ACPS-CP

March 14, 2012

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology Meeting
March 14, 2012, National Harbor, MD

Introduction & Background

Shiew-Mei Huang, Ph.D.
Acting Director
Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
Food and Drug Administration

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

2002: Exposure-response, pediatrics, pharmacogenetics

2003: Pediatrics, pharmacogenetics, drug interactions (transporters, CYP2B6, CYP2C8)

2004: Irinotecan labeling (UGT1A1), drug interactions (transporters, induction, multiple inhibitors), biomarkers

2005: Pharmacogenetics labeling, warfarin labeling (CYP2C9, VKORC1), genomic enrichment design, EOP2A

2006: Drug interactions (transporters), disease models, Tamoxifen labeling (CYP2D6)

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (2)

2008: Pharmacogenetics, quantitative clinical pharmacology, pediatrics, renal impairment

2010: Pharmacogenomics, predictive drug safety, drug interactions (transporters), renal impairment

2011: Rare diseases

2012: Pediatrics (study design considerations, modeling & simulation, PBPK)

The input from the committee has been great and formed the basis of many clinical pharmacology guidance recommendations

Guidance, Compliance & Regulatory Information

- Guidances (Drugs)
- Advertising
- Bioequivalence Recommendations for Specific Products
- Biopharmaceutics
- Biosimilarity
- CMC - Microbiology (Chemistry, Manufacturing, and Controls)
- Chemistry, Manufacturing, and Controls (CMC)
- Clinical / Antimicrobial
- Clinical / Medical
- Clinical Pharmacology
- Combination Products
- Concept Papers
- Current Good Manufacturing Practices (CGMPs)/Compliance
- Drug Safety
- Electronic Submissions
- FDAAA (Food and Drug Administration Amendments Act)
- Generics
- Good Review Practices

Clinical Pharmacology

Below is a sortable listing of Clinical Pharmacology Guidances

Category	Title	Type	Date
Clinical Pharmacology	Clinical Lactation Studies--Study Design, Data Analysis, and Recommendations for Labeling (PDF - 363KB)	Draft Guidance	02/08/05
Clinical Pharmacology	Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies (PDF - 531KB)	Draft Guidance	02/17/11
Clinical Pharmacology	General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (PDF - 37KB)	Draft Guidance	11/01/98
Clinical Pharmacology	Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling (PDF - 319KB)	Draft Guidance	03/22/10
Clinical Pharmacology	Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling (PDF - 324KB)	Draft Guidance	11/01/04
Clinical Pharmacology	Drug Interaction Studies--Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (PDF - 827KB)	Draft Guidance	02/17/12
Clinical Pharmacology	Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications (PDF - 221KB)	Final Guidance	05/05/03
Clinical Pharmacology	Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application (PDF - 519KB)	Final Guidance	02/01/87
Clinical	Pharmacokinetics in Patients with Impaired	Final	05/30/03

Revision ongoing

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm

Update

Email bursts- started in June 2011 (to ASCPT, ACCP, ACCPharmacy)

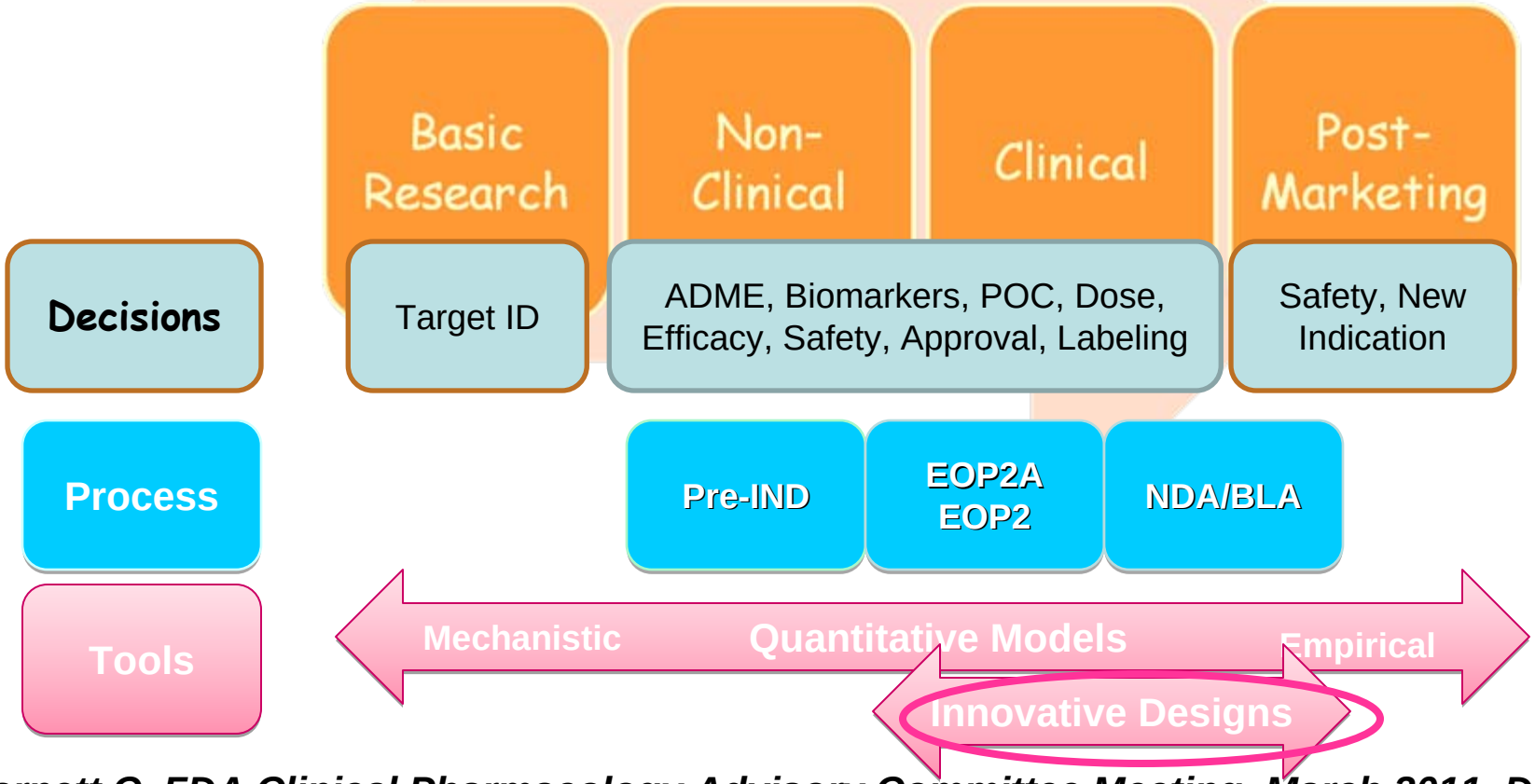
2011:

Boceprevir, telaprevir, crizotinib, vemurafenib, ruxolitinib, digoxin, clobazam, pimozide, asparaginase *Erwinia chrysanthemi*, zolpidem

2012:

Glucarpidase, vismodegib, ivacaftor, cisplatin, axitinib

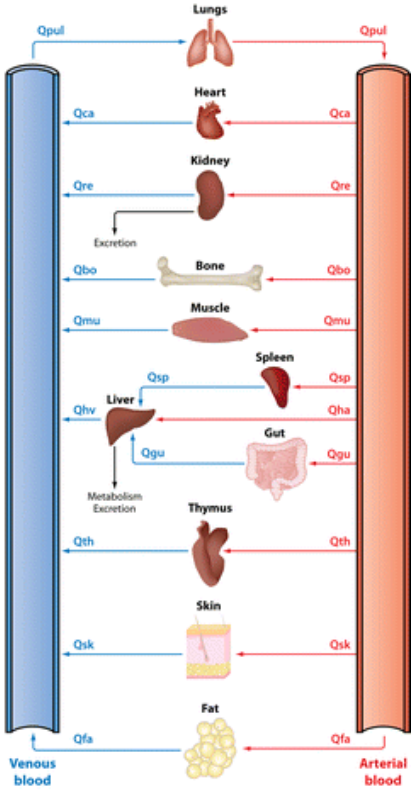
Quantitative Tools During Drug Development



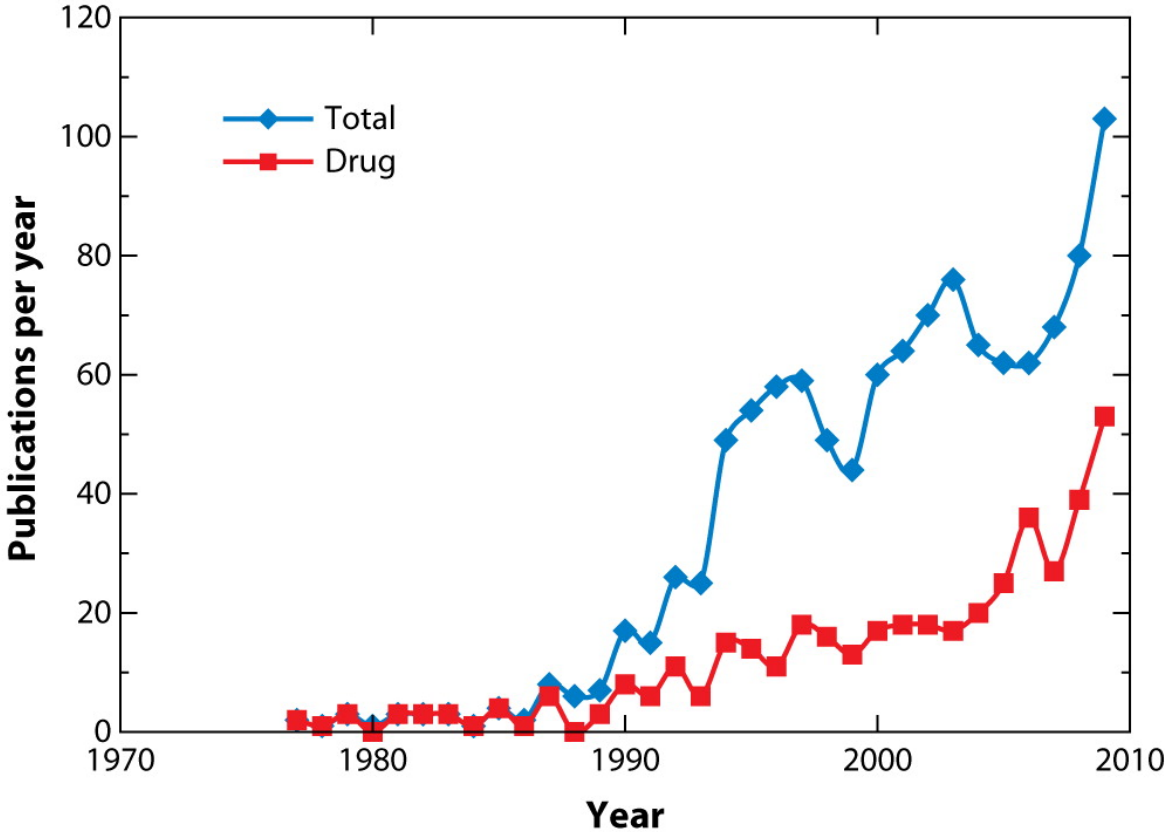
<Garnett C, FDA Clinical Pharmacology Advisory Committee Meeting, March 2011, Dallas, TX>; Advisory Committee Meeting summary published:

Bashaw ED, Huang S-M, Cote TR, et al, Nature Rev Drug Discov 10: 795, 2011>

Applications of Physiologically-Based Pharmacokinetic Modeling (PBPK)



Rowland M, et al. 2011.
Annu. Rev. Pharmacol. Toxicol. 51:45–73



Rowland M, Peck C, Tucker G, Physiologically-based pharmacokinetics in Drug Development and Regulatory Science *Annu Rev Pharmcol Toxicol, 2011*

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→ Utility of PBPK has been or is being incorporated in various clinical pharmacology guidance documents

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm

Utility of PBPK

--From the Office of Clinical Pharmacology, OTS, CDER, FDA--

Zhao P, Zhang L, Grillo JA, et al, Application of Physiologically-based pharmacokinetics (PBPK) Modeling and Simulation in Regulatory Review. *Clin Pharmacol Ther February 2011*

Zhao P, de LT Vieira M, Grillo J, et al, Evaluation of Exposure Change of Non-Renally Eliminated Drugs in Patients with Chronic Kidney Disease Using Physiologically-based Pharmacokinetic Modeling and Simulation. *J Clin Pharmacol January 2012*

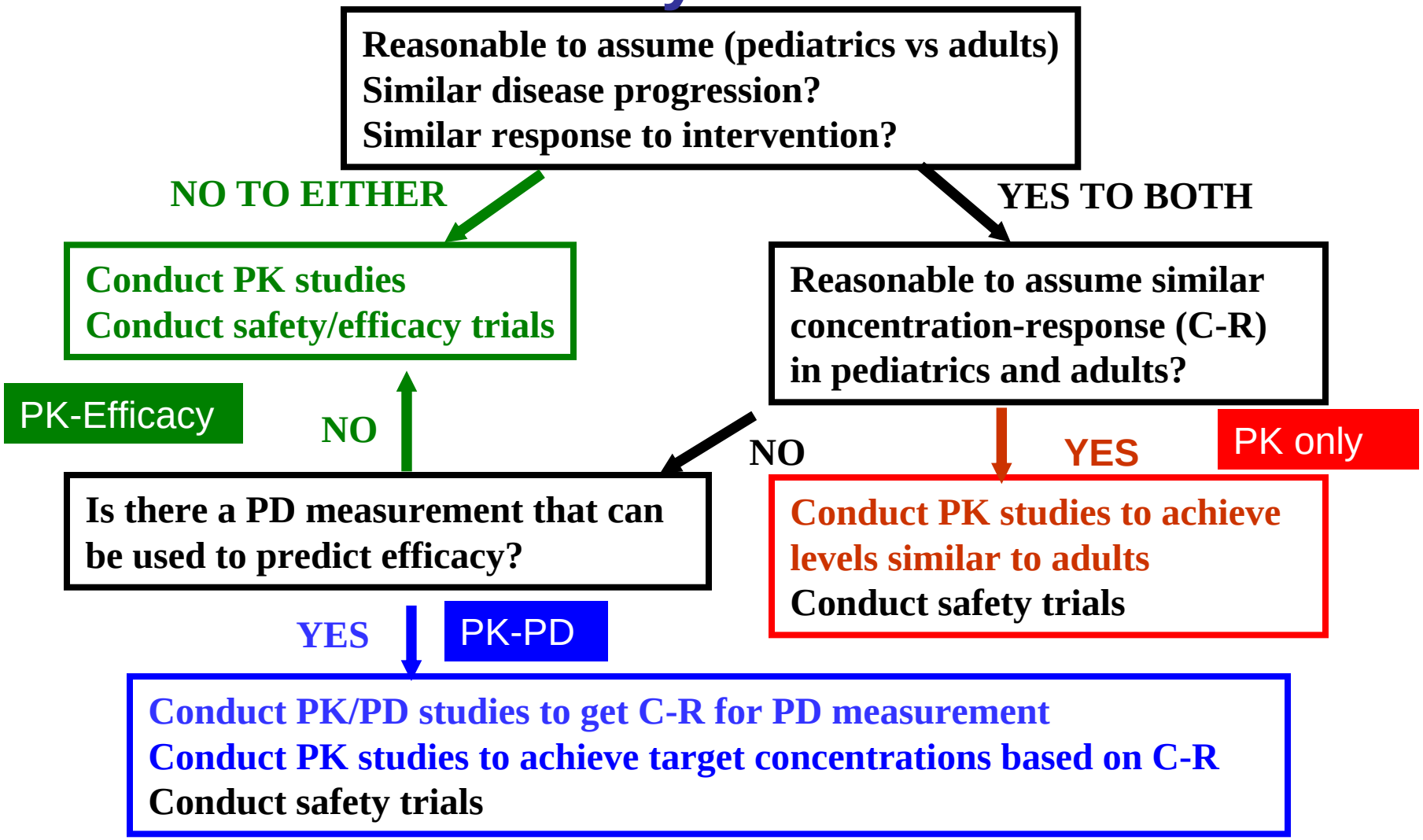
De LT Vieira, Zhao P, Gil Berglund E, et al, Predicting Drug Interaction Potential by Using a Physiologically-based pharmacokinetics (PBPK) Model: Case Study of Telithromycin, a Time-Dependent CYP3A inhibitor. *Clin Pharmacol Ther 2012*

Grillo JA, Zhao P, Bullock J, et al, Utility of a physiologically-based pharmacokinetic (PBPK) modeling approach to quantitatively predict a complex drug-drug-disease interaction scenario with rivaroxaban during the drug review process: implications for clinical practice *Biopharm Drug Disp 2012*

Huang S-M, Rowland M, Application of Physiologically-based pharmacokinetics Modeling in Regulatory Review. *Clin Pharmacol Ther March 2012*

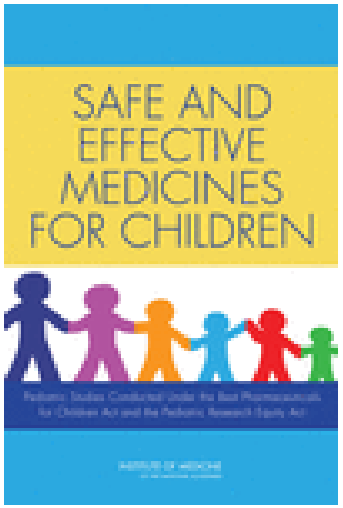
Leong R, De LT Vieira, Zhao P, et al, Regulatory Experience with Physiologically-Based Pharmacokinetic Modeling for Pediatric Drug Trials, *Clin Pharmacol Ther May 2012*

Pediatric Study Decision Tree



http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072109.pdf (2003)
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm073007.pdf (2004)

