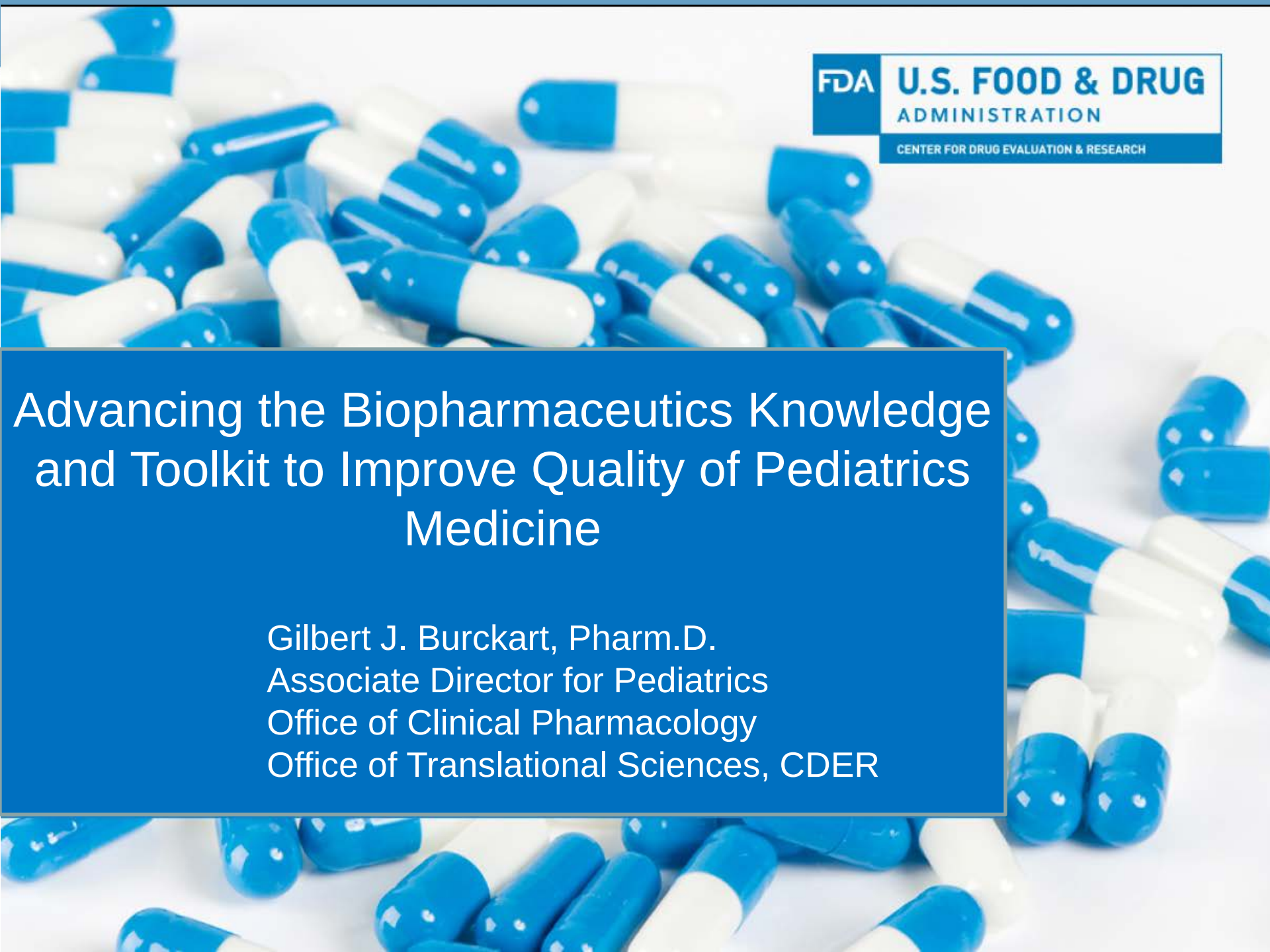

Advancing the Biopharmaceutics Knowledge and Toolkit to Improve Quality of Pediatrics Medicine

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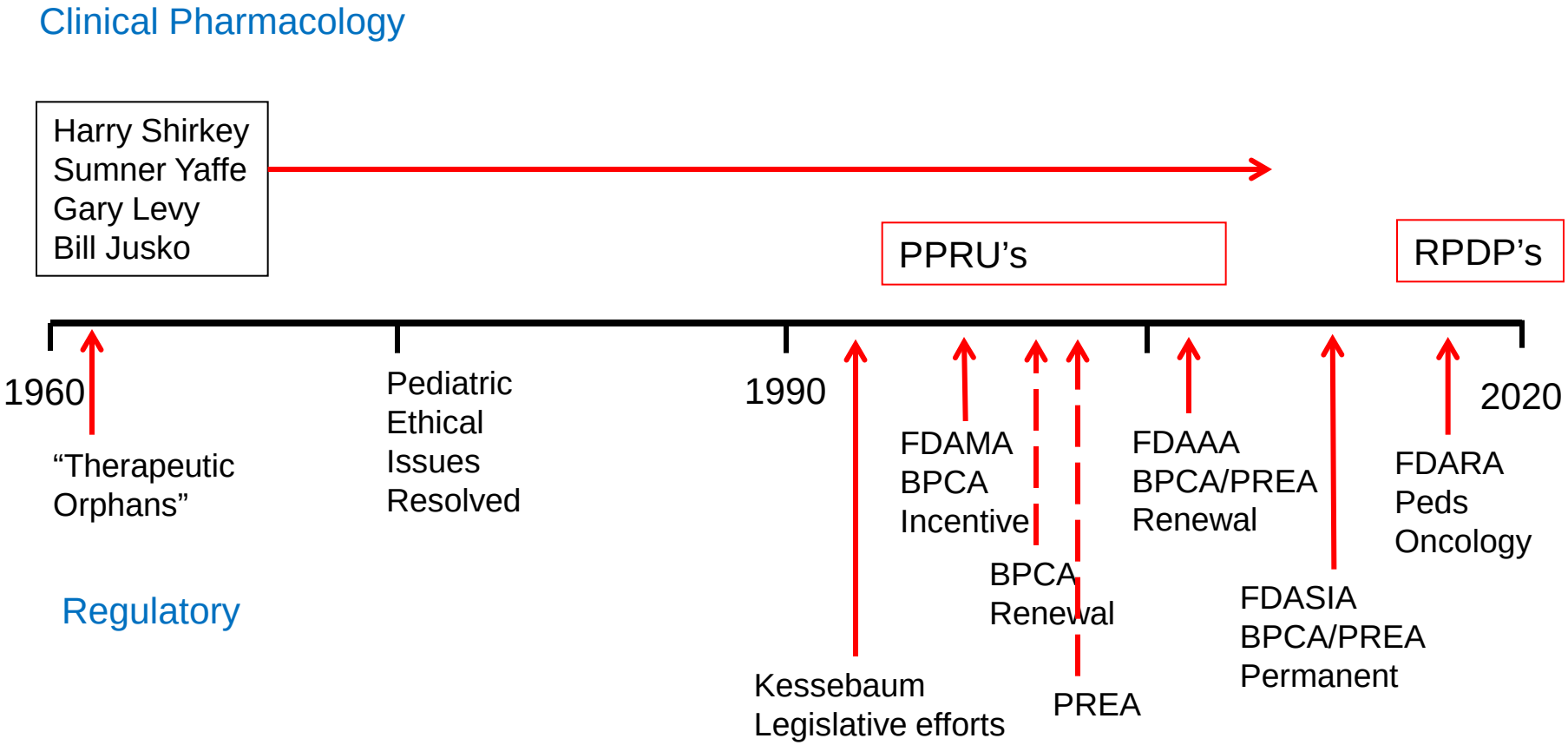
Office of Clinical Pharmacology
Office of Translational Sciences, CDER

- Disclaimer: The content of this presentation is the responsibility of the author, and should not be necessarily interpreted as the position of the US FDA.

