to placebo in the 2nd part of the study
- Poor dose selection, lack of acknowledgment of differences between adults and pediatrics and lack of suitable pediatric formulations as potential failure reasons

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Leveraging Prior Quantitative Knowledge
A case study

- Drug X to be used for immediate blood pressure (BP) control
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Leveraging Prior Quantitative Knowledge

Sponsor and FDA conducted clinical trial simulations (CTS) to substantiate the choice of trial design, dosing regimens and sample size

- Information available to
  - Sponsor and FDA
    - Patient level exposure-response data on drug X in adults
    - Mean exposure-response data on fenoldopam [a]
  - FDA
    - Patient level exposure-response data on fenoldopam in adults and pediatrics
- Inputs for CTS
  - Exposure response model
  - Placebo response model
  - Drop-out model
  - Trial design

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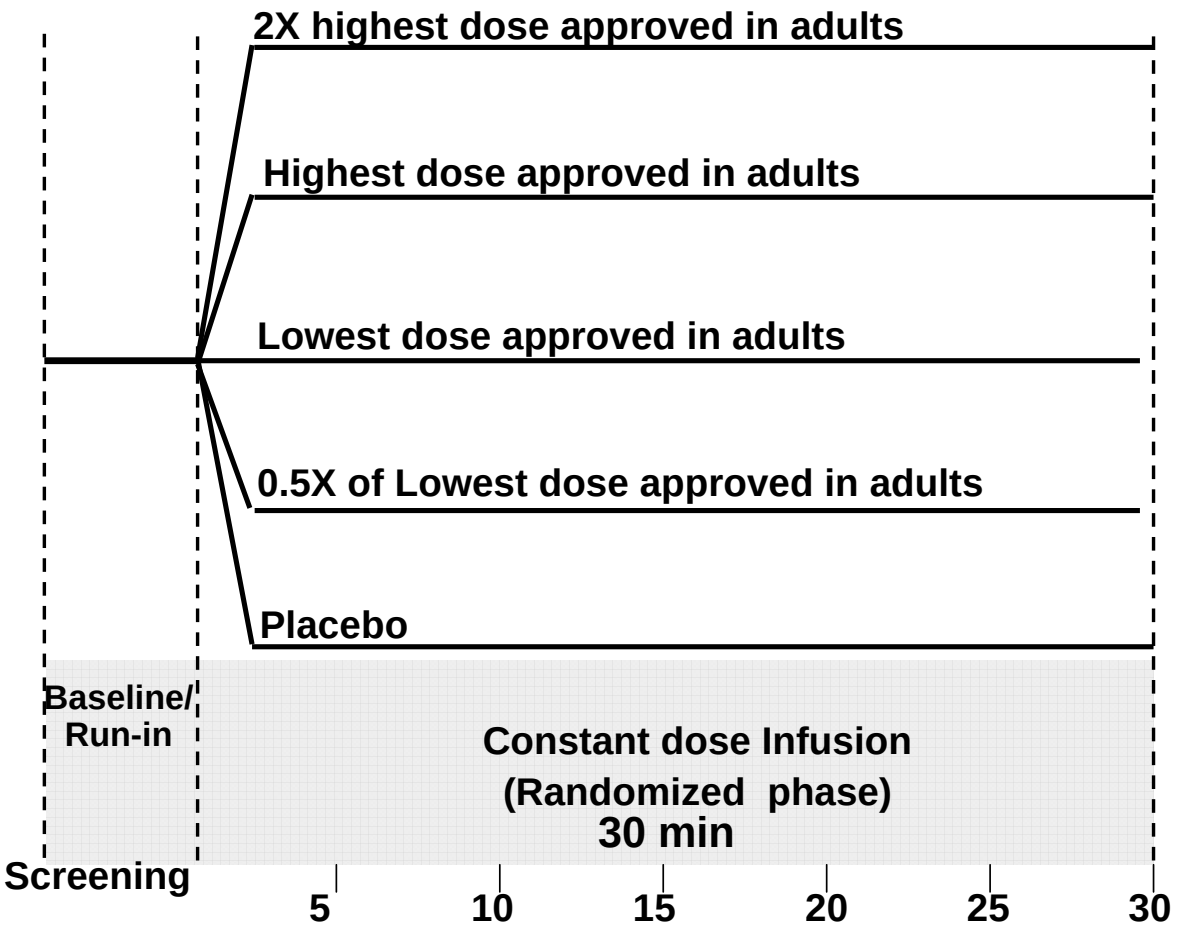
Inputs for CTS