IOM Report on Pediatric Studies February 29, 2012



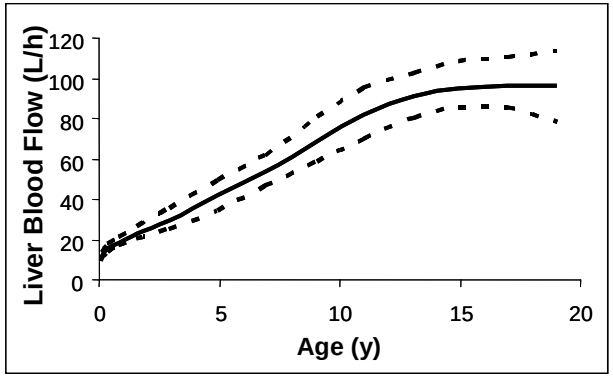
Safe and Effective Medicines for Children: Pediatric Studies Conducted Under BPCA and PREA

Released:	February 29, 2012
Type:	Consensus Report
Topics:	Biomedical and Health Research, Children, Youth and Families
Activity:	Pediatric Studies Conducted under BPCA and PREA
Boards:	Board on Health Sciences Policy, Board on Children, Youth, and Families

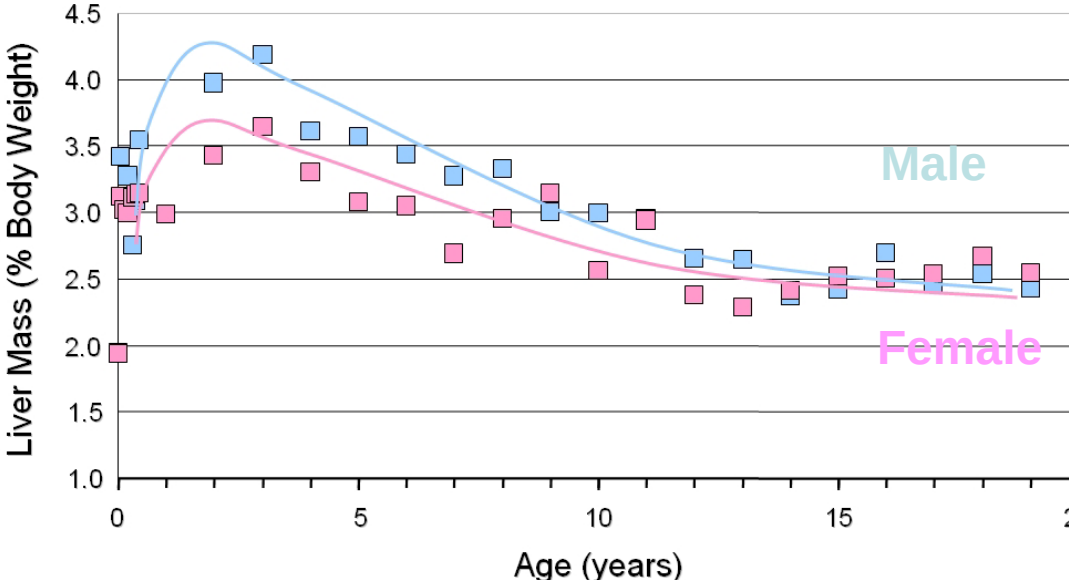
http://www.iom.edu/Reports/2012/Safe-and-Effective-Medicines-for-Children.aspx

Ontogeny

Liver Blood Flow[1]



Liver Mass (%BW)[2]

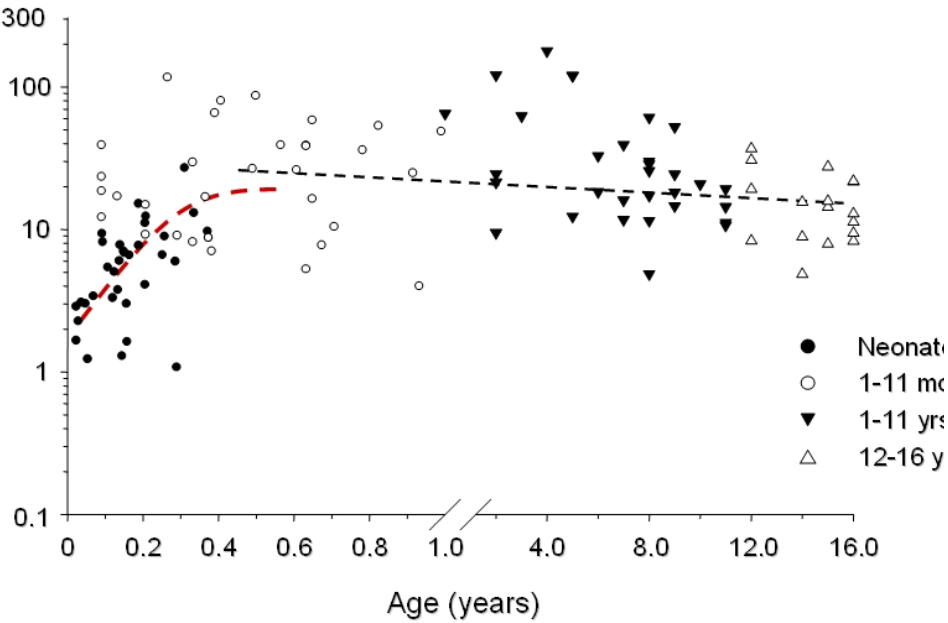


Adapted from

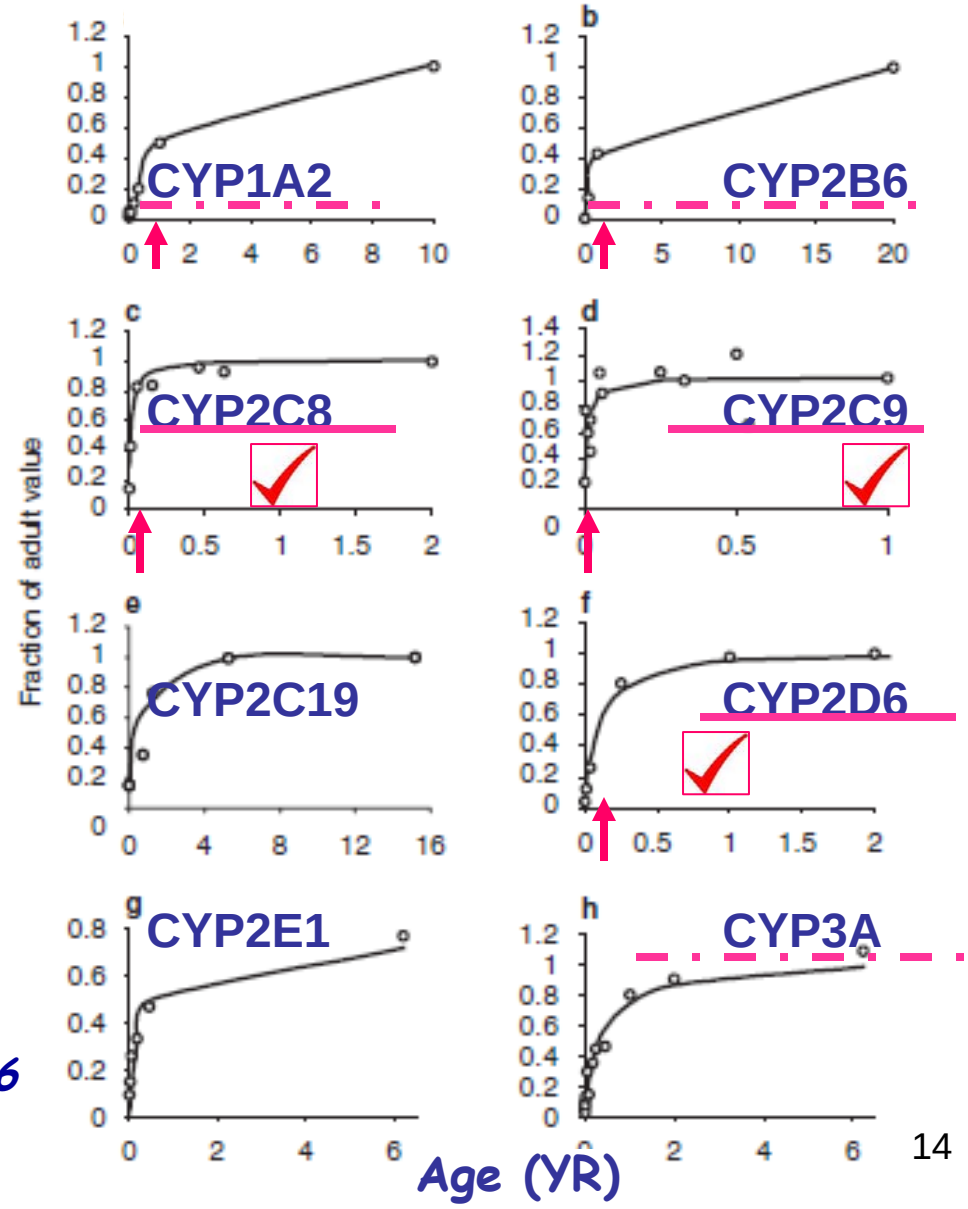
1. *Johnson, Rostami-Hodjegan, Tucker, Clin Pharmacokinet 2006*
2. *Goldman, Becker, Jones, Clements, Leeder, Biomarkers Med 2011 & Johnson TN et al Liver Transplant 2005*

Ontogeny (2)

Pantoprazole[2]



Age (YR)



Adapted from

1. *Johnson et al, Clin Pharmacokinet 2006*
2. *Ward and Kearns, Pediatric Drugs (in press)*

Today's Discussion

- **Topic 1.** Application of modeling and simulation to all pediatric drug development proposals.
- **Topic 2.** Developing metrics for precise estimation of pharmacokinetic parameters in the pediatric population.
- **Topic 3.** Learning from our experience with pediatric studies under

  BPCA (Best Pharmaceuticals for Children Act) and PREA (Pediatric Research Equity Act).
- **Topic 4.** Applications of physiologically-based pharmacokinetic modeling in pediatric studies

Committee Questions

- **Topic 1. Should modeling and simulation methods be considered in all pediatric drug development programs?**

- **Topic 2. The FDA Office of Clinical Pharmacology has proposed a framework to derive sample size in pediatric pharmacokinetic (PK) studies to ensure the quality of pediatric PK data. Is the quality standard based on this framework reasonable?**

- **Topic 3. Can dose(s) for the adolescent (>12 years) population be derived using adult data without the need for a dedicated PK study?**

- **Topic 4. Should the routine use of PBPK in pediatric drug development, when possible, be recommended at the present time?**

Acknowledgements

Clinical Pharmacology AC Working Group

- **Office of Clinical Pharmacology**

  Gil Burckart, Dionna Green, Shiew-Mei Huang,

  Pravin Jadhav, Lokesh Jain, Insook Kim, Kevin Krudys, Christine Le, Qi Liu, Jeremiah Momper, Lily Mulugeta, Shirley Seo, Veneeta Tandon, Lei Zhang, Ping Zhao

- **Office of New Drugs**

  Alyson Karesh, Lisa Mathis

- **Office of Pediatric Therapeutics**

  Cathy Lee, Robert “Skip” Nelson, Bill Rodriguez, Michelle Roth-Cline

Lessons Learned from BPCA and PREA Studies Under FDAAA

Gilbert J. Burckart, Pharm.D.
Associate Director
Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research

Types of Pediatric Studies Conducted Under BPCA and PREA

Breakdown of FDAAA completed pediatric studies Sept. 27, 2007 – Dec. 31, 2011

Type of Study	BPCA	BPCA + PREA	PREA	Total
Efficacy/Safety	42	28	167	237
PK/Safety	8	29	17	54
PK/PD	14	7	8	29
Safety	5	4	23	32
Other	0	4	4	8
Total	**69**	**72**	**219**	**360**

Total number of patients in completed FDAAA studies: 166,646

21,822 in BPCA studies; 30,093 in CDER PREA studies;

114,731 in CBER PREA studies (Vaccines and Blood Products)

Improving Pediatric Dosing Through Pediatric Initiatives: What We Have Learned

William Rodriguez, MD, PhD, Arzu Selen, PhD, Debbie Avant, RPh, Chandra Chaurasia, PhD, Terrie Crescenzi, RPh, Gerlie Gieser, PhD, Jennifer Di Giacinto, PharmD, Shiew-Mei Huang, PhD, Peter Lee, PhD, Lisa Mathis, MD, Dianne Murphy, MD, Shirley Murphy, MD, Rosemary Roberts, MD, Hari Cheryl Sachs, MD, Sandra Suarez, PhD, Veneeta Tandon, PhD, Ramana S. Uppoor, PhD

Food and Drug Administration, Rockville, Maryland

Pediatrics 2008;121;530-539

108 Written Requests, representing 250 studies by 42 sponsors.

Primary finding: Highly variable drug clearance between drugs and within age groups

FDAAA Studies Conducted Under BPCA and PREA

As of November 17, 2011

PEDIATRIC LABELING	PREA PMR No. Number (%)	No PREA PMR Number (%)	TOTAL of 137 Number (%)
Labeled for pediatric use in some age group	51 (37%)	52 (38%)	103 (75%)
Not labeled for pediatric use	6 (4%)	20 (15%)	26 (19%)
Not labeled for pediatric use for the studied indication (other pediatric labeling)	2 (2%)	6 (4%)	8 (6%)

Completed Pediatric Studies (no PREA PMR)

- Labeled for pediatric use n=52 (67%)

- Not labeled for pediatric use for the studied indication
  - Not labeled for pediatric use n=20
  - Labeled, but not for this indication n=6
  - TOTAL this category n=26 (33%)

Reasons for Trials Not Resulting in a Pediatric Indication

- Different pediatric indication than in adults (14 products)
  - No dose range investigated in 6 out of 14
- Exposure was limited to the adult drug exposure (n=5)
- No dose range investigated in 8 products
- Trial design failure for 4 products
  - Met the study endpoint, but was not given the pediatric indication (3 products)
- Insufficient sample size (n=2); poor data quality (n=2); efficacy not established for indication approved in adults (n=3);

Examples of Studies Not Leading to an Approved Pediatric Indication

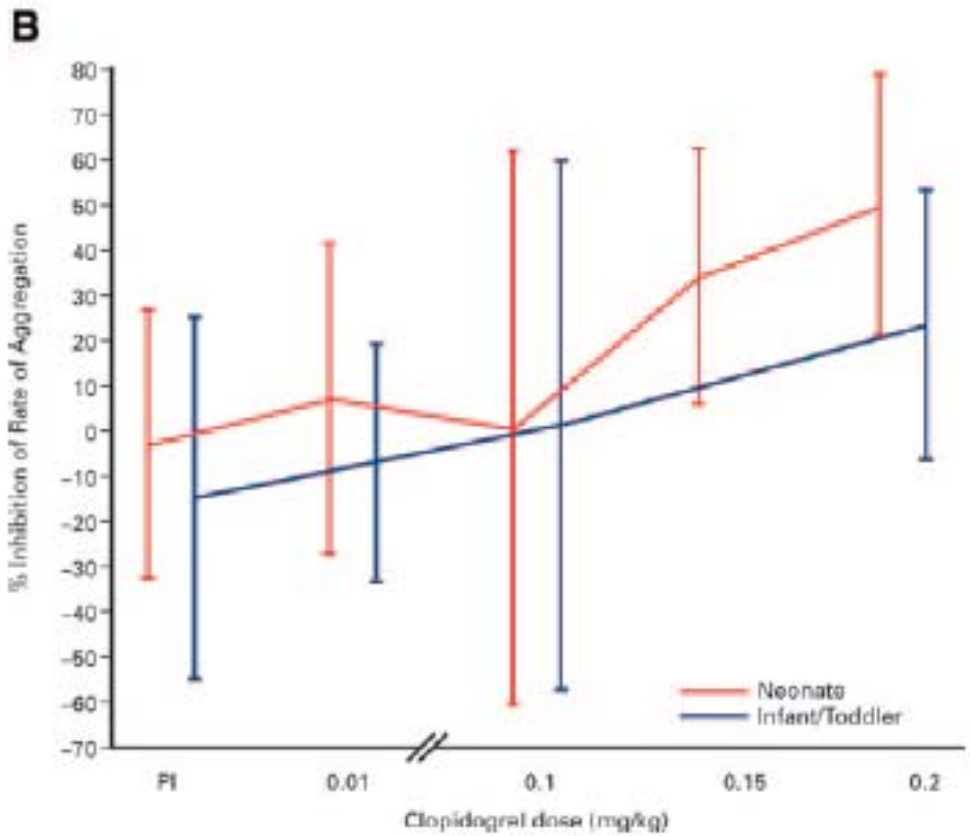
- Poor dose selection
  - Plavix (clopidogrel)
- Trial design failure
  - Famvir (famciclovir)
- Insufficient sample size
  - Argatroban

Poor Dose Selection

- Clopidogrel pediatric history
  - 2001- Initial WR in response to a sponsor PPSR
  - 2005 – Finkelstein published pediatric case series receiving clopidogrel
    - Dose 1 – 6 mg/kg/day (average 2.3 mg/kg/day)
    - Conclusion: Well tolerated; suggest 1 mg/kg/day starting dose
  - 2006 – *Blood* publication of clopidogrel response and critical nature of CYP2C19 polymorphisms
  - 2007 – August – Final revision of Clopidogrel Written Request issued (no dose specified at this point)

Results of the Platelet Inhibition in Children On Clopidogrel (PICOLO) Study

"The upcoming Clopidogrel to Lower Arterial thrombotic Risk In Neonates and infants Trial (CLARINET) is a multicenter, randomized, controlled trial that will assess efficacy and safety of the presently established dose of clopidogrel 0.2 mg/kg/day in neonates and infants……"



Li JS et al. Circulation 2008;117;553-559

Clopidogrel Pediatric Study

- Sponsor conducted an efficacy/safety study in **906** neonates and infants to evaluate clopidogrel (0.2 mg/kg/day) for the reduction of thrombosis in children with systemic to pulmonary artery shunts (CLARINET).
- Clinical Pharmacology Review: "The geometric mean SR26334 Cmax (measurement on Day 1 between 0.17 and 3 hours post-dose) from 5 neonate patients in **PICOLO** receiving the 0.2 mg/kg dose was **0.03 mg/L**. According to the relative BA study, the mean Cmax of SR26334 following a single 75 mg dose in healthy adult male volunteers ranged from **2.8 to 3.3 mg/L**. This difference is **remarkable**……. "

Clopidogrel Pediatric Study

- No significant difference between clopidogrel and placebo for either the primary efficacy endpoint or bleeding
  - Consistent with insufficient clopidogrel exposure
- Medical Review noted that "at a minimum, given the uncertainties of dose selection, more than one dose should have been tested in the confirmatory trial."
- Pediatric exclusivity granted on 01/20/11

Trial Design Failure

- **Famvir (famciclovir)**
- Initial Written Request issued in 2001, early in the BPCA process
- WR was modeled after a valacyclovir WR
- Some indications in pediatric patients for HSV and VZV (e.g. chickenpox) are not indications in adults

Famvir (famciclovir)

- Sponsor conducted 3 PK studies in 118 children (1 month – 12 years) with HSV or VZV infection (varying indications) pursuant to the pediatric WR
  - **An efficacy study was not requested**
- The results are reported in the Pediatric Use section, but no indication was given
  - "**Efficacy cannot be extrapolated from adults**…"
- Pediatric exclusivity granted 9/21/09

Insufficient Sample Size

- **Argatroban**
- The sponsor submitted results of a single pharmacokinetic /pharmacodynamic (PK/PD) and safety study undertaken in response to a Written Request (WR) for pediatric studies.
  - A total of 18 pediatric patients (8 patients less than 6 months of age, 6 patients 6 months up to 8 years of age, and 4 patients 8 years and older) were studied.
  - The results did not demonstrate efficacy, due to an insufficient sample size and study design (no efficacy evaluation).
- The Pharmacometrics Division of OCP devised a pediatric dose, based on modeling and simulation, which was less than ½ of the adult dose, and this dose was included in the label.
- Since the WR was for 24 patients, exclusivity was not granted.