Objectives

- Provide an overview of considerations for incorporation of model-informed drug development to benefit pediatric programs, including:
  - Brief history and progress to date;
  - Current toolkit for model-informed drug development (MIDD);
  - Opportunities for progress in pediatrics using MIDD.

Timeline for Pediatric Drug Development



The Father of Pediatric Clinical Pharmacology: Dr. Sumner Yaffe

-Stanford, Director of the Clinical Research Center for Premature Infants

-Developed Pediatric Clin Pharm programs at Buffalo (**1963**) and Philadelphia Children's Hospitals

-**At Buffalo, collaborated with Dr.'s Gary Levy and Bill Jusko, and incorporated pharmacokinetics into pediatric clinical pharmacology studies.**

-Long time supporter of the Pediatric Pharmacy Advocacy Group (PPAG), and the Yaffe Award is given annually

-**Director of the Center for Research for Mothers and Children at the National Institute of Child Health and Human Development, National Institutes of Health**

Created the Pediatric Pharmacology Research Units (PPRU's) as a trial of integrated pediatric research sites (now the Research in Pediatric Developmental Pharmacology specialized centers)

Dr. Gary Levy

- Joined SUNY-B faculty in **1960**;
- Most-highly noted for leading the developing quantitative relationships between drug concentrations and response or PK/PD with a strong focus on discerning pharmacologic (PK of PD) mechanisms.
- the **quantitative aspects of <u>pharmacodynamics</u> did not begin until the 1960s when Gary and his students published their seminal articles** that described the mathematical relationships between drug concentrations and pharmacological effects.

https://pharmacy.buffalo.edu/news-events/events/annual-events/levy-lecture.html

Yaffe/Levy/Jusko's influence through the 1970's, 1980's and 1990's:

Pediatric Clin Pharm embraced translational science and biopharmaceutics: MIDD has been a natural part of pediatric drug use from the beginning!

Clinical Implications of Salicylate-Induced Liver Damage

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State University of New York
Children's Hospital of Buffalo
Buffalo, NY 14222
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Division of Clinical Pharmacology
Children's Hospital of Philadelphia
34th St and Civic Center Blvd
Philadelphia, PA 19104

Clinical Implications of Perinatal Pharmacology*

S. J. Yaffe

RIBOFLAVIN ABSORPTION AND EXCRETION IN THE NEONATE

William J. Jusko, Ph.D., Narinder Khanna, M.D., Gerhard Levy, Pharm.D., Leo Stern, M.D., and Sumner J. Yaffe, M.D.

Pharmacokinetics of Methicillin in Patients with Cystic Fibrosis

Sumner J. Yaffe, Louise M. Gerbracht, Louis L. Mosovich, Mary E. Mattar, Michele Danish, and William J. Jusko

From the Departments of Pediatrics and Pharmaceutics, Schools of Medicine and Pharmacy, State University of New York at Buffalo; Children's Hospital; and Millard Fillmore Hospital, Buffalo, New York

Breakdown of BPCA and PREA Completed Pediatric Studies

Years	BPCA	PREA	Both
2002-2007			87*
2007-2012	28	105	31
2012-present	47	211	11

* Total number of products

Orphan Drug Products that Included Pediatric Patients 2000-2018

Orphan drug products with pediatric studies	Number of Products
Small molecule drugs	97 (102 indications)
Biologicals	65 (75 indications)

How are we doing?

- Over 1,200 pediatric studies have now been submitted to the FDA;
- Of 189 products studied under pediatric exclusivity (1998-2012), pediatric labeling was not established for 78 (**42% failed**) [*Pediatrics 2014;134:e512–e518]*
- Failures were on the basis of dosing, differences in disease process, trial design, placebo response, etc
  - **Momper JD, Mulugeta Y, Burckart GJ. Failed pediatric drug development trials. *Clinical Pharmacology and Therapeutics* 2015; doi: 10.1002/cpt.142**
- ***Failure rate presently (2012-2018) is approximately 20-25%****

*** Green DJ…. Burckart GJ. Primary Endpoints in Pediatric Efficacy Trials Submitted to the US FDA. *The Journal of Clinical Pharmacology 2018;* DOI: 10.1002/jcph.1109**

How do we dramatically reduce pediatric study failures and improve the quality of pediatric medicines?

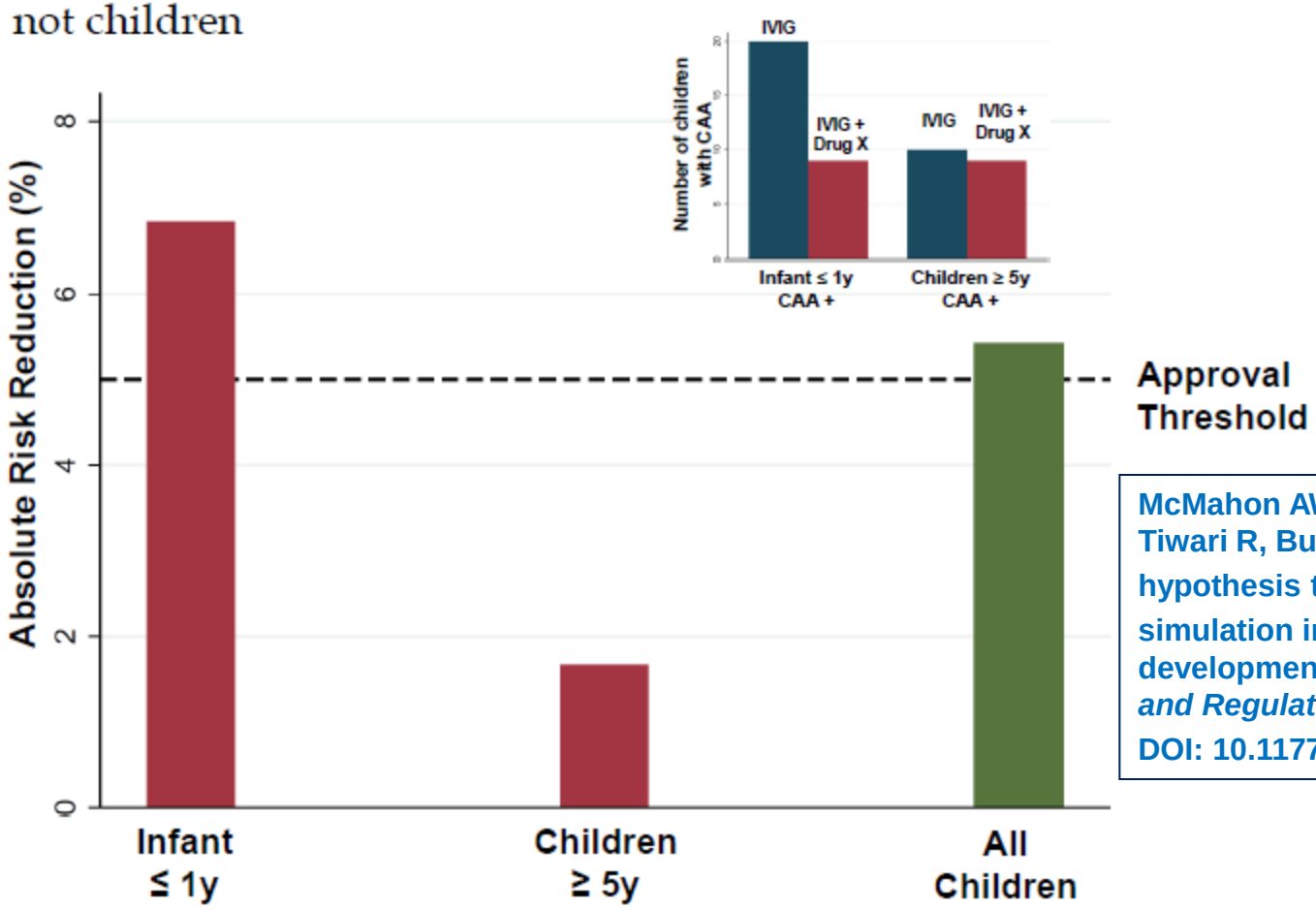
1. Focus on the therapeutic areas which were a problem;
2. Optimally use the regulatory mechanisms available;
3. Optimize pediatric study design;
4. Plan for the future (TOOLS).