- Exposure response model
  - Patient level adult data for Drug X
- Placebo response model
  - Patient level pediatric data for fenoldopam
- Drop-out model
  - Patient level pediatric data for fenoldopam
  - Clinical experience: Subjects with $>$25% decrease in DBP discontinue

Trial Design and Statistical Tests



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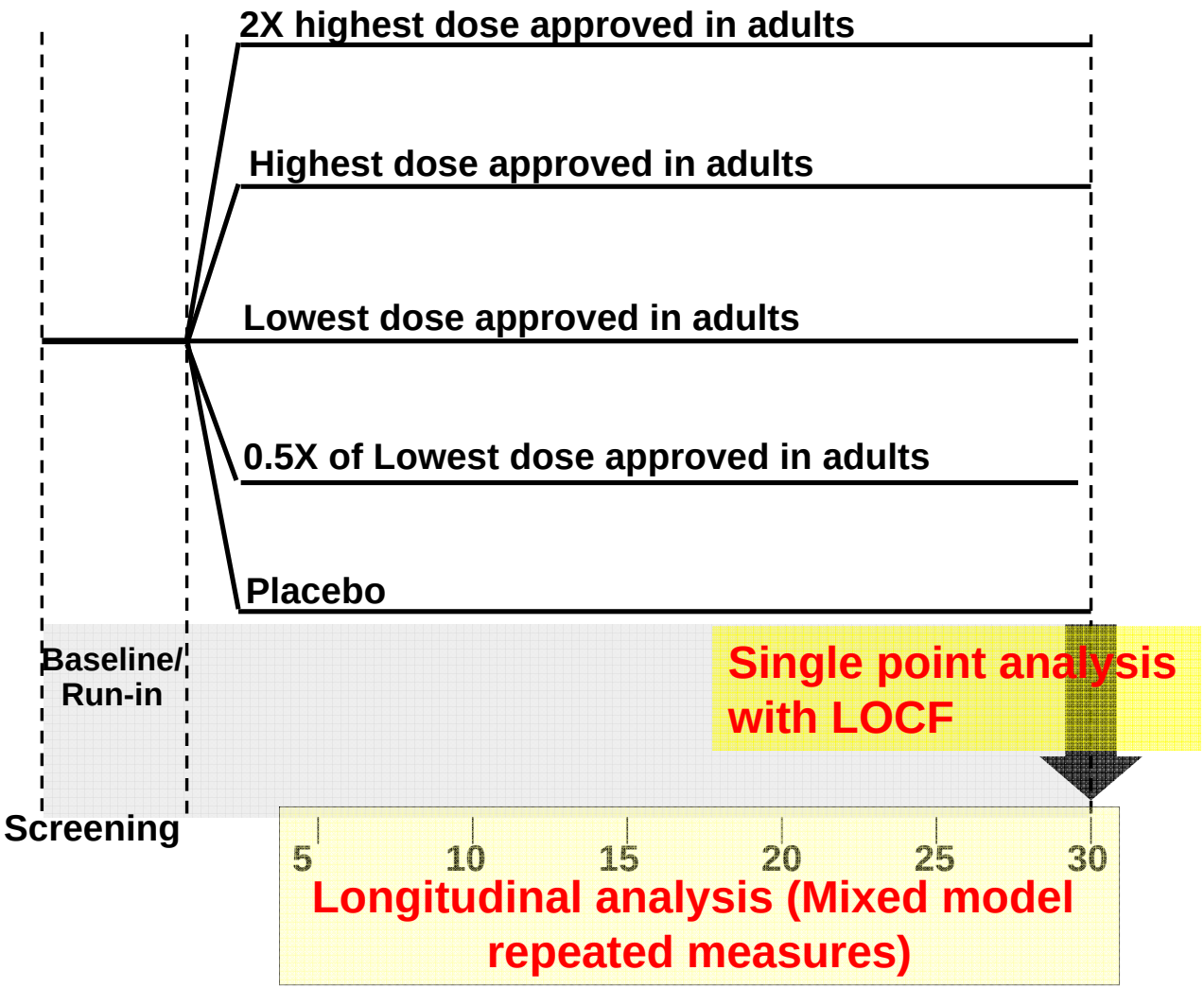
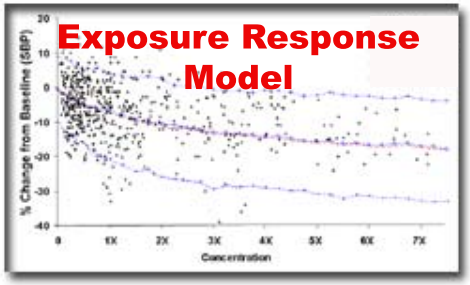
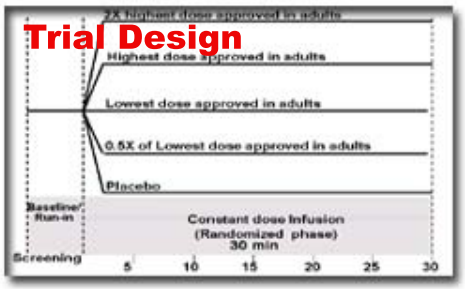