Question

- Could the requirement for the review of the simulated pediatric clinical trial prior to initiation have changed the outcomes of these examples?
  - Dose …….. Yes
  - Sample size calculation……. Yes
  - Pediatric trial design …….. Probably Yes

Planning is the Key

- FDA Guidance recommends early meetings for discussion of the pediatric assessment and plan
  - PREA Guidance: "For these (i.e. life-threatening illness) products, FDA encourages applicants to discuss the pediatric plan at **pre-investigational new drug (pre-IND) meetings and end-of-phase 1 meetings."**
  - "For products that are not intended for treatment of life-threatening or severely debilitating illnesses, applicants are encouraged to submit and **discuss the pediatric plan no later than the end-of-phase 2 meeting**."
- The European Medicines Agency requires submission of the Pediatric Investigational Plan (PIP) at the end-of-phase 1

Planning is the Key

PhRMA Statement Before the Institute of Medicine Committee on Pediatric Studies Conducted Under BPCA and PREA

- "PhRMA strongly believes that the necessity of every study under BPCA or PREA should be carefully evaluated before allowing such study to be conducted.
- FDA should endeavor to make the best use of existing data (published or otherwise) as well as information the Agency may garner from other regulatory authorities."

http://www.phrma.org/phrma-statement-institute-medicine-committee-pediatric-studies-conducted-under-bpca-prea

Clinical Pharmacology Planning

- Background information
  - Early discussion and planning is essential;
  - Modeling and simulation should be used in pediatric study design for all development programs;
  - Getting to the right dose is still problematic;
  - Pharmacogenetics should be incorporated, when appropriate, in pediatric clinical pharmacology studies;
  - Sample size for pediatric PK studies should be designed to provide precise estimates;
  - Pediatric formulations are a critical part of the development plan; and
  - Avoiding unnecessary studies is a scientific and ethical issue.

Summary

- Experience with pediatric studies under FDAAA (BPCA/PREA) has demonstrated that planning for dose finding, sample size identification and trial design is critical.

- Planning on the part of the sponsor and the FDA review divisions is essential for the success of pediatric trials.

- New clinical pharmacology tools should help us to optimize the use of pediatric study data, and increase the success rate for labeled pediatric indications.

Adolescent PK Studies Under PREA and BPCA

Lily Mulugeta, Pharm.D

Clinical Pharmacology Reviewer
Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research

Background

- Requirements/incentives to conduct clinical studies in pediatric patients (PREA/BPCA)

- Greater emphasis on evaluating pharmacokinetics of drugs in pediatric patients
  - Consideration for physiologic differences between pediatric patients and adults

PK Studies in Children

- Determine dosage regimen
- Factors for consideration
  - Relative bioavailability of the new formulation compared to the adult formulation
  - Age of the pediatric population
  - Therapeutic index of the drug
  - Pharmacokinetic data from the adult population
  - Body size of the pediatric study population

Guidance for Industry: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products *DRAFT GUIDANCE Nov 1998*

Scientific Necessity in Children

- Children should only be enrolled in a clinical trial if necessary to answer an important scientific question:
  - Determine the type and timing of clinical studies required for establishing "safe and effective" pediatric use of drugs, biologics and devices

- Children should only be enrolled if essential (i.e., no other option, whether animal or adult human)

Minimize Risks and Equitable Selection [US 21 CFR 56.111(a)(1) and (b)]
Adapted from Office of Pediatric Therapeutics (Michelle Roth-Cline, MD)

A Key Question

Can adult data be used to predict clearance in adolescents without the need of a dedicated PK study?

Methodology

- Drug products studied in adolescents under PREA/BPCA identified from FDA web-based public database (Sept 2007-Dec 2011)
- Data retrieved from clinical pharmacology review, product label, or literature
- Total body clearance (CL) of drugs in adolescents* compared to adults
- Predicted CL using allometric scaling compared to observed CL in adolescents:
  - Predicted CL= Adult CL * (adolescent wt/70kg) $^{0.75}$

* Adolescents defined as 12-17 years of age

Characteristics of Adolescent PK Studies

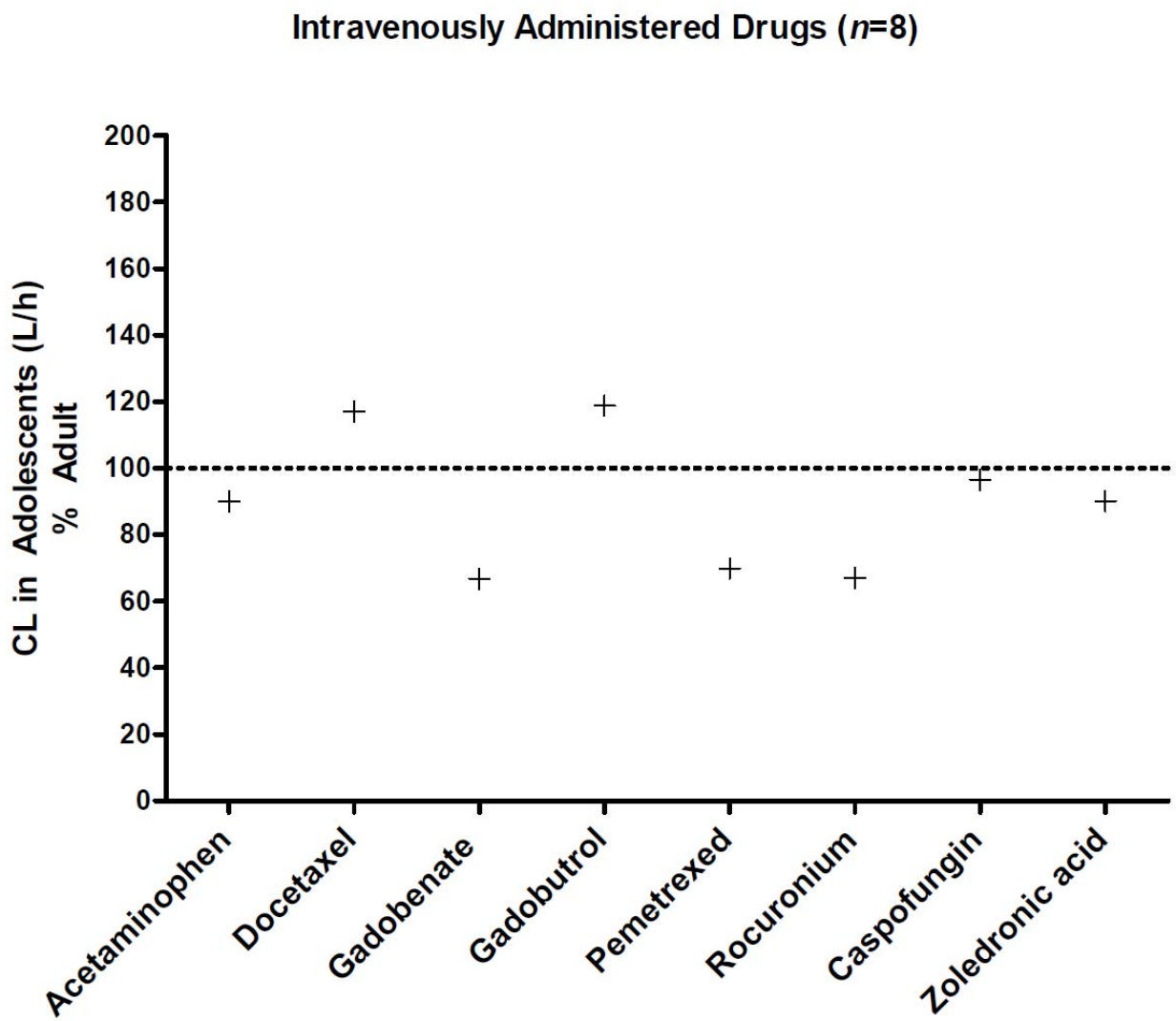
- A total of 83 PK studies for 57 drug products from 9/27/07 to 12/31/11

- 42/57 (74%) drugs had pediatric PK data in adolescent patients
  - 27/42 (64%): oral (19) , IV (8) drugs
    - Renally excreted: 9
    - Primarily metabolized: 18
  - 15/42 (36%): other routes (e.g. topical, inhalation, SC, IM...)

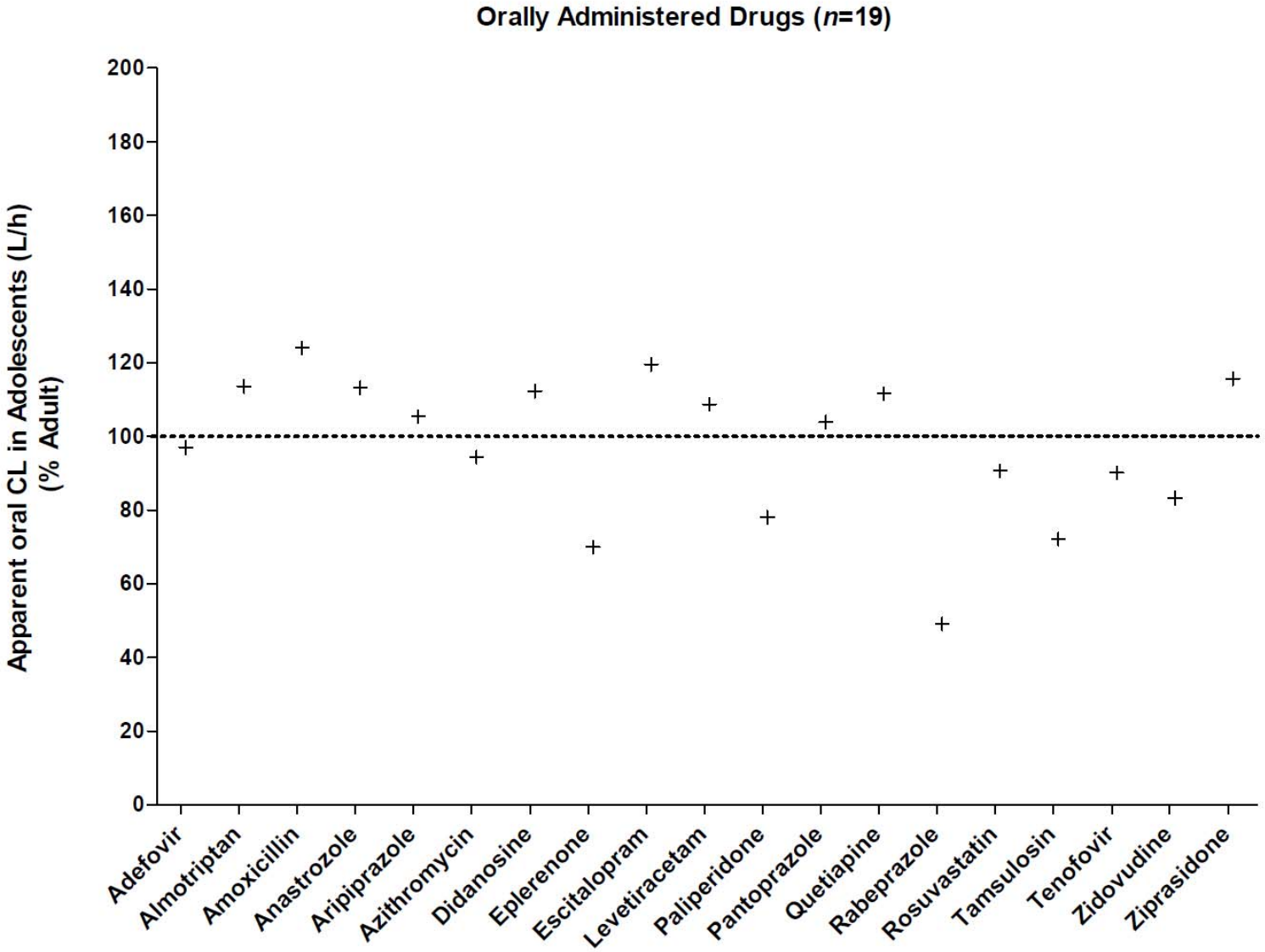
Characteristics of Adolescent PK Studies (cont'd)

- Focus for review: IV and oral drugs
- 21 of the 27 drugs reviewed received an adolescent indication
  - Efficacy not demonstrated: anastrozole, docetaxel, eplerenone, pemetrexed, zoledronic acid
  - Label change pending: ziprasidone
- Age group studied:
  - 12-17 years: 15 products
  - 10-17 years: 4 products (Paliperidone, rosuvastatin, ziprasidone, anastrozole)
  - 9-17 years: 1 product (zoledronic acid)
  - 7-16 years: 2 product (amoxicillin, levetiracetam)
- Mean weight range: 39.6 to 68.0 kg

Summary of Results

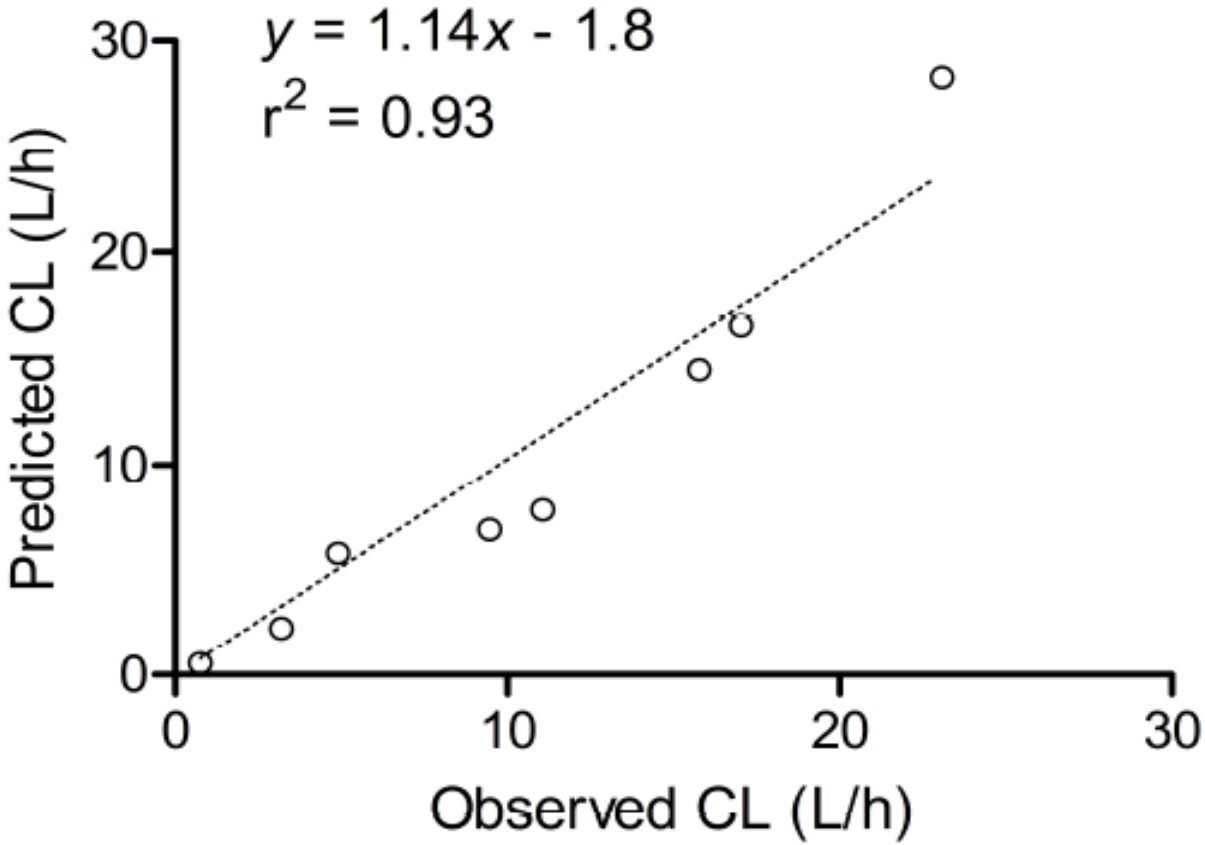


Summary of Results (Cont'd)