Plan for the Future of Pediatric Drug Development

- Clinical Trial Simulation should be the standard for pediatric study planning;
- Use new tools for assessing pediatric efficacy and safety;
- Model-Informed Drug Development for pediatrics
  - Advances in areas not previously possible

Clinical Trial Simulation Prediction of Outcome of Pediatric Trials

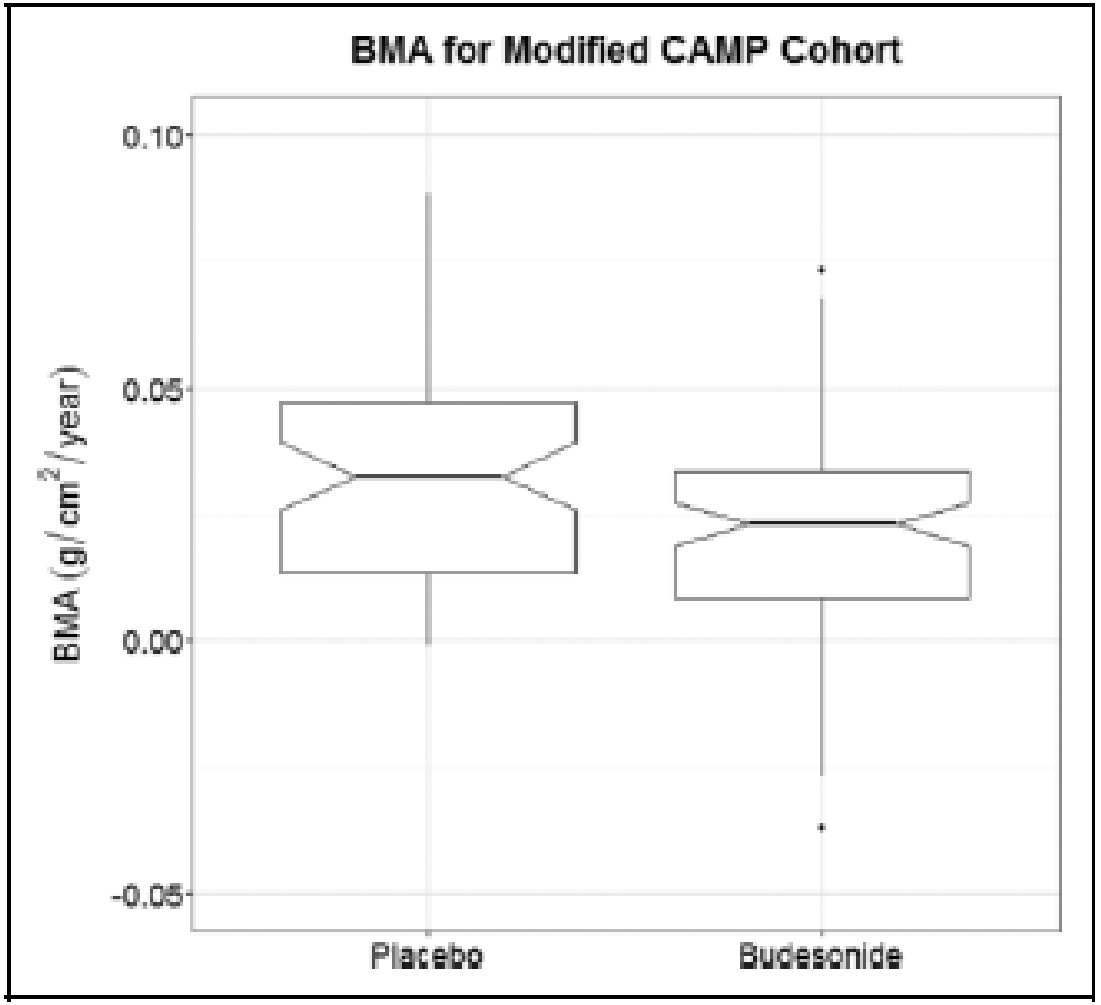
Hypothesis 2: Drug X + IVIG decreases risk of CAA in infants but not children



McMahon AW, Watt K, Wang J, Green D, Tiwari R, Burckart GJ. Stratification, hypothesis testing, and clinical trial simulation in pediatric drug development. *Therapeutic Innovation and Regulatory Science* 2016; DOI: 10.1177/2168479016651661

Using New Tools For Assessing Pediatric Safety

Maas BM…… Burckart GJ. Bone mineral density to assess pediatric bone health in drug development. *Therapeutic Innovation and Regulatory Science* 2017; DOI: 10.1177/2168479017709047



Reasons to Support MIDD for Pediatrics

- The **ethical necessity** to use as few a number of pediatric patients in studies as possible.
- The need to **extend FDA labeling to as much of the age-spectrum** of pediatric patients as possible.
- The need to **adhere to regulatory policy related to efficacy evaluation or extrapolation and safety evaluation** in situations where there are few pediatric patients.
- The need to fill in the **gap in knowledge related to pediatric DDI's, BE, and other studies** not conducted in the pediatric population.
- The need to **provide clinically-relevant drug use information** to pediatric practitioners **for as many agents as possible**.