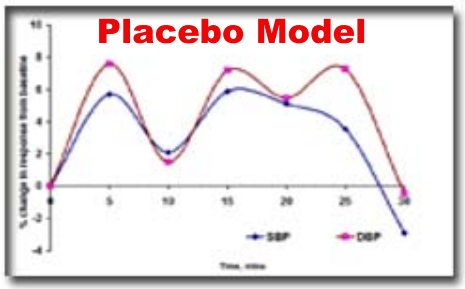
Simulation Experiment

Exposure-response, placebo model, trial design and drop-out assumptions





Dropout model



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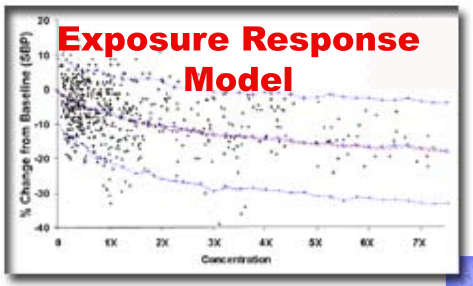

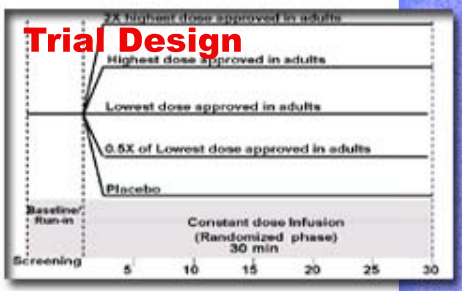

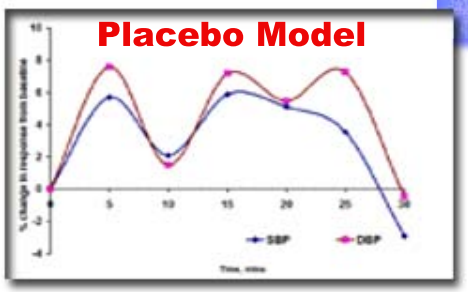

Dropout model

Simulation Scenarios

Adults = Pediatrics
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(Emax 0.75x : EC50 1.5x)
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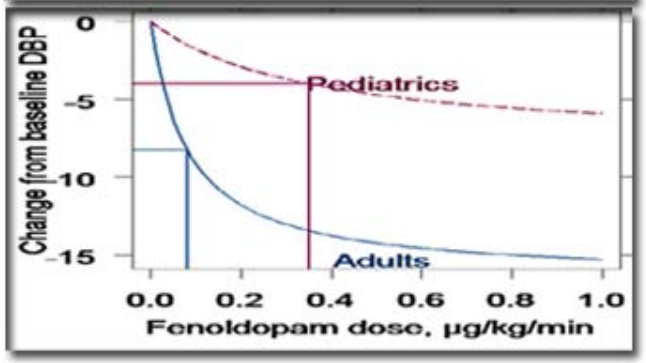