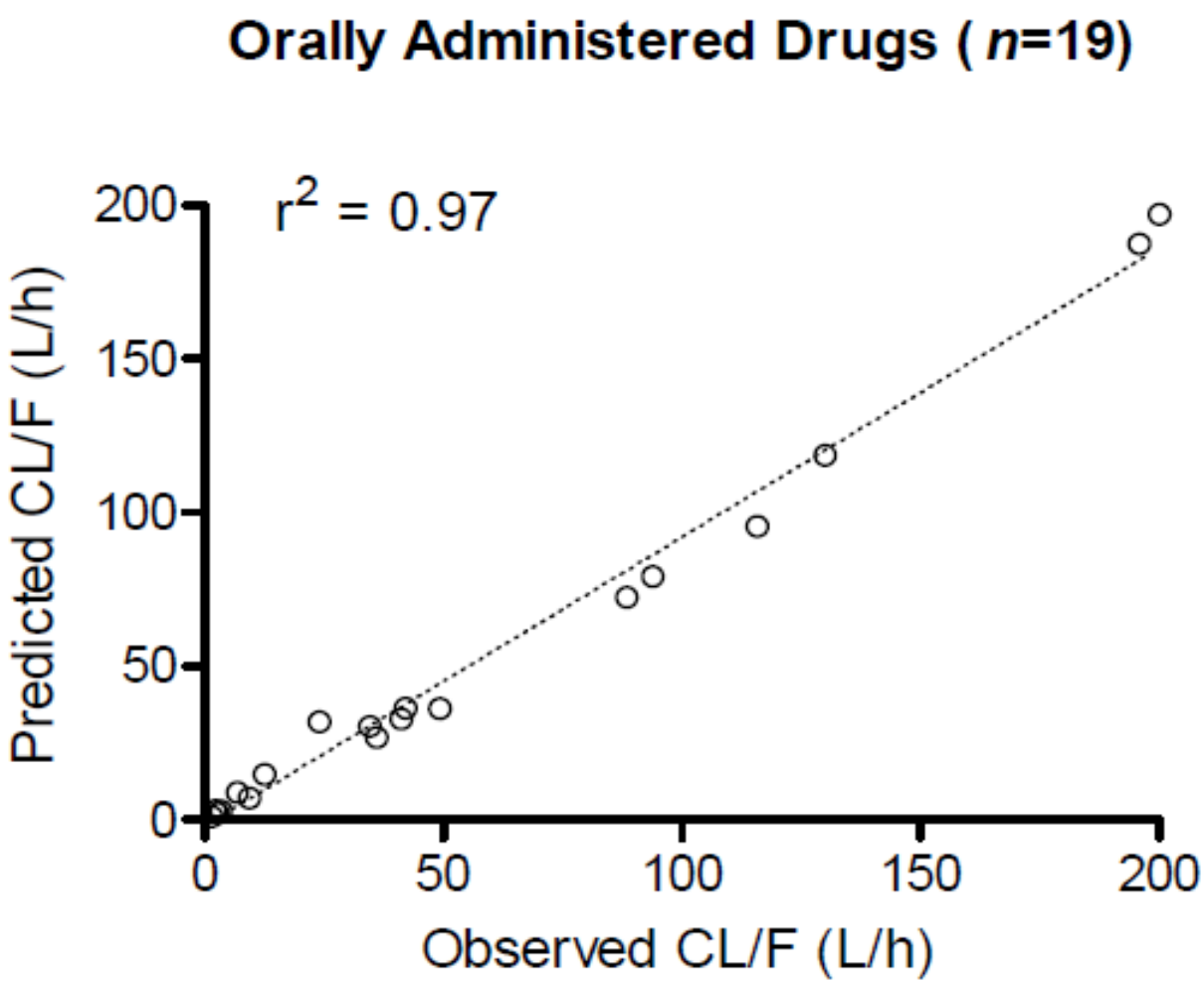


Prediction of Clearance (IV)

Intravenously Administered Drugs (*n*=8)



Prediction of CL (Oral)



FDA Approved Doses

- Approved adolescent dose same as adult:
  - 22/22; 100%
- Weight based dosing in pts with low body weight
  - 3/22; 13.6%
    - mg/kg dosing not to exceed approved adult dose
  - Azithromycin, tenofovir, zidovudine

Conclusion

- Based on the reviewed data, adult PK data may be used to predict clearance in adolescents using allometric scaling without the need of a dedicated PK study in adolescents
- Sparse PK sampling may be incorporated in efficacy or safety studies for exposure-response analysis
- Considerations may need to be given:
  - Drugs with narrow therapeutic range
  - Potential differences in the pediatric population to be studied compared to adults
    - Differences in intrinsic factors

KINETIC MODELING AND SIMULATION

The Children's Hospital *of* Philadelphia®
A pediatric healthcare network

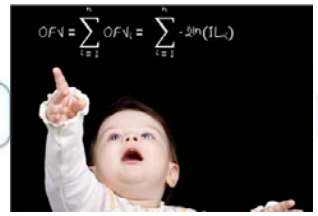
Role of Modeling and Simulation to Support Pediatric Drug Development:

Academic Perspective

Jeffrey S. Barrett, PhD, FCP

Director, Laboratory for Applied PK/PD
The Children's Hospital of Philadelphia

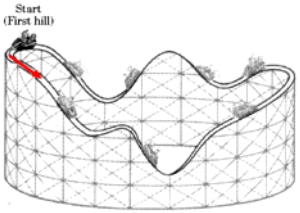
Outline

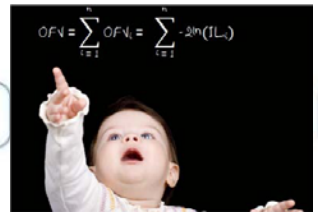


- **The landscape for M&S in Pediatrics**
  - An overview of current efforts
- **Past, Current and Best Practices**
  - Are we there yet?
  - Lets not hurt ourselves with the back patting . . .
  - Aligning M&S to assess design and objectives
  - FDA position paper
- **TBD (current knowledge gaps)**
- **How do we feel about M&S?**
  - **Questionnaire results**

Pediatric M&S Landscape

A lesson in bridge construction





PIP for EMA submission

Pre-Clinical Development

Initial Patient Trials (Phase II)

Drug Discovery

Healthy Volunteer Testing (Phase I)

Pregnancy

Pediatrics

Special Population Trials (Post-approval commitments)

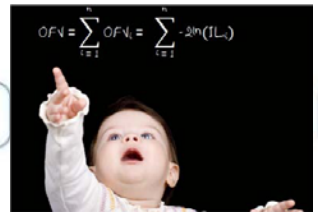
Patient Efficacy Trials (Phase III)

Renal and hepatic impairment

Product Launch Post-approval Trials (Phase IV)

Pediatric M&S Landscape

The Report card for M&S in Pediatrics

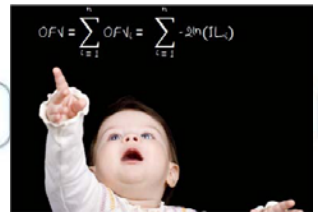


B+

- With some variation . . . most sponsors and investigators understand that they need to design a proper pediatric trial when warranted.
- General recognition that sampling, sample size and assumptions about PK/PD favor leveraging adult data if available AND using M&S.
  - Still the occasional cut – n – paste from the adult protocol
- Dosing requirements and management of pharmacotherapy continue to be a challenge in neonates especially.

Pediatric M&S Landscape

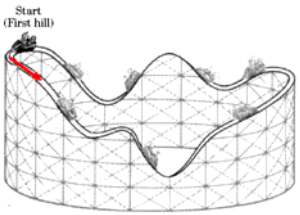
Milestones



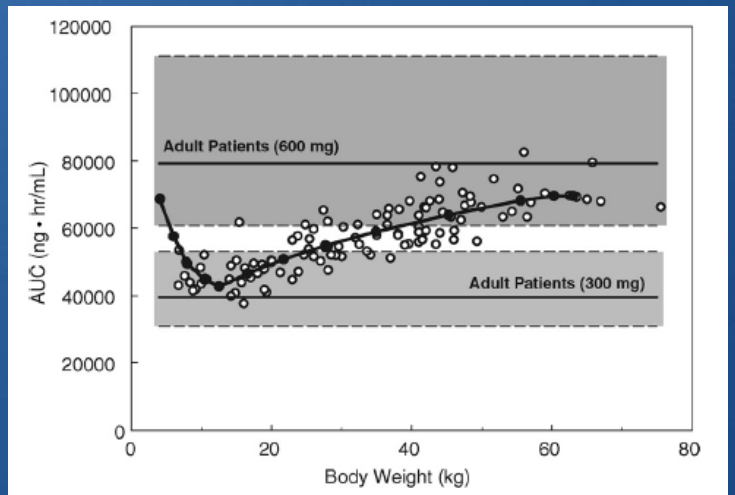
- Better appreciation for treatment of “size” across age strata - distinction from other factors that explain variability in PK processes
- Quantitative description of CYP ontogeny
- Greater experience with organ maturational effects (though the “data” has not caught up)
- Greater appreciation for the relevant physiologic factors of the developing child that affect ADME processes

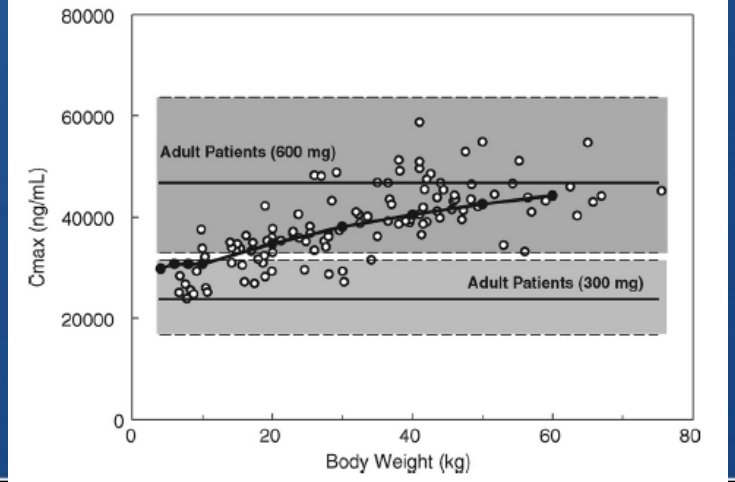
Pediatric M&S Landscape

Top 5 Uses of M&S in Pediatrics



1. Analysis of sparsely sampled pediatric PK data to fulfill regulatory requirement for PK/Safety



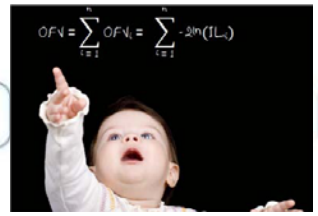


" . . . we demonstrated here the efficacy and safety of peramivir in children with pH1N1 virus infection. The peramivir exposures of children given a 10-mg/kg dose were within the range of exposures at which the efficacy and safety have been confirmed in adults, suggesting that an efficacy and safety in children similar to the efficacy and safety of peramivir in adults can be expected."

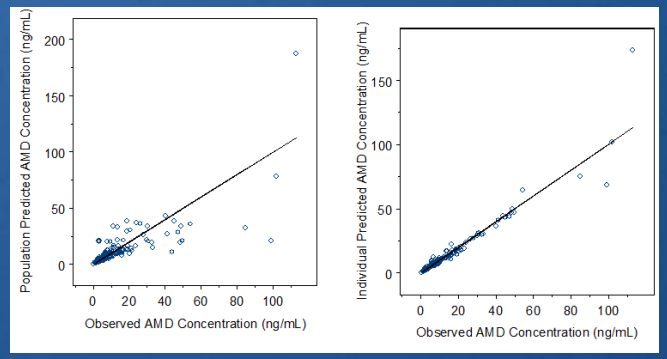
Sugaya N, Kohno S, Ishibashi T, Wajima T, Takahashi T. Efficacy, safety, and pharmacokinetics of intravenous peramivir in children with 2009 pandemic H1N1 influenza A virus infection. Antimicrob Agents Chemother. 2012 Jan;56(1):369-77.

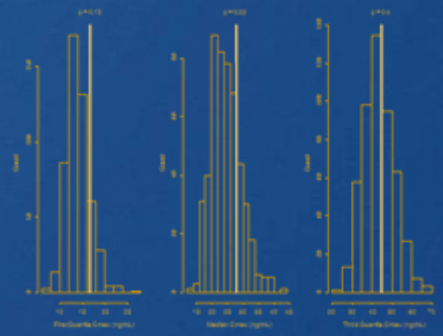
Pediatric M&S Landscape

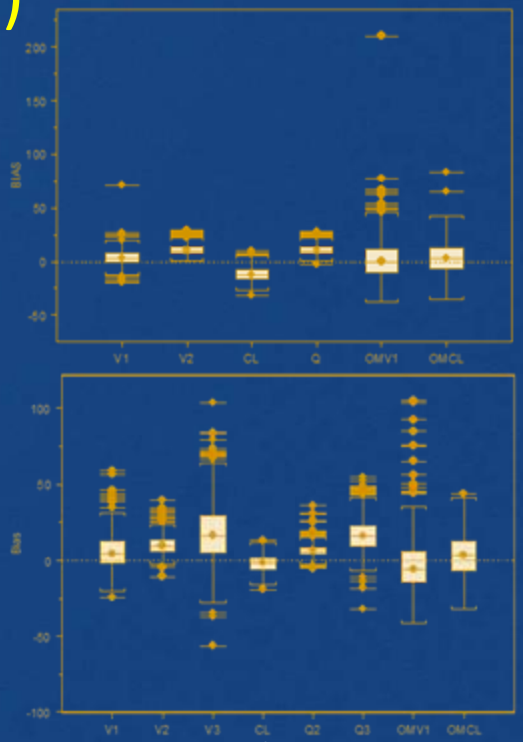
Top 5 Uses of M&S in Pediatrics

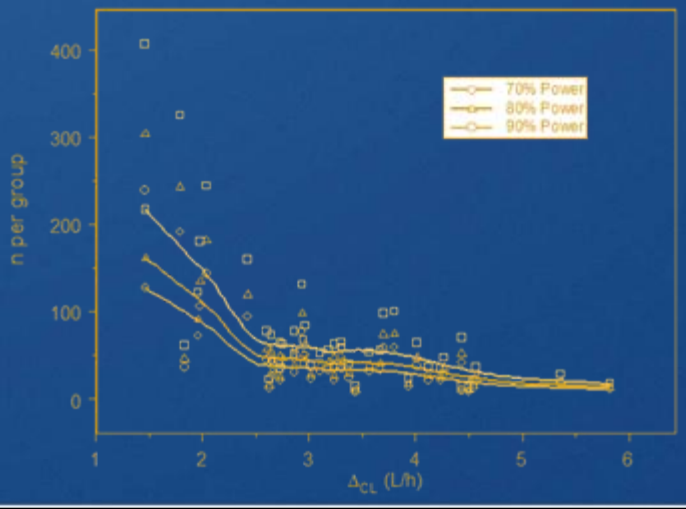


2. Simulations to guide the proposed sampling scheme, sample size and dose selection of prospective pediatric trials (usually the PK/Safety trial above)









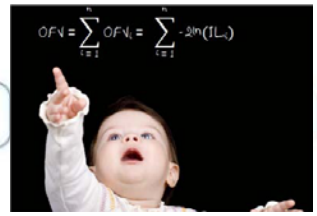
Model used to verify sample size, sampling scheme and dosing rules

Barrett JS, Gupta M, Mondick JT. Model-based Drug Development for Oncology Agents. *Expert Opinion on Drug Discovery* 2(2): 185-209, 2007.

Mondick JT, Gibiansky L, Gastonguay MR, Skolnik J, Veal GJ, Boddy A, Adamson PC, Barrett JS. Population Pharmacokinetics of Actinomycin-D in Children and Young Adults. *J Clin Pharmacol:* 48(1): 35-42, 2008

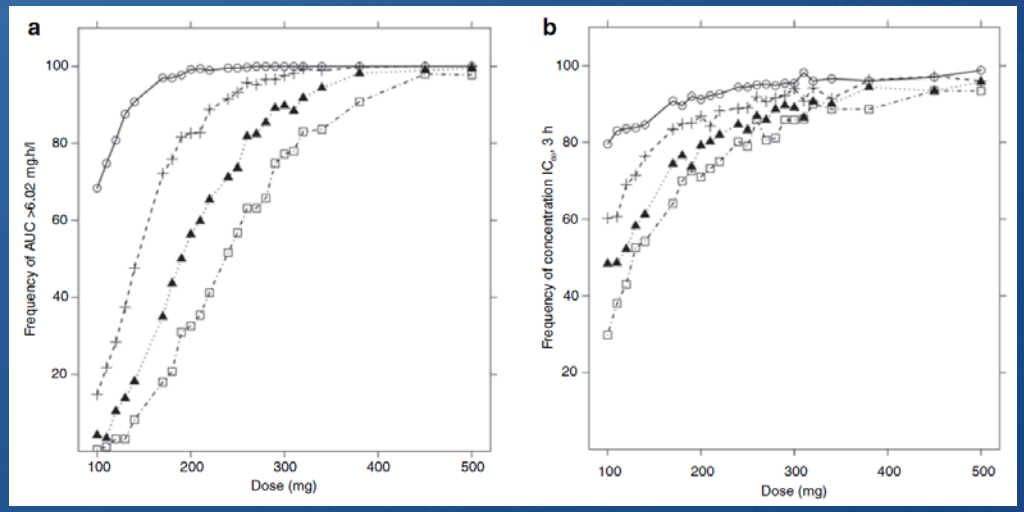
Pediatric M&S Landscape

Top 5 Uses of M&S in Pediatrics



3. FTIP dose selection

- Allometric scaling from animals (TK) and /or adults (PPK) relative to margin of safety or PD targets



Cella M, Gorter de Vries F, Burger D, Danhof M, Della Pasqua O. A model-based approach to dose selection in early pediatric development. Clin Pharmacol Ther. 2010 Mar;87(3):294-302.