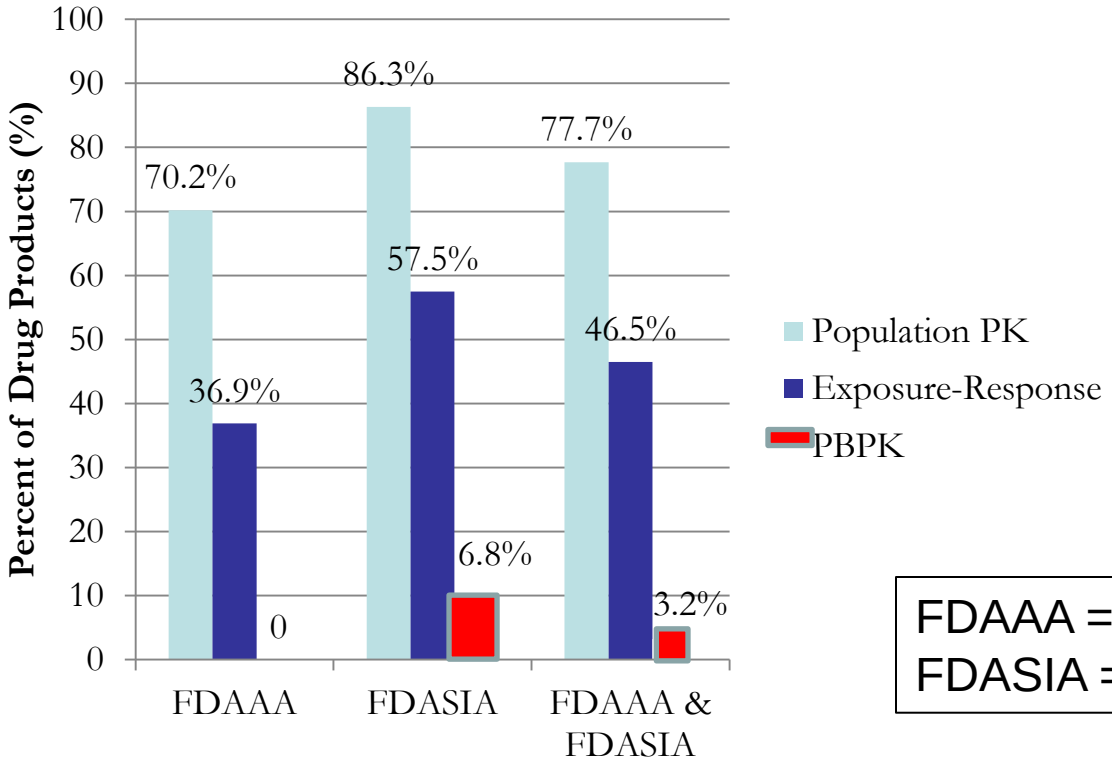
Ethical Necessity - Additional Safeguards for Children; 21 CFR 50 Subpart D

- Research involving children either
  - must be restricted to "**minimal**" risk or a "**minor increase over minimal**" risk absent a potential for direct benefit to the enrolled child, or
    - 21 CFR 50.51/53; 45 CFR 46.404/406
  - must present risks that are justified by the "**prospect of direct benefit"** to the child; the balance of which is at least as favorable as any available alternatives
    - » 21 CFR 50.52; 45 CFR 46.405
- **Permission** by parents or guardians and **assent** by children must be solicited (21 CFR 50.55)