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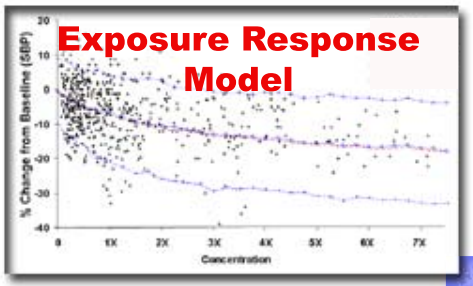

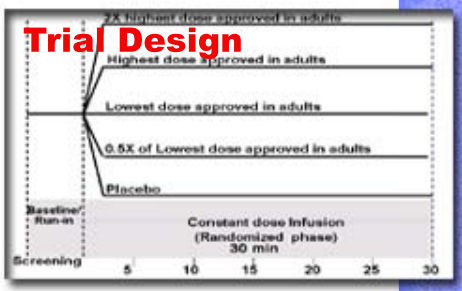

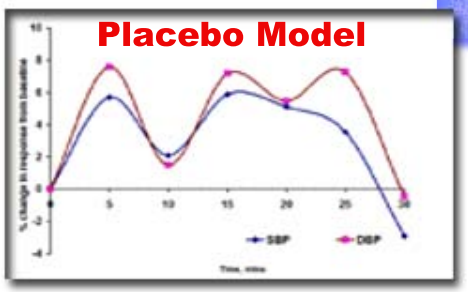

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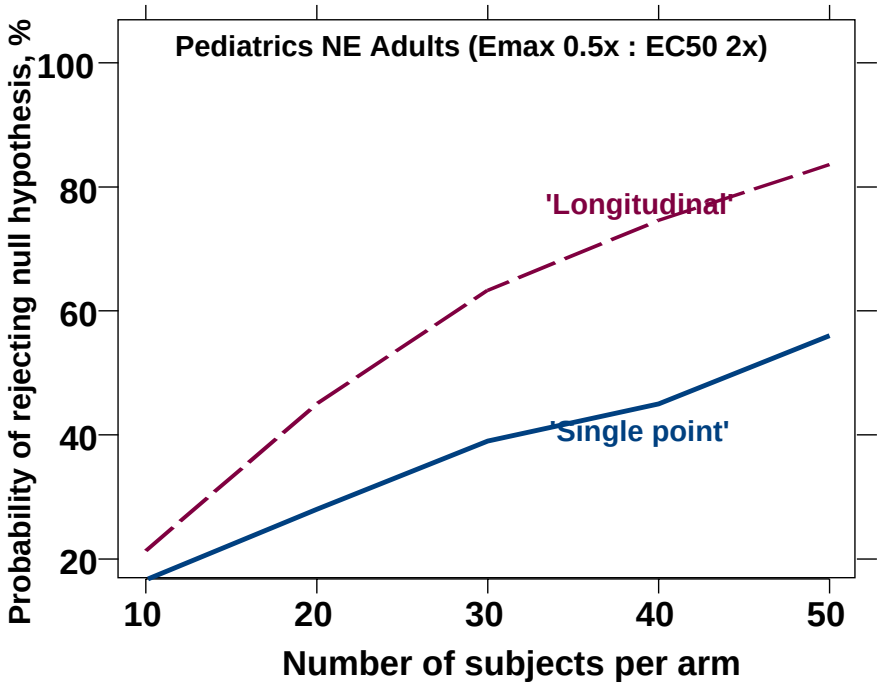
Expected Pediatric Data