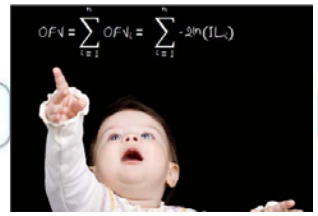
Table 2 Model-based dosing recommendations

Weight (kg)	Clinical dose (mg)	Recommended dose based on AUC (mg)	Difference compared with clinical dose (%)	Recommended dose based on IC_{80} (mg)	Difference compared with clinical dose (%)
10	80	120	+50	110	+37
20	160	190	+19	170	+6
30	240	260	+8	210	−13
40	300	320	+7	240	−20

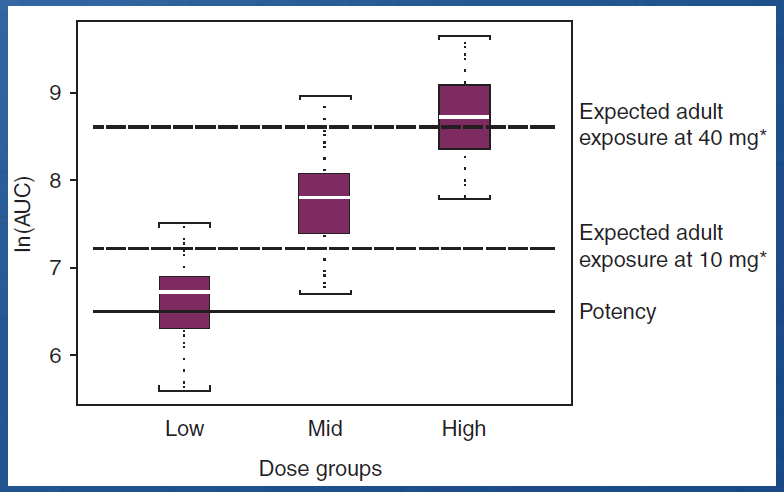
The current clinical dosage has been derived empirically (8 mg/kg twice daily with a maximum of 300 mg); simulated doses are based on target adult exposure, defined for the purposes of bridging as area under the plasma concentration–time curve (AUC) = 6.02 mg·h/l, or plasma concentrations >IC_{80} for ≥3 h.

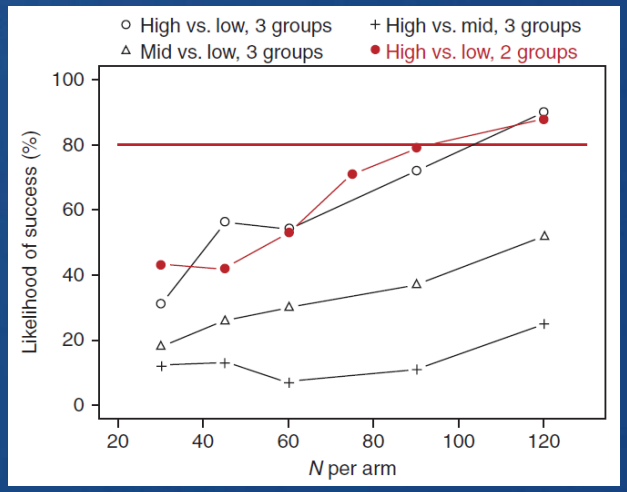
Pediatric M&S Landscape

Top 5 Uses of M&S in Pediatrics



4. Simulations of dosing requirements to achieve therapeutic equivalence to adult experience or target activity based on pediatric PK/PD outcomes





Salazar DE, Song SH, Shi J, Rohatagi S, Heyrman R, Wada DR, Carrothers TJ. The use of modeling and simulation to guide clinical development of olmesartan medoxomil in pediatric subjects. Clin Pharmacol Ther. 2012 Feb;91(2):250-6.

Table 1 Comparison of three vs. two dose groups

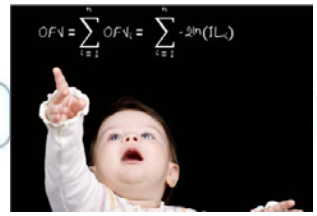
		DBP vs. dose			DBP vs. log (dose)			DBP vs. dose/weight		
Number of groups	Number of subjects/group	Mean (mm Hg/mg)	Success (%)	CV (%)	Mean (mm Hg/mg)	Success (%)	CV (%)	Mean (mm Hg/mg)	Success (%)	CV (%)
3	60	−0.068	45	50	−1.24	57	46	−3.18	37	47
2	60	−0.074	50	45	−1.22	54	42	−3.51	45	52
2	90	−0.083	76	34	−1.37	79	33	−3.94	72	39

Success = % of 100 trials showing slope different from zero.

CV, coefficient of variation of estimate of slope; DBP, diastolic blood pressure.

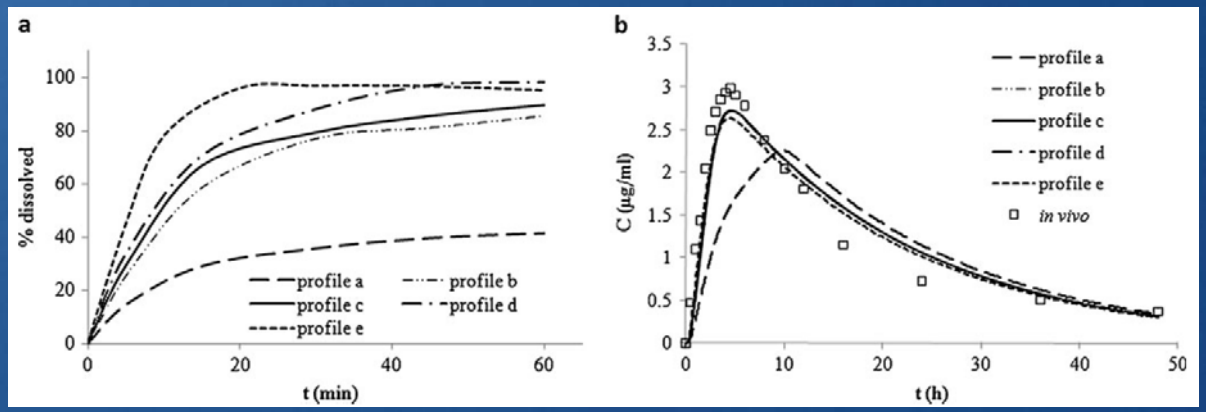
Pediatric M&S Landscape

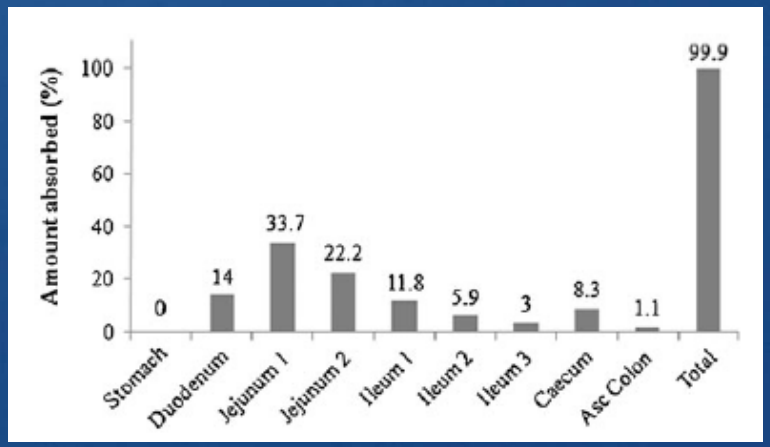
Top 5 Uses of M&S in Pediatrics



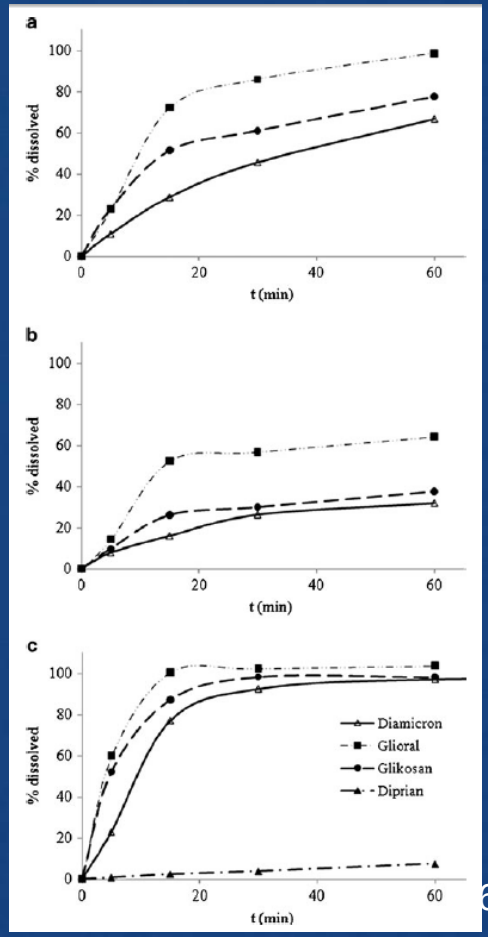
5. Pediatric Formulation Feasibility Simulations

- Simulating absorption based on pre-formulation data



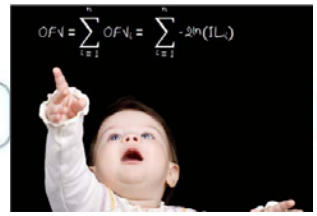


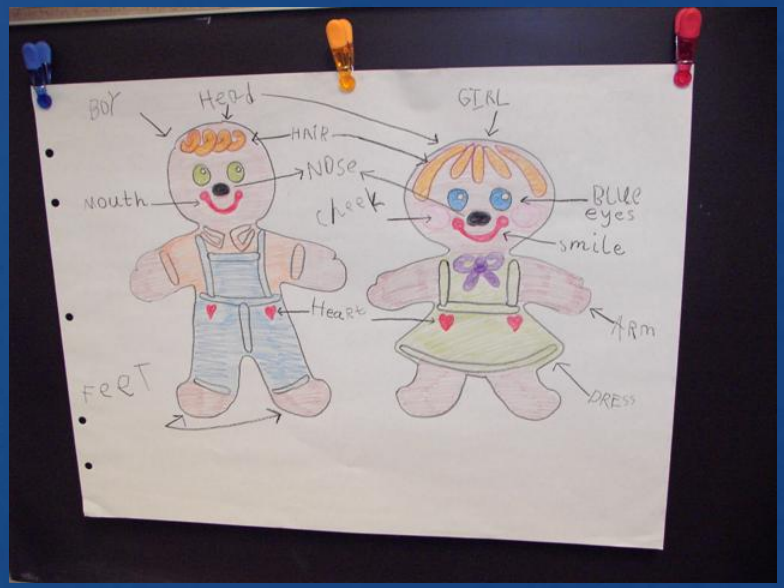
Grbic S, Parojcic J, Ibric S, Djuric Z. In vitro-in vivo correlation for gliclazide immediate-release tablets based on mechanistic absorption simulation. AAPS PharmSciTech. 2011 Mar;12(1):165-71.



Pediatric Priors

Nice to know vs Need to know

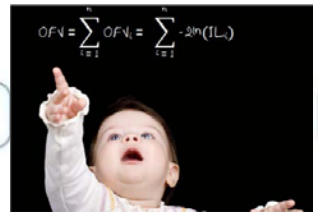




- Depends on trial objectives
- Generally,
  - Prevalence of pediatric indication
  - Natural history or disease trajectory – time course of signs and symptoms → what to measure
  - Likely commonality of therapeutic window from adults
  - "At risk" subpopulations – extremes that may warrant dosing modifications
  - Drug properties / behavior (*in vitro, in vivo, in silico* . . .)
  - Target definition – disease biology

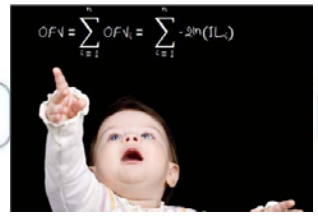
The Protocol:

Key Areas for Consideration



- Study Design
  - Treatment Groups (Choice and number)
  - Parallel vs Cross-over; Open-label vs blinded
  - Placebo, active control, (or not)
  - Sample size
- Dose
  - Adult equivalence vs pediatric endpoints
  - # dose groups, duration
  - Rules for age, weight, organ function criteria or guidance wrt toxicity
- Response Measures
  - Blood collection (timing and density of sampling)
  - PK vs PD vs objectives
  - Age-based stratification

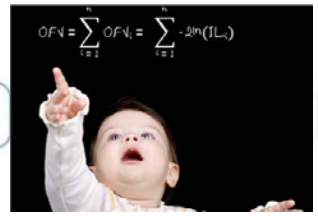
Critical Design Elements



- Dose Selection
- Sample Size
- Sampling Scheme

Dose Selection

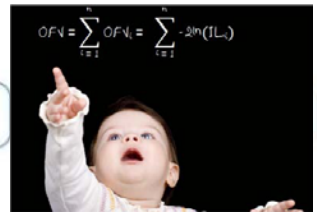
Dose Finding or Equivalence Approach?

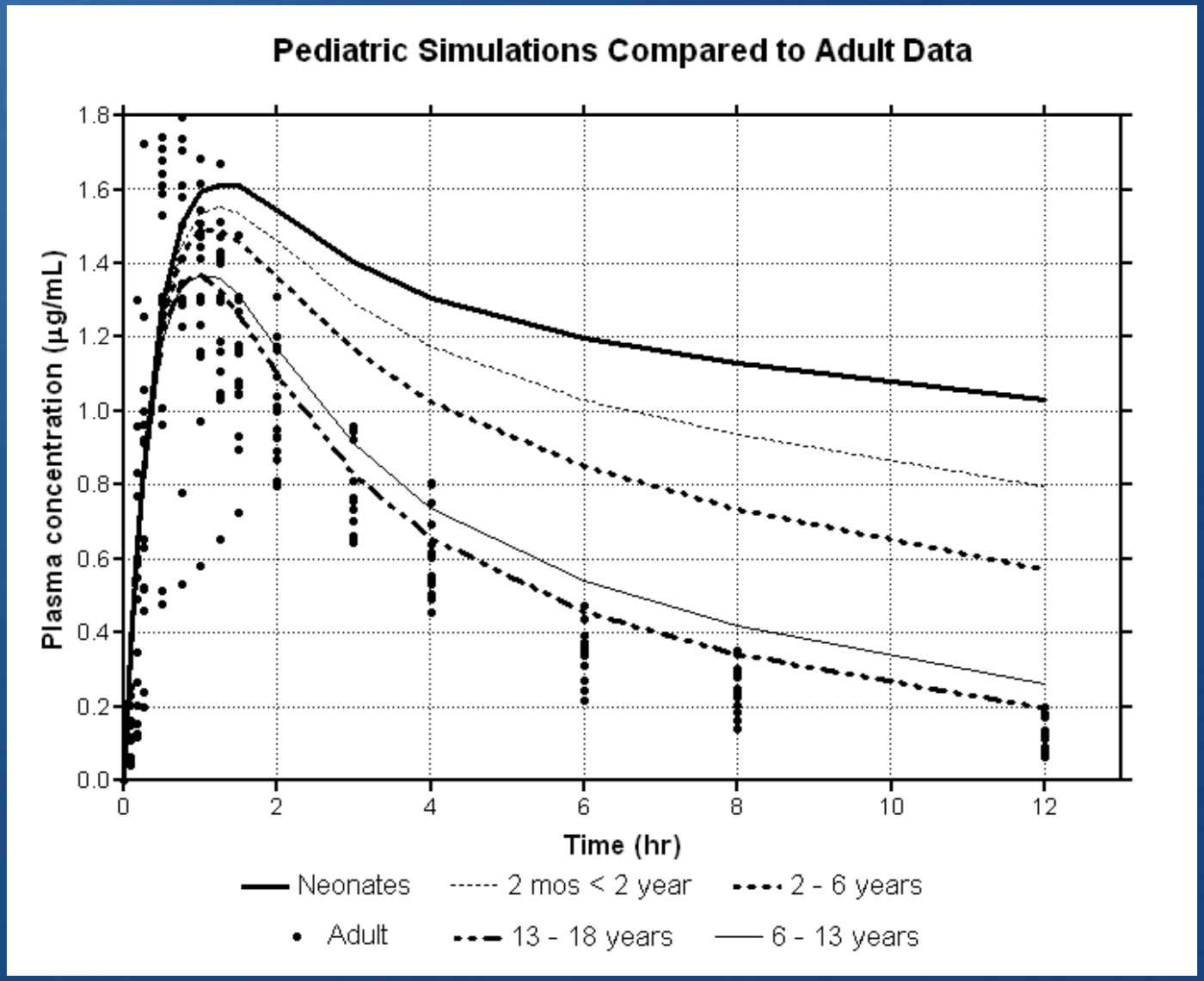


- Dose Finding
  - A target / endpoint is known or theorized based on adult or other data; dose-exposure to be defined
- Equivalence Approach
  - Exposure requirements based on adult experience – "equivalent" safety and efficacy assumed by matching exposure

Dose Selection

Equivalence Approach – How best accomplished?

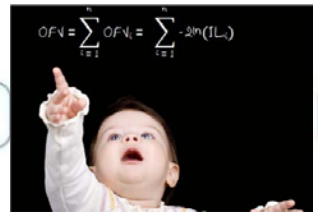




FDA Position Paper

Sample size guidance for pediatric PK and safety studies

Far enough or too far? . . . *Is this the right question?*



BRIEF REPORT

Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies

Yaning Wang, PhD, Pravin R. Jadhav, PhD, Mallika Lala, PhD, and Jogarao V Gobburu, PhD

Keywords: *pediatric drug development; pharmacokinet-*

Journal of Clinical Pharmacology, XXXX;XX:xxx-xxx

"The study must be prospectively powered to target a 95% CI [confidence interval] within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for DRUG NAME in each pediatric sub-group with at least 80% power."