Additional Safeguards for Children
21 CFR 50 Subpart D

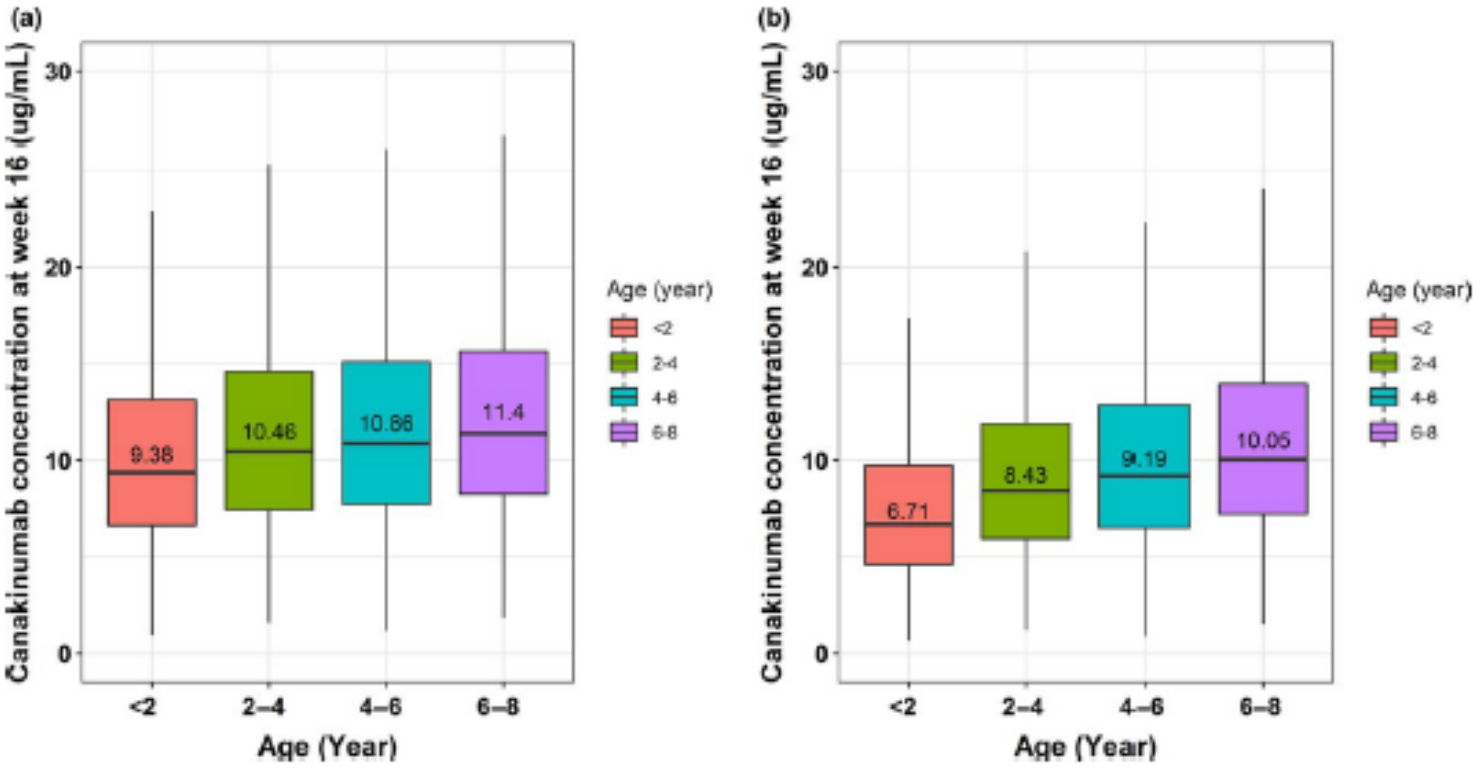
Courtesy: Dr. Melanie Bhatnagar, FDA

Types of Modeling Used in Pediatrics Under FDAAA and FDASIA



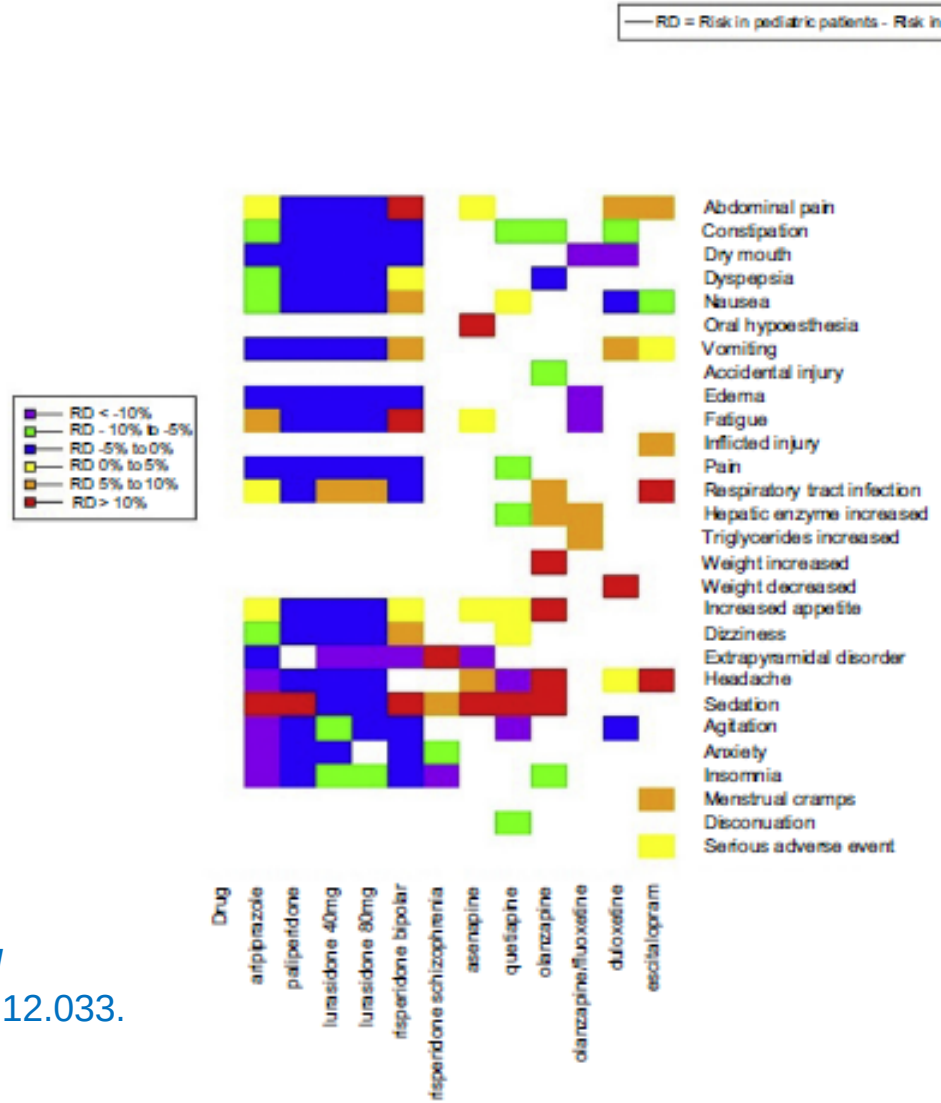
FDAAA = 2007-2012
FDASIA = 2012-present

Extending the Age-Range for Pediatric Labeling - Canakinumab



Zhuang L, Chen J, Yu J, Marathe A, Sahajwalla C, Borigini M, Maynard J, Burckart GJ, and Wang Y. Dosage Considerations for Canakinumab in Children with Periodic Fever Syndromes. *Clinical Pharmacology and Therapeutics* 2018; doi: 10.1002/cpt.1302

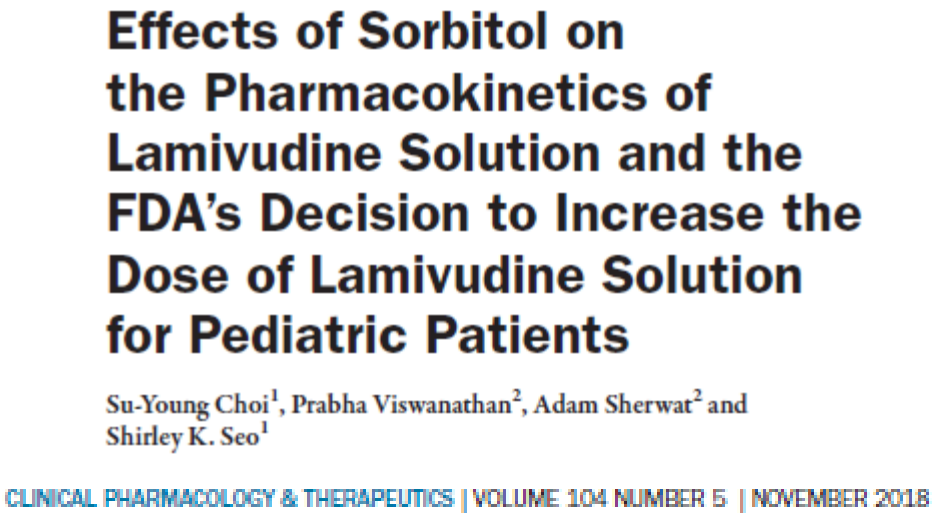
Adhering to Regulatory Policy and Providing Pediatric Safety Information



Liu XI, Schuette P, Burckart GJ, et al. A Comparison of Pediatric and Adult Safety Studies for Antipsychotic and Antidepressant Drugs Submitted to the US FDA. *The Journal of Pediatrics* 2019; doi: 10.1016/j.jpeds.2018.12.033.

Filling the Gap: Pediatric BE Information

- Adult BE studies are accepted for pediatric formulations;
- Can MIDD consider all of the pediatric factors for BE?