Longitudinal Analysis More Powerful than Single Point Analysis

Sample size of 40 should be adequate



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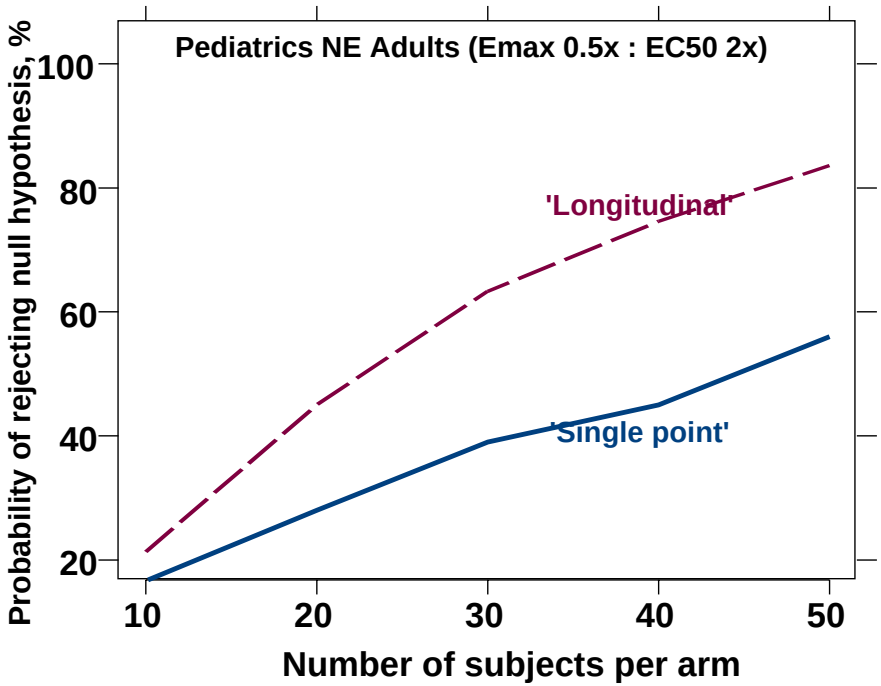

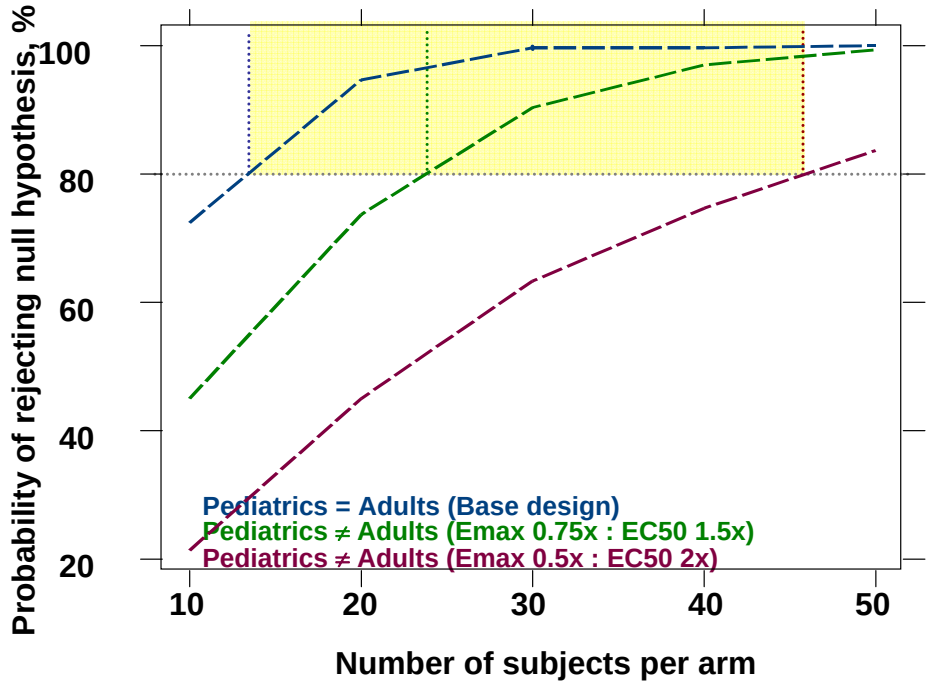

Key Findings

Leveraging prior knowledge allowed us to

- ***effectively use prior knowledge*** **to develop a pediatric written request**
- make *informed decisions* on dose range, number of subjects, sampling scheme and statistical tests
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Internal and External Experts

Clinical Pharmacology

Joga Gobburu PhD, Pharmacometrics, Office of Clinical Pharmacology
Patrick Marroum PhD, Office of Clinical Pharmacology
Mehul Mehta PhD, Office of Clinical Pharmacology

Clinical

Norman Stockbridge MD, Division of CardioRenal Drug Products
Lisa Mathis MD, Pediatric and Maternal Health Staff
Abraham Karkowsky MD, Division of CardioRenal Drug Products

Statistics

Jialu Zhang PhD, Office of Biostatistics
Jim Huang PhD, Office of Biostatistics

Others

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