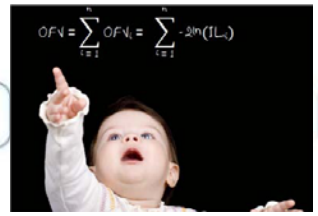
CRITERIA TO DERIVE SAMPLE SIZE WHEN DESIGNING PEDIATRIC PK STUDIES

Table II Feasibility of Regulatory Requirement for 3 Pediatric Studies Based on the Noncompartment Analysis Method

Drug	Age Group	No.	%CV_CL	Pass CL?	Power CL	%CV_V	Pass V?	Power V
Piperacillin (Zosyn)	3 to <6 mo	11	42	Yes	0.88	26	Yes	1
	6 to <12 mo	5	44	No	0.2	44	No	0.2
	1 to <2 y	8	29	Yes	0.95	17	Yes	1
	2 to <6 y	12	35	Yes	0.99	37	Yes	0.99
	6 to <12 y	20	50	Yes	1	35	Yes	1
	12 to 18 y	3	27	No	0.23	40	No	0.12
Guanfacine (Intuniv)	6 to <12 y	7	44	No	0.39	48	No	0.3
	12 to <16 y	14	27	Yes	1	34	Yes	1
Ertapenem (Invanz)	3 to <6 mo	6	49	No	0.21	33	No	0.58
	6 to <12 mo	12	23	Yes	1	15	Yes	1
	1 to <2 y	15	25	Yes	1	26	Yes	1
	2 to <6 y	9	23	Yes	1	32	Yes	0.95
	6 to <12 y	16	45	Yes	0.99	39	Yes	1
	12 to 18 y	13	44	Yes	0.95	41	Yes	0.98

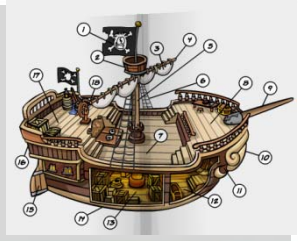
Pass CL and Pass V indicate whether or not the age subgroup meets the requirement, and Power CL and Power V indicate the retrospective power calculation.

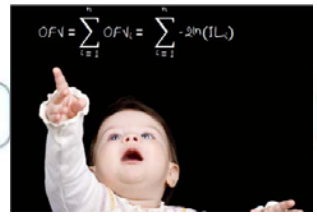
We “leverage” what we know



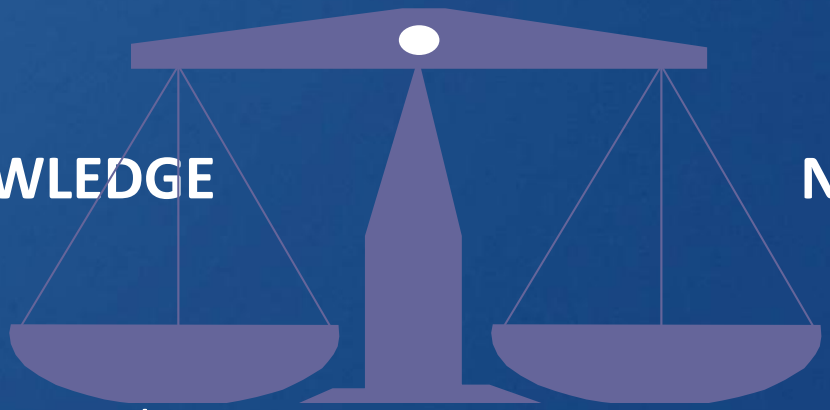
- Characteristics about the drug
  - Data (observed and parameterized), models, assumptions
- Characteristics about the disease
  - Prevalence and progression (qualitative and quantitative)
  - How assessed
- Adult experience
  - Comparison of disease or indication
  - Comparison of the populations
- What and how we want to assess in a trial → design

Putting it all together . .





- By incorporating prior information about the parameter(s), a posterior distribution for the parameter(s) can be obtained and inferences on the model parameters and their functions can be made.



PRIOR KNOWLEDGE

- Adult model and parameters
- Link between pediatric and adult PK (and PD)

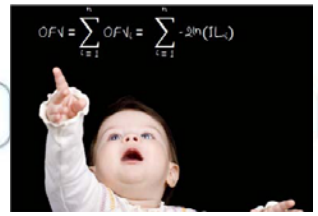
NEW DATA

- New PK (and PD) data from pediatric patients

- Bayes Theorem in practice. . . But it doesn't have to be this complicated to benefit from prior knowledge!

Pediatric M&S TBD

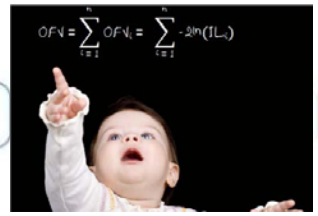
Still on the plate . . .



- More, better and quantitative biomarkers
  - M&S illustrations of how such data can be used
- PD assessments and models linked to outcomes
- Quantitative description of non-CYP ontogeny
- Quantitative description of transporter ontogeny
- Better understanding of physiologic spaces
- Better, more informative labels
- Better integration of modeling results with caregiver guidance

Pediatric M&S TBD

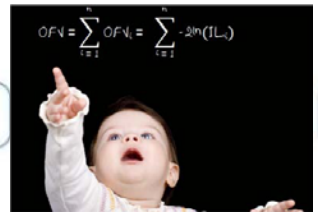
Still on the plate . . .



- Integration of M&S and pharmacoepidemiology for pediatric diseases / indications
- M&S and signaling pathways for pharmacotherapeutic strategies (DDI, ADRs, long-term toxicities)
- Pediatric disease progression
- Physiologic description of pediatric subpopulations (Obesity, SMA, MD, etc)
- Co-morbidities as covariates
- PD metrics for difficult to assess pediatric indications (e.g., pain)

Pediatric M&S Survey

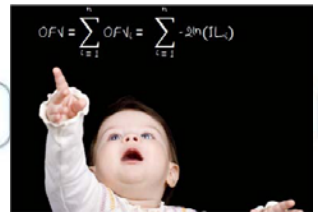
Preliminary Results - Responder Demographics



- 32 Total responders
- 17 from PhRMA, 6 from CROs, 9 from Academic Medical Research Institutes
- 6 different companies represented: GSK, Astra Zeneca, Biogen, Amgen, Pfizer and Roche

Pediatric M&S Survey

Preliminary Results



5. Are you directly involved with the design, analysis, or conduct on pediatric clinical trials (Phase I – III)?

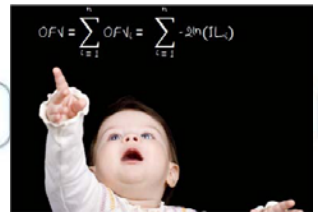
	Response Percent	Response Count
Yes	100.0%	35
No, (If no, what is your role in pediatric R&D?)	0.0%	0

6. Which phases of pediatric drug development have you been involved with? (check all that apply)

	Response Percent	Response Count
Preclinical	31.4%	11
Phase I	71.4%	25
Phase II	80.0%	28
Phase III	60.0%	21

Pediatric M&S Survey

Preliminary Results - Responder Demographics



7. Which aspects are you involved with? (check all that apply)

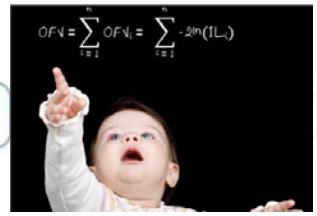
	Response Percent	Response Count
Protocol design	**91.4%**	**32**
Data Analysis	85.7%	30
Study Conduct	34.3%	12
Other (please specify)		1

8. Check the field that best represents your background

	Response Percent	Response Count
Physician (Please specify specialization in Other)	22.9%	8
Modeler / Pharmacometrician	**65.7%**	**23**
Study Statistician	0.0%	0
Nurse	0.0%	0
non-Physician PI	11.4%	4
Project Manager	0.0%	0

Pediatric M&S Survey

Preliminary Results



9. Does your organization routinely employ M&S to guide pediatric clinical trials?

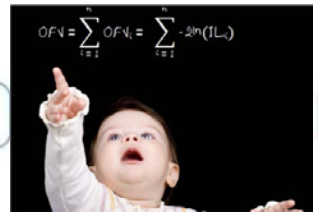
	Response Percent	Response Count
Yes	87.1%	27
No, (If no, what do you think the primary reason is)	12.9%	4

10. Do you feel all members of the project teams you've been on appreciate the value of M&S to guide pediatric clinical trials?

	Response Percent	Response Count
Yes	25.8%	8
No	6.5%	2
Not sure	9.7%	3
Some, but not all	58.1%	18

Pediatric M&S Survey

Preliminary Results

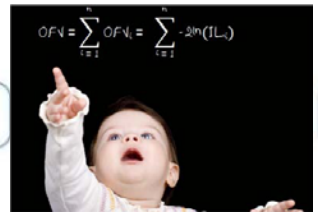


11. Identify importance for using M&S to guide pediatric trials?

	Least Important									M Impo
Time to complete analyses	12.9% (4)	9.7% (3)	6.5% (2)	9.7% (3)	12.9% (4)	3.2% (1)	**16.1% (5)**	9.7% (3)	12.9% (4)	6.5
Cost of analyses (time, personnel investment, etc)	9.7% (3)	9.7% (3)	9.7% (3)	**16.1% (5)**	9.7% (3)	6.5% (2)	**16.1% (5)**	12.9% (4)	6.5% (2)	3.2
Regulatory value (justification for design constructs)	9.7% (3)	0.0% (0)	3.2% (1)	0.0% (0)	0.0% (0)	3.2% (1)	0.0% (0)	19.4% (6)	29.0% (9)	**35. (1**
Certainty of Predictions	9.7% (3)	0.0% (0)	0.0% (0)	0.0% (0)	6.5% (2)	12.9% (4)	12.9% (4)	**29.0% (9)**	19.4% (6)	9.7
Confidence with Methodology	9.7% (3)	0.0% (0)	0.0% (0)	0.0% (0)	9.7% (3)	12.9% (4)	9.7% (3)	**35.5% (11)**	16.1% (5)	6.5
Methodology Utilized (e.g., Adult-scaled pop-PK, PBPK, other in silico methods)	9.7% (3)	3.2% (1)	3.2% (1)	0.0% (0)	0.0% (0)	**19.4% (6)**	**19.4% (6)**	12.9% (4)	12.9% (4)	**19.4**

Pediatric M&S Survey

Preliminary Results - Responder Demographics

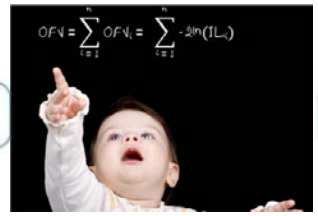


12. Rank the list below with respect to overall importance (Enter 1 through 6, 1 unique choice per topic)

	Response Average	Response Total	Response Count
Time to complete analyses	3.97	123	31
Cost of analyses	**4.48**	**139**	31
Regulatory value	1.81	56	31
Certainty of Predictions	3.16	98	31
Confidence with Methodology	3.32	103	31
Methodology Utilized	3.77	117	31

Pediatric M&S Survey

Preliminary Results

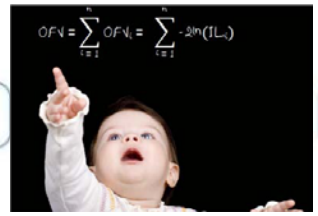


13. Identify importance of M&S outputs to guide pediatric trials?

	Least Important									Mo Impor
Dose Selection	9.7% (3)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	3.2% (1)	3.2% (1)	12.9% (4)	19.4% (6)	**51.6 (16**
Sample Size (number of subjects, strata etc)	9.7% (3)	0.0% (0)	0.0% (0)	0.0% (0)	3.2% (1)	6.5% (2)	3.2% (1)	**35.5% (11)**	19.4% (6)	22.6%
Sampling Scheme (number and timing of PK and /or PD endpoints)	9.7% (3)	0.0% (0)	0.0% (0)	0.0% (0)	9.7% (3)	0.0% (0)	0.0% (0)	**32.3% (10)**	29.0% (9)	19.4%
Clinical Trial Outcomes – Probability of Success	9.7% (3)	0.0% (0)	0.0% (0)	0.0% (0)	3.2% (1)	3.2% (1)	19.4% (6)	**41.9% (13)**	19.4% (6)	3.2%
Design Alternatives – Clinical Trial Simulation	9.7% (3)	0.0% (0)	0.0% (0)	0.0% (0)	6.5% (2)	**19.4% (6)**	16.1% (5)	**19.4% (6)**	**19.4% (6)**	9.7%
Disease Progression	12.9% (4)	9.7% (3)	3.2% (1)	0.0% (0)	16.1% (5)	12.9% (4)	16.1% (5)	**19.4% (6)**	6.5% (2)	3.2%
IVIVC (for pediatric formulation design)	12.9% (4)	9.7% (3)	6.5% (2)	0.0% (0)	**35.5% (11)**	9.7% (3)	6.5% (2)	9.7% (3)	6.5% (2)	3.2%

Pediatric M&S Survey

Preliminary Results - Responder Demographics

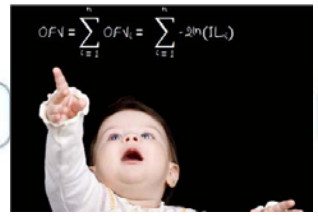


14. Rank the list below with respect to overall importance (Enter 1 through 7, 1 unique choice per topic)

	Response Average	Response Total	Response Count
Dose Selection	1.26	39	31
Sample Size	2.71	84	31
Sampling Scheme	3.16	98	31
Clinical Trial Outcomes	3.87	120	31
Design Alternatives	4.29	133	31
Disease Progression	5.65	175	31
IVIVC	**6.32**	**196**	31

Pediatric M&S Survey

Preliminary Results



15. What incentive would be necessary for you to conduct M&S for planning every pediatric development program or research initiative? (check one)

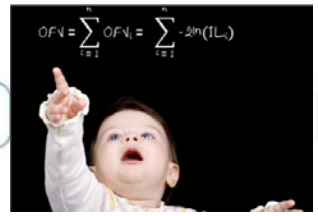
	Response Percent	Response Count
None	**25.8%**	**8**
Senior management "buy-in"	9.7%	3
Regulatory incentive	**25.8%**	**8**
Additional staff / infrastructure	**25.8%**	**8**
Enough time	0.0%	0
Better / consistent data processes	12.9%	4

16. What percentage of pediatric trials that you have supported has relied on M&S in some way?

	Response Percent	Response Count
None	0.0%	0
Less than 50%	22.2%	6
Between 50 – 80%	11.1%	3
Majority (> 80%)	**51.9%**	**14**
All	14.8%	4

Pediatric M&S Survey

Preliminary Results - Responder Demographics



17. What methodologies have you had exposure to when M&S has been employed at your organization? (check all that apply)

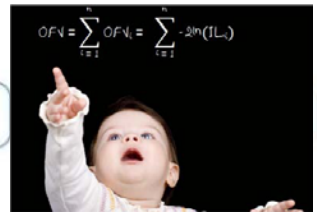
	Response Percent	Response Count
PBPK	37.0%	10
Adult-scaled Pop-PK	**92.6%**	**25**
Clinical Trial Simulation	81.5%	22
Disease progression modeling	40.7%	11
IVIVC (M&S for formulation design)	18.5%	5

18. Provide the percentage of pediatric trials for which each of these methodologies have been used?

	None	< 50%	50 – 80%	> 80%	All	Rating Average	Response Count
PBPK	**50.0% (12)**	25.0% (6)	12.5% (3)	8.3% (2)	4.2% (1)	1.92	24
Adult-scaled Pop-PK	0.0% (0)	18.5% (5)	25.9% (7)	**29.6% (8)**	25.9% (7)	3.63	27
Clinical Trial Simulation	4.0% (1)	20.0% (5)	24.0% (6)	**32.0% (8)**	20.0% (5)	3.44	25
Disease progression modeling	36.0% (9)	**48.0% (12)**	8.0% (2)	4.0% (1)	4.0% (1)	1.92	25
IVIVC	**56.5% (13)**	39.1% (9)	4.3% (1)	0.0% (0)	0.0% (0)	1.48	23

Pediatric M&S Survey

Preliminary Results



19. Rate your confidence with the methodologies listed below:

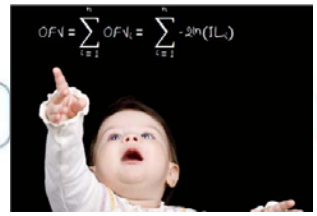
	None	Somewhat	Fully confident	Can't assess	Rating Average	Response Count
PBPK	0.0% (0)	**63.0% (17)**	25.9% (7)	11.1% (3)	2.48	27
IVIVC	7.4% (2)	**48.1% (13)**	14.8% (4)	29.6% (8)	2.67	27
Adult-scaled Pop-PK	0.0% (0)	40.7% (11)	**59.3% (16)**	0.0% (0)	2.59	27
Clinical Trial Simulation	0.0% (0)	25.9% (7)	**74.1% (20)**	0.0% (0)	2.74	27
Disease progression modeling	7.4% (2)	**44.4% (12)**	29.6% (8)	18.5% (5)	2.59	27

20. Has your organization utilized pediatric-specific databases as inputs to M&S outputs?

	Response Percent	Response Count
Yes	**51.9%**	**14**
No	14.8%	4
Not sure	14.8%	4
Some, but not all	18.5%	5

Pediatric M&S Survey

Preliminary Results



21. How have pediatric-specific databases been used at your organization?

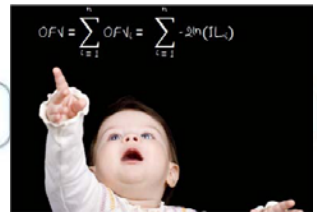
	Response Percent	Response Count
Population indication identification (confirmation of target population)	55.6%	15
Drug utilization (frequency of agent or drug class use in certain indications)	48.1%	13
Population characteristics (physiologic priors)	**74.1%**	**20**
Pediatric-specific disease prevalence or progression	55.6%	15
Other (please specify)		3

22. Do you feel that your organization's experience with M&S to guide pediatric clinical trials as been positive?

	Response Percent	Response Count
Yes	**81.5%**	**22**
No	3.7%	1
Not sure	3.7%	1
Some, but not all	11.1%	3
answered question		**27**
skipped question		**8**

Pediatric M&S Survey

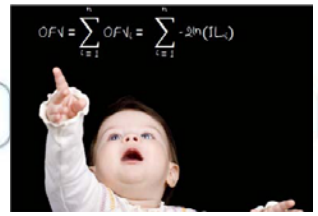
Preliminary Results



23. What do you feel is the biggest challenge to provide additional confidence in adopting M&S to guide pediatric clinical trials in the future? (Choose only one)

	Response Percent	Response Count
More and better pediatric-specific PK/PD models	**55.6%**	**15**
Better PK prediction at lower age strata	18.5%	5
Improvement in pediatric PBPK disposition models	11.1%	3
Improvement in pediatric absorption models	0.0%	0
More and better pediatric-specific disease progression models	11.1%	3
None – very confident in current capabilities to support current trials	3.7%	1

Conclusions



- Utility of M&S to guide pediatric drug development well appreciated and part of common practice
  - Comfort with all approaches not the same
- More informed use of prior information is evolving. Better use of databases is likely.
- Discipline is becoming more intimately connected with therapeutic area thought leaders – good news for children.