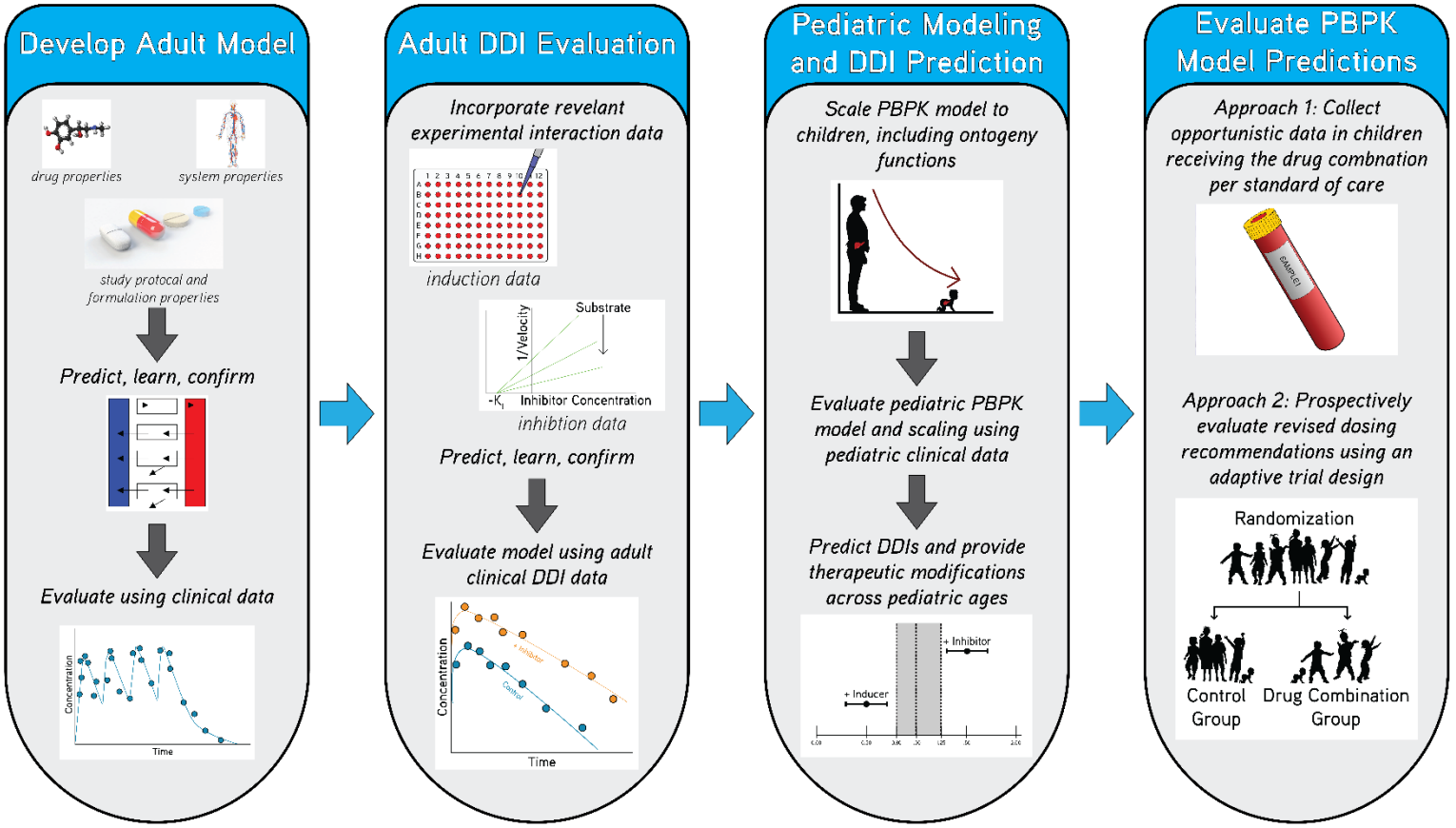


Effects of Sorbitol on the Pharmacokinetics of Lamivudine Solution and the FDA's Decision to Increase the Dose of Lamivudine Solution for Pediatric Patients

Su-Young Choi[1], Prabha Viswanathan[2], Adam Sherwat[2] and Shirley K. Seo[1]

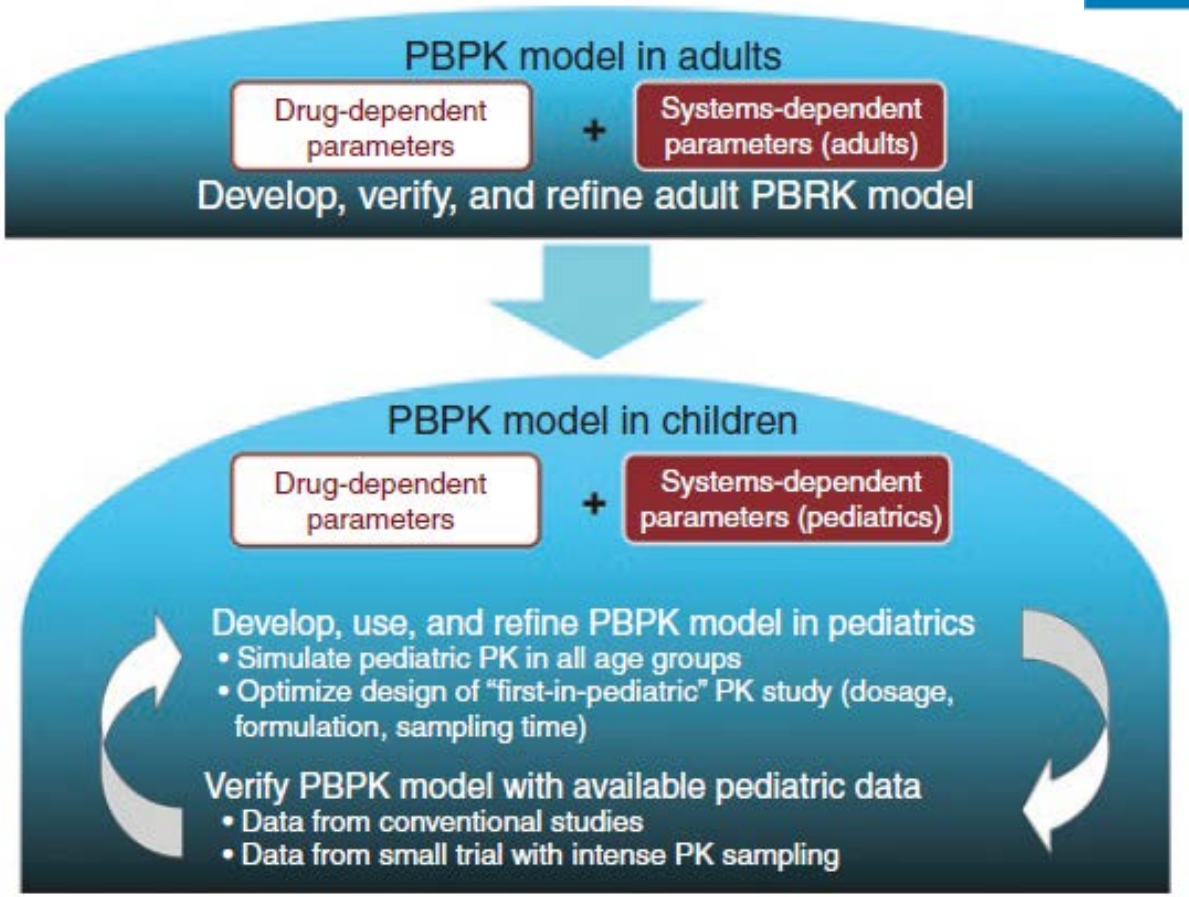
CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 104 NUMBER 5 | NOVEMBER 2018

Filling the Gap: Pediatric DDI's and PBPK



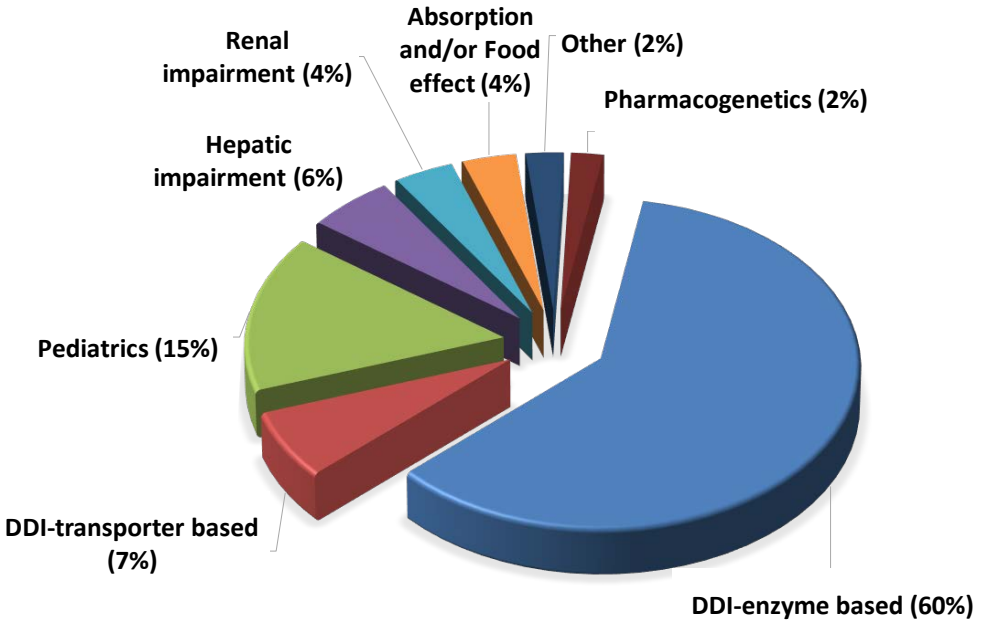
Salerno SN, Burckart GJ, Huang SM, Gonzalez D. Pediatric Drug-Drug Interaction Studies: Barriers and Opportunities. *Clinical Pharmacology and Therapeutics* 2018; doi:10.1002/cpt.1234

Physiologically-Based PK in Pediatric Patients

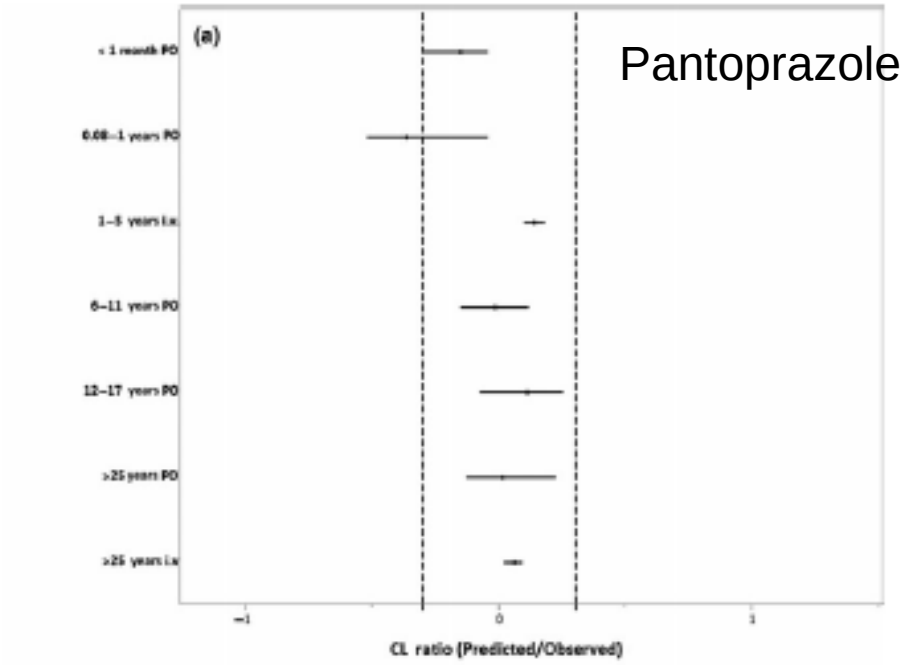


Leong R, Vieira MLT, Zhao P, Mulugeta Y, Lee CS, Huang S-M, Burckart GJ. Regulatory experience with physiologically-based pharmacokinetic modeling for pediatric drug trials. *Clinical Pharmacology and Therapeutics* 2012; 91:926-931.

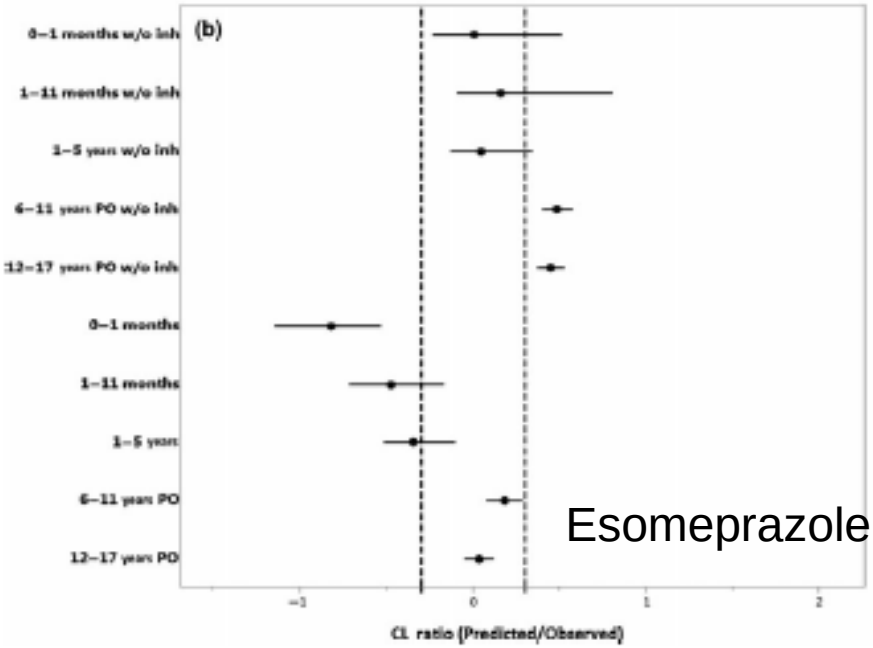
PBPK Submissions to FDA/OCP: 2008-2017



M Grimstein, Y Yang, X Zhang, J Grillo, S-M Huang, I Zineh, Y Wang. ***J Pharm Sci*** Jan 2019