Regulatory Perspective of Modeling and Simulation in Pediatric Drug Development

Kevin M. Krudys, Ph.D.
Pharmacometrics Reviewer
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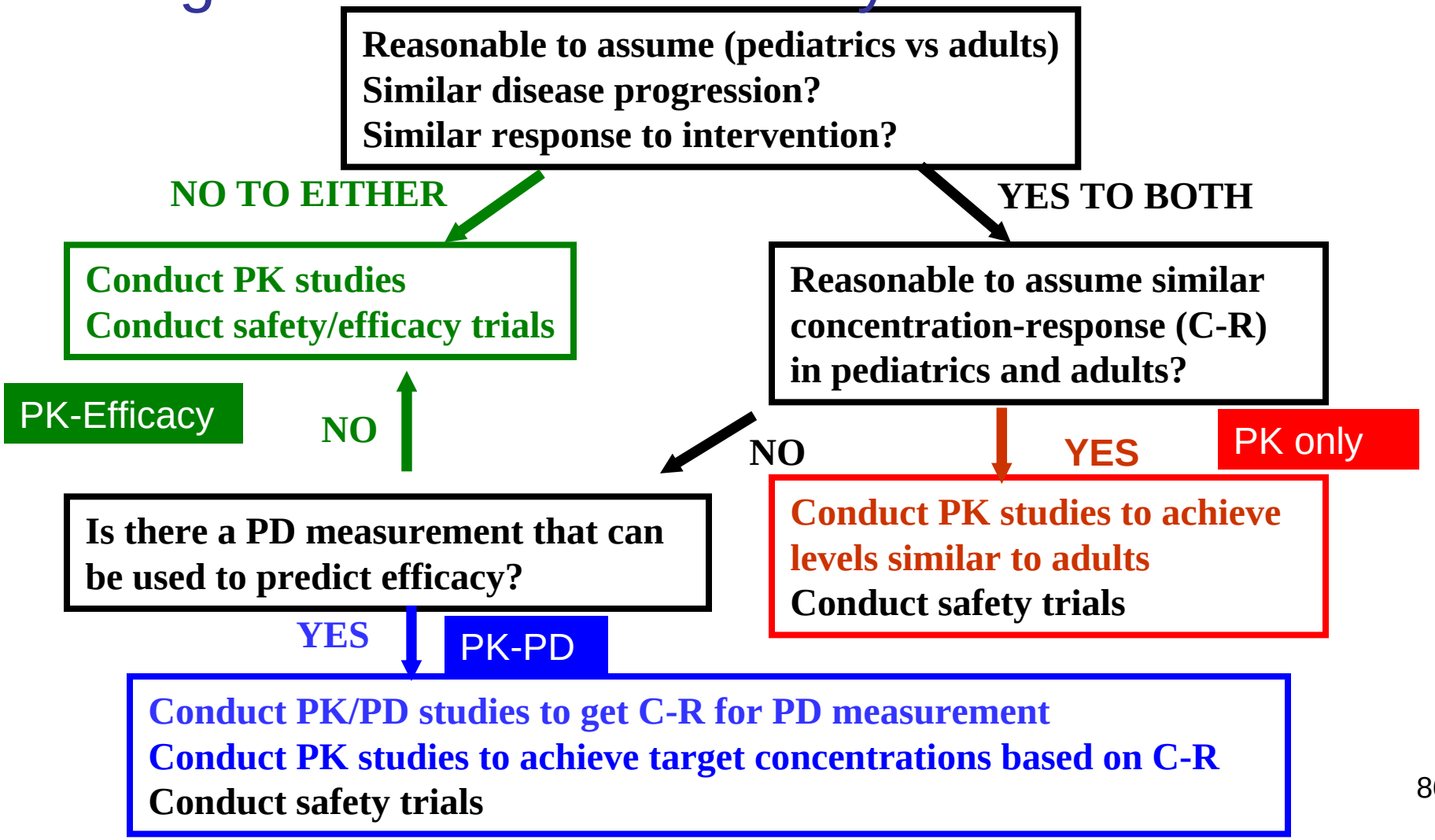
Office of Translational Sciences
Center for Drug Evaluation and Research

Using Modeling and Simulation to Navigate the Pediatric Study Decision Tree



Different Regulatory Paths
PEDIATRICS

Matching drug exposure in pediatrics Busulfex® (busulfan) Injection, Zosyn®, (piperacillin/tazobactam), Levaquin®, (levofloxacin), Videx® (didanosine), Xyzal®, (levocetirizine dihydrochloride), and Digoxin Elixir

Exposure–response of biomarker or clinical endpoint data Trileptal® (oxcarbazepine), Betapace® (sotalol) and Argatroban Injection® (argatroban)

Effectiveness study plus matching drug exposures Celebrex® (celecoxib), Humira® (adalimumab), Ilaris® (canakinumab), and Corlopam® (fenoldopam)

FDA Approach to Pediatric Drug Development

Simulate2Design

Power PK Study
Sample size, Sampling scheme
Power Registration study
Dose range selection,
Endpoints, Analyses

Model4Decision

Exposure-Response to Support Approval & Dosing

Gobburu, FDA Pediatric Advisory Committee meeting, 2009
Liu, FDA Oncology Drugs Advisory Committee meeting, 2010

Optimizing Design of Pediatric PK Studies

- Pediatric PK data is useful for:
  - Selecting dose for pivotal efficacy studies
  - Assessing relationship between exposure and efficacy and safety
  - Support dosing and approval decisions

REGULATORY CHALLENGE:

Sample size for pediatric PK and safety studies has varied widely without clear justification, affecting approval and exclusivity decisions.

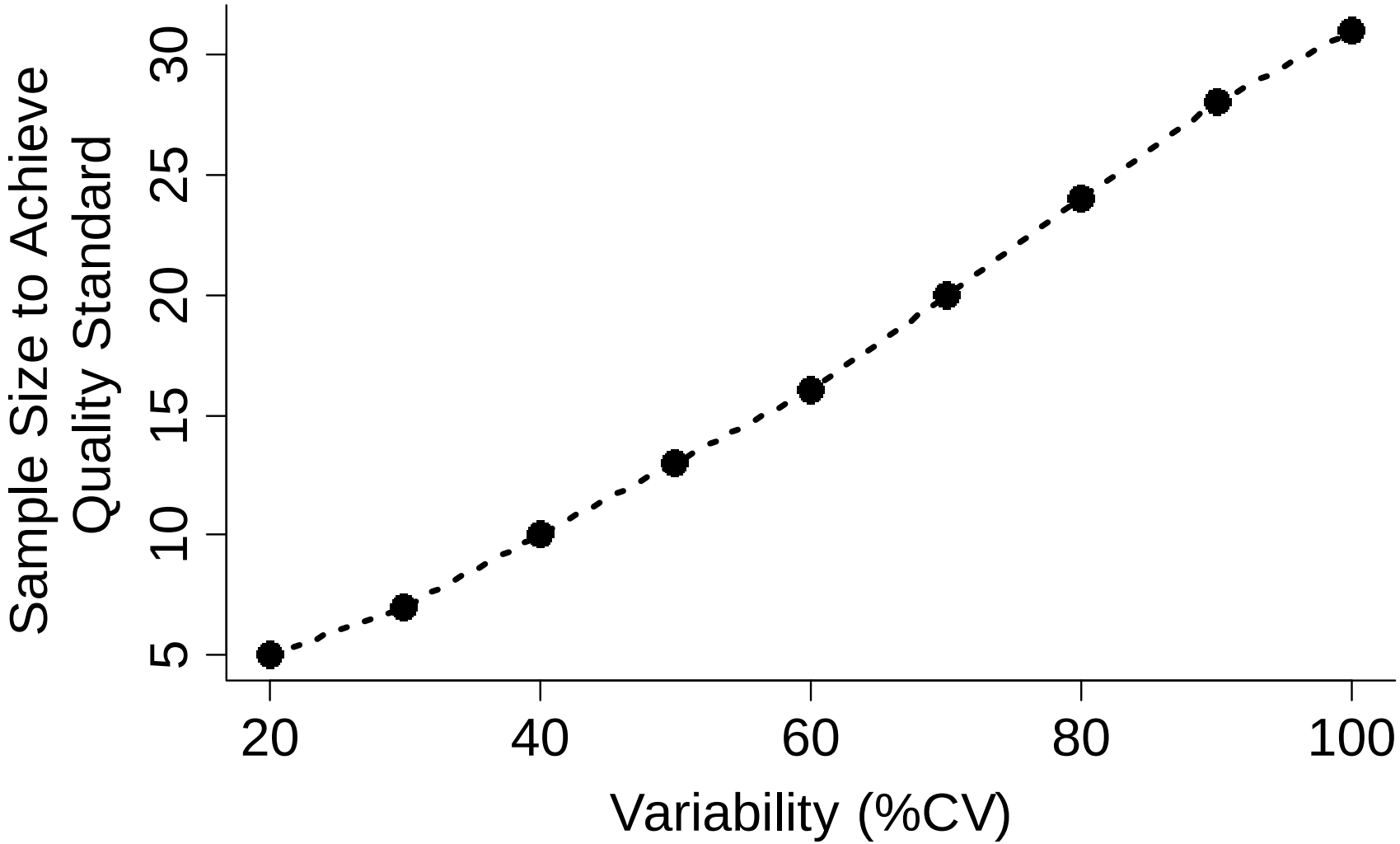
Framework for Sample Size Determination

- Need for uniform definition for study quality for PK studies
- Goal of PK study is to ensure precise estimation of important PK parameters
- Important factors influencing the design of pediatric PK studies include sampling scheme and expected level of between subject variability

The study must be prospectively powered to target a 95% CI within 60% to 140% of the geometric mean estimates of clearance and volume of distribution for DRUG in each pediatric sub-group with at least 80% power.

Wang Y et al., J Clin Pharmacol 2011 Dec 12

Sample Size Per Age Group for Different Levels of Variability



Impact of Sample Size Standard

EXPECTATION

Sponsors justify the choice of sample size and sampling scheme for pediatric trials through modeling of adult or relevant pediatric data and simulation of pediatric study

BENEFITS

1. Provides a consistent rationale for sample size determination
2. Ensures a starting point for objective *discussion* between sponsors and FDA
3. Ensures informative design of pediatric clinical trials to derive rational dosing recommendations

Aims of Modeling & Simulation in Pediatric Drug Development

- Effectively use prior knowledge to develop pediatric written requests (WR) and pediatric plans
- Make more informed decisions on dose range, number of subjects, sampling scheme and primary endpoints
- Improve design of studies to derive rational dosing recommendations
- Vision: Design by Simulation (100% WR and Pediatric Plans)

Case Study 1: Leveraging Pediatric Data from a Failed Program

- Sponsor is studying a drug to treat a symptomatic condition in a pediatric population
- Knowledge from prior study with similar drug
  - 2 trials in children 5 to 10 years of age receiving ½ adult dose failed to show efficacy
  - Exposure-response analysis revealed that children <35 kg had comparable exposure to adults and better response of PD endpoint compared to children >35 kg

Using Simulation to Design Pediatric Program

- Sponsor used previous information to support dose selection, age groups and study design
- Step-wise approach was proposed
  - Study 1: Adult dose for patients >25 kg
    - Adult PK model and allometric scaling used to predict exposure at proposed dose
  - Study 2: Half of adult dose for patients <25 kg

Interaction with FDA

"We advise that exposure-response modeling (for both effectiveness and safety) from Study 1 be used to simulate the design of Study 2, including selection of doses. You should discuss the results of the clinical trial simulation of Study 2 with us…"

"A control group may not be needed for Study 2 if the relationship between exposure and response is planned to be used as evidence of effectiveness."

Case Study 2: Leveraging Adult Data

- Sponsor is studying a first in class drug for pediatric indication
- Pediatric development plan included:
  - Study 1: Dose-finding study (three cohorts)
  - Study 2: Placebo-controlled efficacy and safety study
- Important to find lowest effective dose for pediatric patients

Interaction with FDA

"Justification should be provided for the proposed doses, dosing intervals, dose increments and duration of treatment…An analysis of the exposure-effect relationship in adults should be established. You should use this relationship to derive the range of doses in pediatric patients via simulations…"

"You should utilize all available information in adults to derive an optimal sparse sampling scheme that will provide characterization of the pharmacokinetics."

Using Simulation to Design Pediatric Program

- Sponsor developed PK/PD model from adult data
  - Allometric scaling used to predict pediatric exposure
  - Indirect response model to describe relationship between concentrations and serum PD marker
- Simulations were essential to:
  - Provide rational dosing recommendations predicted to bracket the response observed in adults
  - Design sparse sampling scheme

Expectations for Modeling & Simulation Approach to Pediatric Drug Development

1. Justify sample size and sampling scheme
2. Fully explore the tolerated dose range, where applicable
3. Substantiate design of effectiveness and safety trials using modeling and simulation
4. Perform exposure-response analysis to support approval and dosing

Pediatric PBPK models: development and application for dose guidance

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uwaterloo.ca

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Presentation Structure

- Current status of pediatric PBPK model components (ADME)
- Appropriate workflow for the development of pediatric PBPK models
- Examples of use

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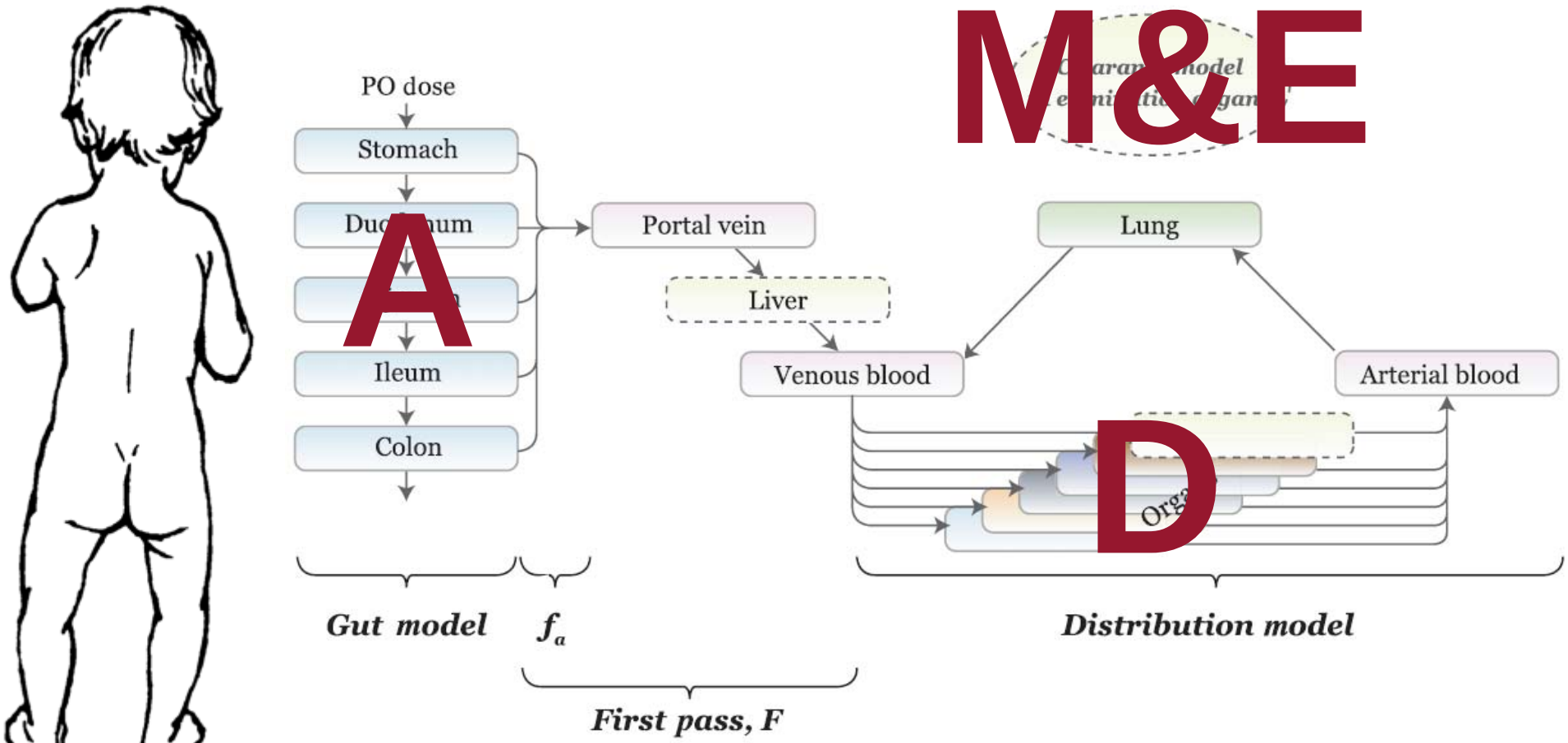
PBPK structure



Absorption

- Models predict bioavailability and rate of absorption

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Absorption

- Physiological models of the GI tract usually based on Advanced Compartmental Absorption and Transit (ACAT) model[1] or continuous flow model[2]

Physiological Inputs	Drug-specific Inputs
Gut size and volume	Solubility
Absorptive surface area	Formulation
Gastric & intestinal pH	Particle/molecular size
Small intestinal transit time	Lipophilicity
Gastric emptying time	Acid/base properties
Enzyme/transporter expression	
Intestinal permeability	

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[1] Agoram et al. 2001. *Adv Drug Deliv Rev*. **50**(S1): S41–S67.
[2] Willmann et al. 2003. *Pharm Res*. 20(11): 1766-71.