Pantoprazole



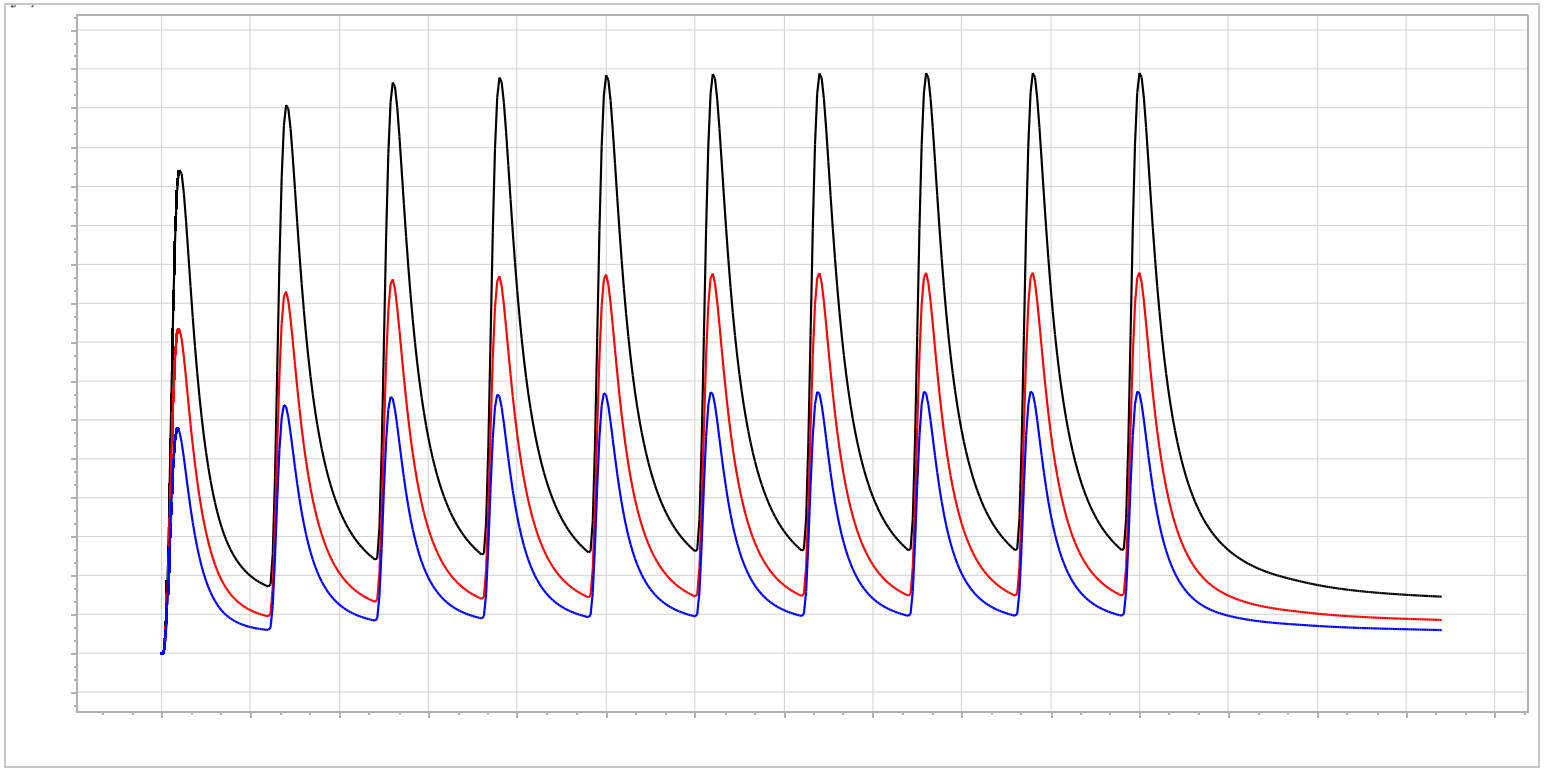
Esomeprazole

Pediatric Ontogeny and PBPK

PBPK can demonstrate when our understanding of the ontogeny of enzymes and transporters does not fit with the observed concentrations in the youngest pediatric patients.

Duan P, Wu F, Moore JN, Fisher J, Crentsil V, Gonzalez D, Zhang L, Burckart GJ, Wang J. **Assessing CYP2C19 Ontogeny in Neonates and Infants Using Physiologically-Based Pharmacokinetic Models: Impact of Enzyme Maturation versus Inhibition**. *CPT: Pharmacometrics & Systems Pharmacology* 2018; doi:10.1002/psp4.12350

Maternal-Fetal Pharmacology and PBPK

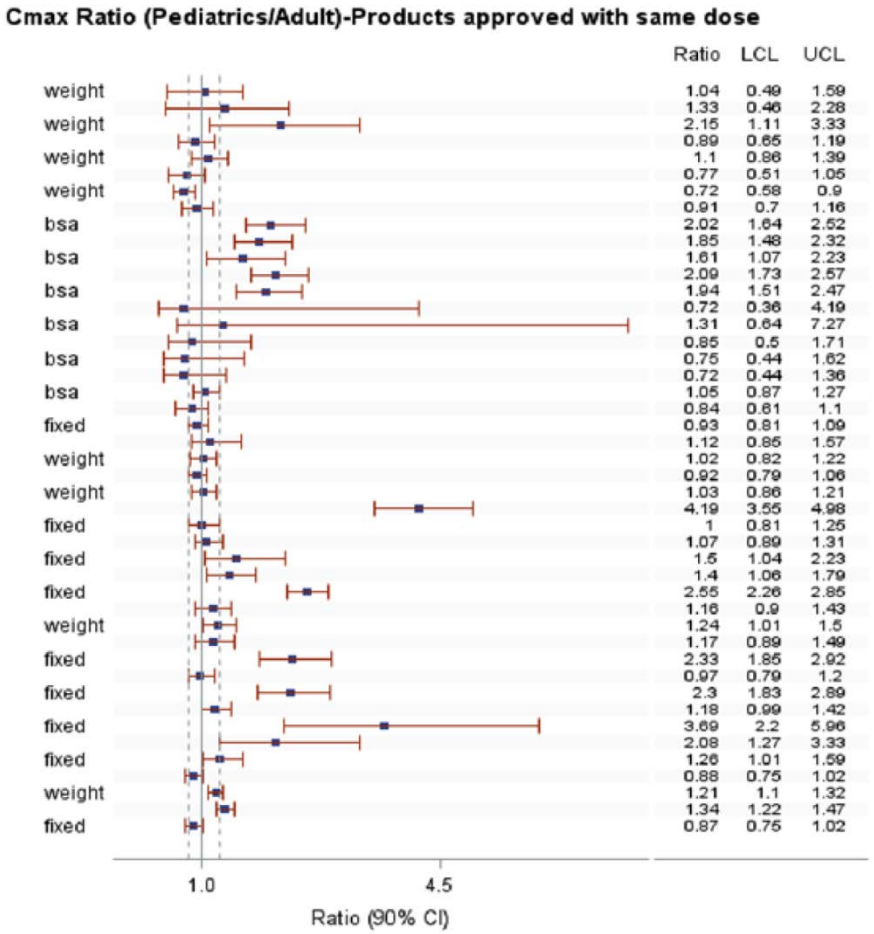


Legend: non-preg (black) vs. 2nd trimester(red) vs. 3rd trimester (blue)

Optimizing the Use of Prior Experience with a Drug or Drug Class or Therapeutic Indication

- **“course of the disease and the drug’s effects are sufficiently similar”**
  - Leveraging prior experience (actual adult and pediatric data is always a higher level of evidence, and informs M&S)
    - e.g. Partial onset seizures
  - Clinical trial simulation
    - Kawasaki’s example
  - Disease modeling
- **“evidence of common drug metabolism and similar concentration - response relationships in each population”**
  - Matching pediatric exposure to adult exposure
  - Exposure-response analysis
  - Physiologically-based PK

MIDD doesn't always work – Exposure Matching Agreement (Cmax)



- Only 7 of 86 trials had predefined acceptance boundries;
- Pediatric Cmax were generally higher than adult Cmax;
- Range of Cmax ratios (pediatric/adult) was 0.63 to 4.19

Mulugeta Y……Burckart GJ. Exposure matching criteria for extrapolation of efficacy in pediatric drug development. *Journal of Clinical Pharmacology 2*016; 56:1326-1334.

Combining Adolescents into Adult Efficacy Trials: A successful strategy

Combined	Success	Failure	Lower 95% CI	Upper 95% CI
Yes	85	10	81.9	94.6
No	94	45	59.4	75
Total	179	55		

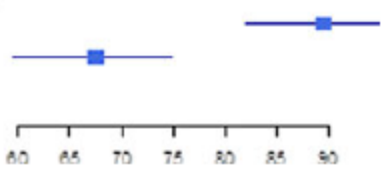


Figure 1. Success and failure of pediatric trials when the trials were combined with adult efficacy trials. Shown are the number of pediatric trials that were combined (yes) and were not combined (no) with adult trials, the upper and lower bounds of the 95% confidence intervals (CIs), and a graphical depiction of the confidence intervals.

Green DJ…. Burckart GJ. Primary Endpoints in Pediatric Efficacy Trials Submitted to the US FDA. ***The Journal of Clinical Pharmacology 2018;*** **DOI: 10.1002/jcph.1109**

Choose the Right Pediatric Dose

- Dose ranging – always test more than one pediatric dose (lesson from pediatric hypertension treatment)
- Ontogeny - Especially under 2 years of age, consider maturation effects on drug metabolism and response;
- Pharmacogenetic effects - recommendations developed in adults may or may not pertain to pediatrics
  - Green D…. Burckart GJ. Pharmacogenomic information in FDA-approved drug labels: Application to pediatric patients. *Clinical Pharmacology and Therapeutics* 2016; 99:622-632; doi:10.1002/cpt.330

Summary

1. Pediatric drug development has made tremendous progress in the past 11 years;
   - Failure rate from 42% down to 20% for drug development studies
2. MIDD will continue to find new applications in pediatrics to the benefit of pediatric patients;
3. Optimizing pediatric study designs is still a challenge in the face of such diverse clinical problems;
4. Pediatric MIDD works best in the context of a multi-disciplinary team of clinicians, clinical pharmacologists, biostatisticians and pharmacometricians.