Age-dependent physiology

Increase with age

Size and volume

Absorptive SA

Enzyme/transporter expression

Decrease with age

Gastric pH

Gastric emptying time

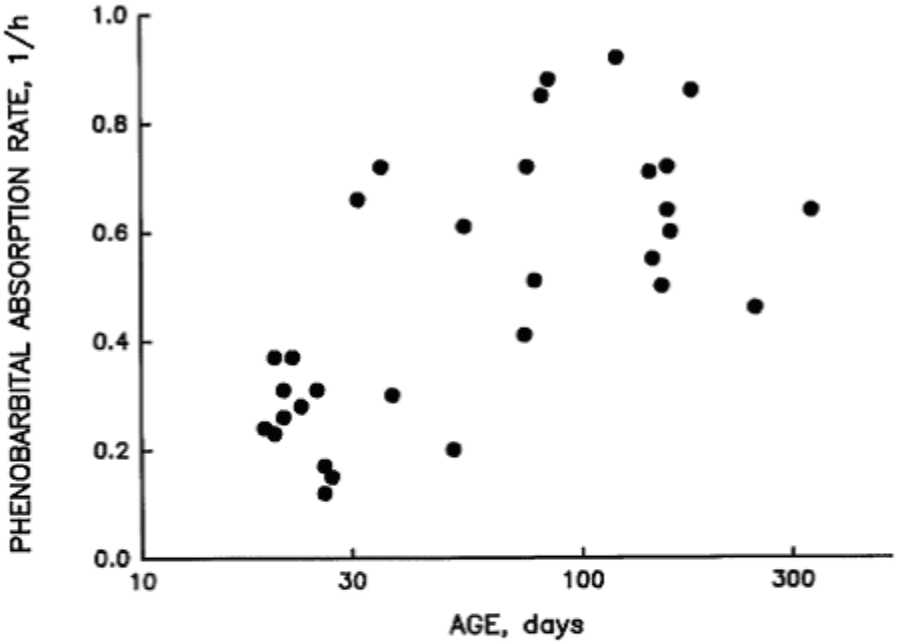
Change with age

Intestinal permeability

(para- to transcellular)

Intestinal fluid contents

(increase in bile acid/salt &



Distribution

- Models predict extent of distribution (V_{ss}), and extent & rate of organ uptake
- Important for defining time to steady state and peak-trough ratio

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Distribution

Physiological Inputs

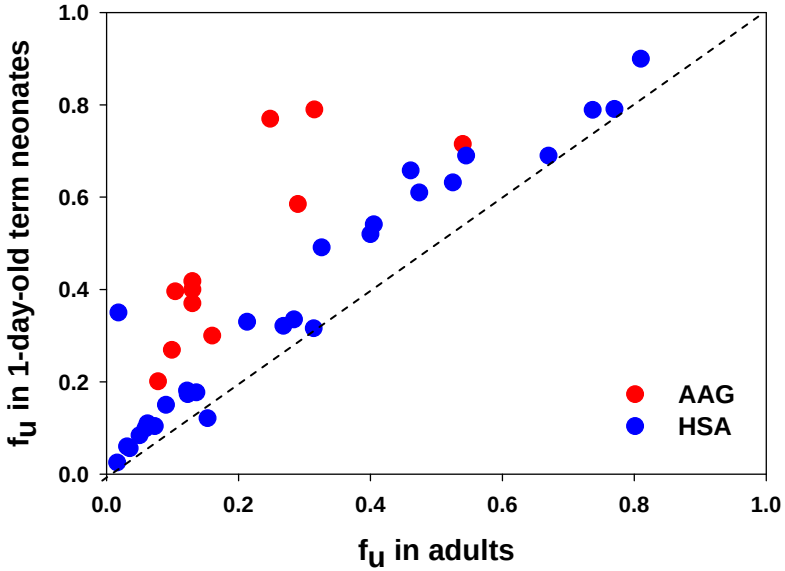
Tissue volumes
Tissue blood flows (Q)
Tissue composition
Transporter abundance

Drug-specific Inputs

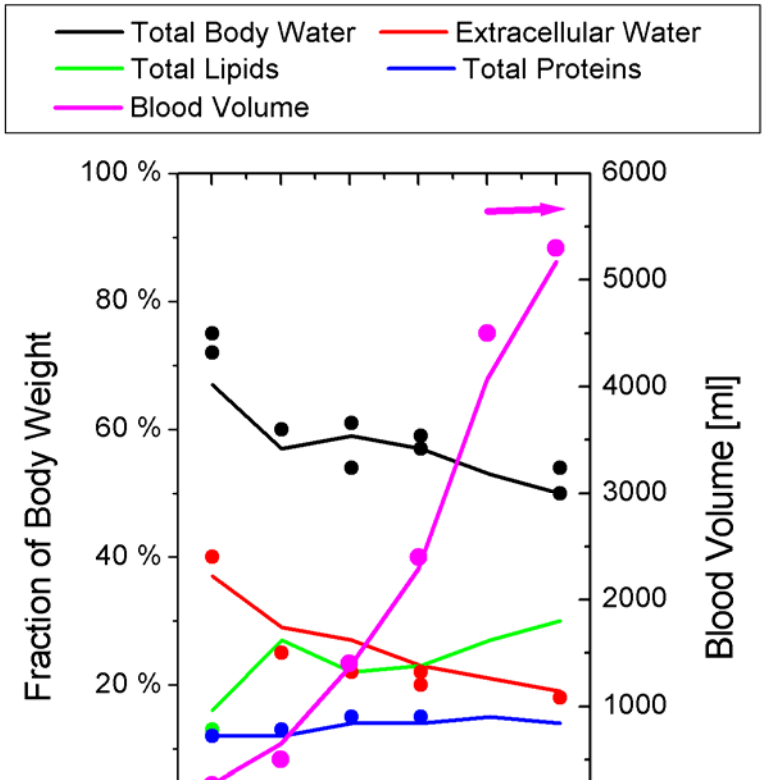
Transporter constants (V_{max}, K_m)
Particle/molecular size
Lipophilicity
Acid/base properties

Tissue: plasma partition coefficients (Kp)
Permeability x surface area (PSA)
Unbound fraction in plasma (fu)

Physiological changes affecting distribution



Observed unbound fraction in plasma in 1-d term neonates compared to adults for a



Clearance

- Models predict age-dependent organ-specific elimination

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Clearance - allometry

$$CL_{child} = CL_{adult}\left(\frac{BW_{child}}{BW_{adult}}\right)^{0.75}$$

Allometric scaling accounts for size differences, not maturity

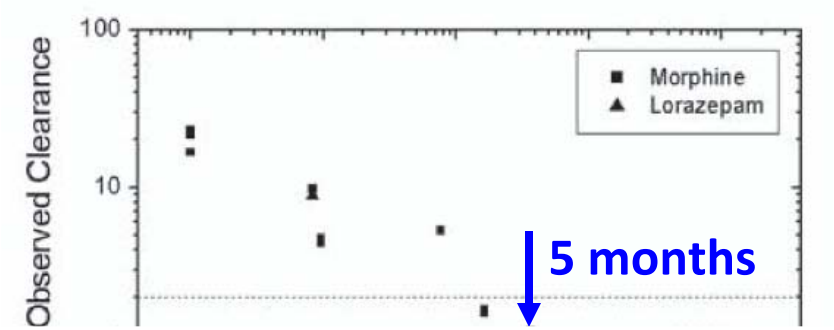
This is a reasonable means of scaling clearance beyond the age at which:

Enzyme activity$_{child}$ ≈ Enzyme activity$_{adult}$

UGT2B7

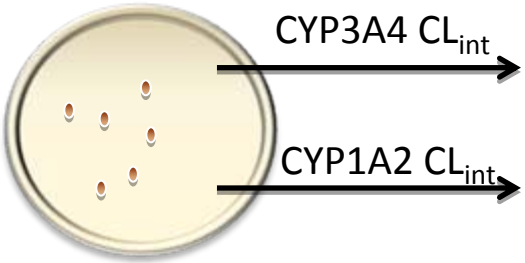
5% of adult activity in term neonates

Close to adult activity at age 3-6 months



Clearance – e.g. hepatic metabolism

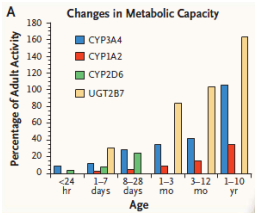
***In vitro* to *in vivo*[1]**



CYP3A4 CL_{int}

CYP1A2 CL_{int}

Relate abundance of isoform *in vitro* to *in vivo* abundance



→

CYP3A4 $CL_{int,child}$

CYP1A2 $CL_{int,child}$

↓

$Q_{liver,child}$, LW_{child}, $f_{u,child}$

↓

$CL_{H,child} = CL_{H,3A4} + CL_{H,1A2}$

***In vivo*$_{adult}$ to *in vivo*$_{child}$[2]**

$CL_{H,3A4} = CL_{total} * f_{m,3A4}$

↓

$CL_{H,child}$

↑

Pitfalls of clearance scaling

Common missing data

1. Pathways and/or fraction of pathway responsible for clearance
2. Age dependence of relevant enzyme activity
3. Role and age dependence of transporter activity

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Prior information available for guiding pediatric dosing

Approved drug for use in adults

1. PK data from adults and from off-label use in children
2. Investigators brochure (maybe)
3. Literature data

Drug candidate undergone human testing

EMEA – mandatory ped. plan prior to first adult submission

FDA – ped. plan prior to drug registration

1. PK data from adults
2. Investigators brochure
3. No data in children

Drug candidate – ped. indication only

1. No human PK data
2. Investigators brochure

IB – animal PK, PK linearity, elimination pathways, enzyme/transporter Km, Vmax or CL_{int} (which may be scaled), potential for DDI, CaCo-2 permeability, protein binding…

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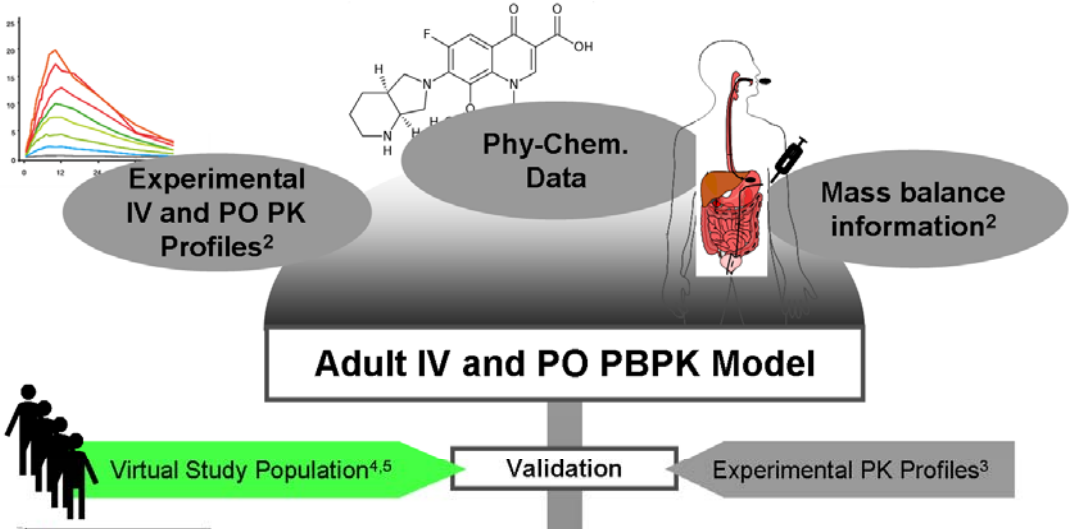
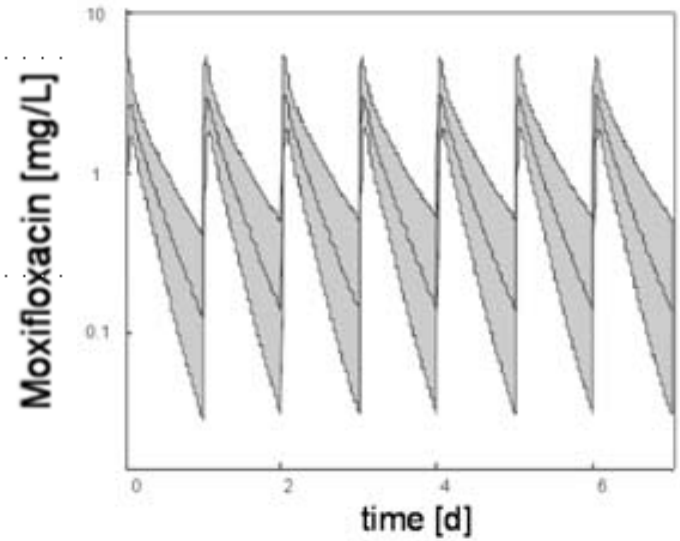
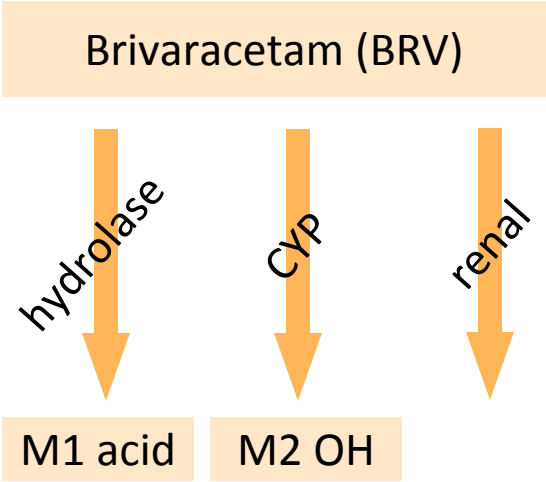




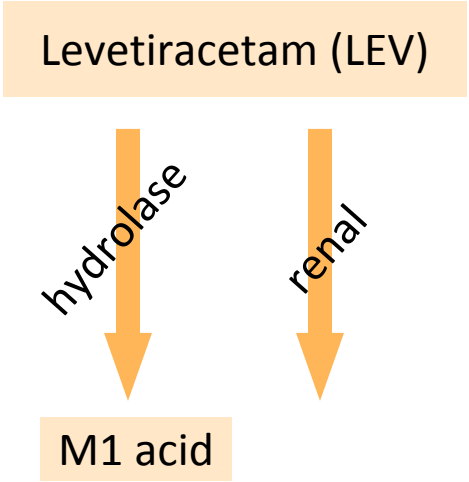
6 month-olds, multiple oral dosing regimen

Pediatric PK prediction

Brivaracetam – in development



Levetiracetam – benchmark drug



Armel Stockis, UCB Pharma, Belgium
Presented at Pediatric Pharmacology Webinar, September 3, 2009

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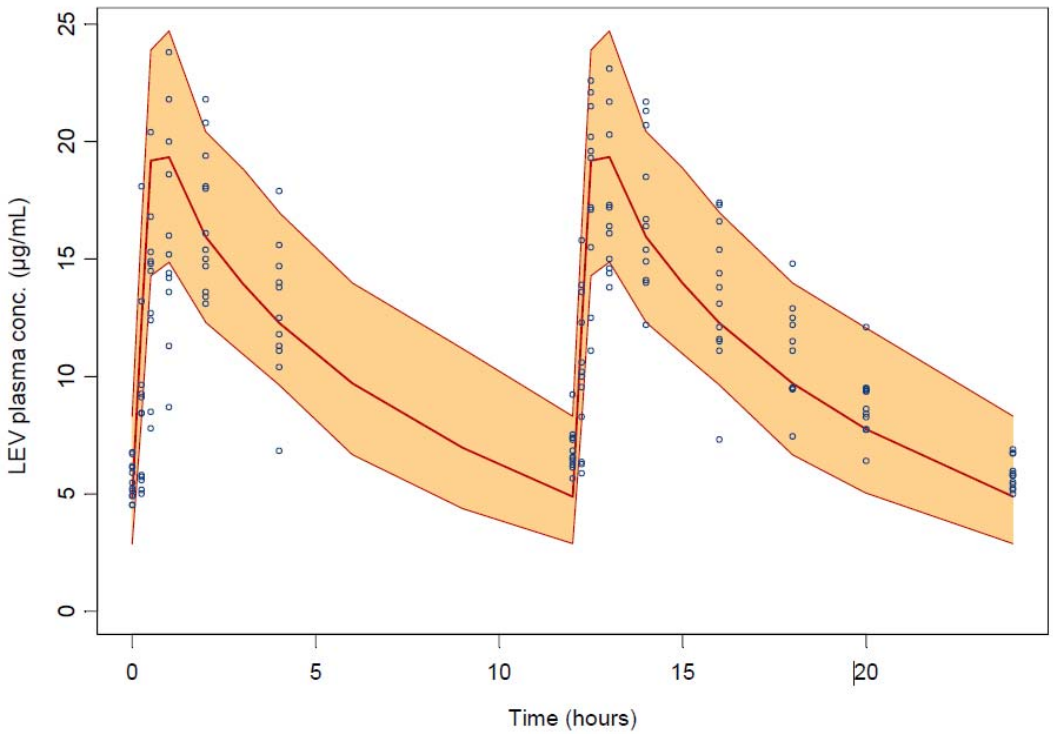
Work-flow

1. Develop adult Levetiracetam Pop-PBPK model



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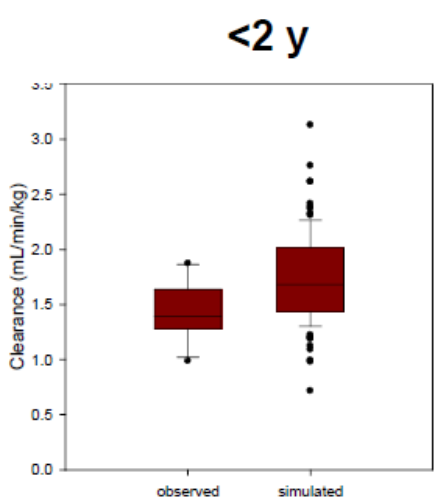
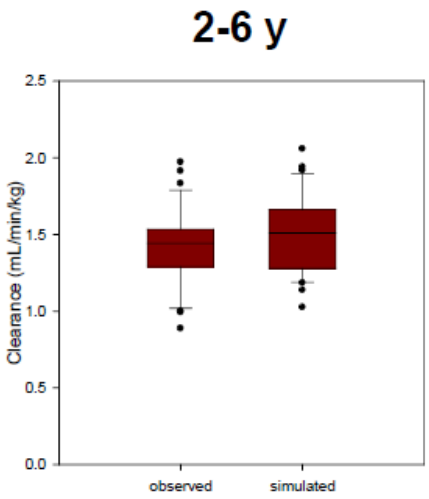
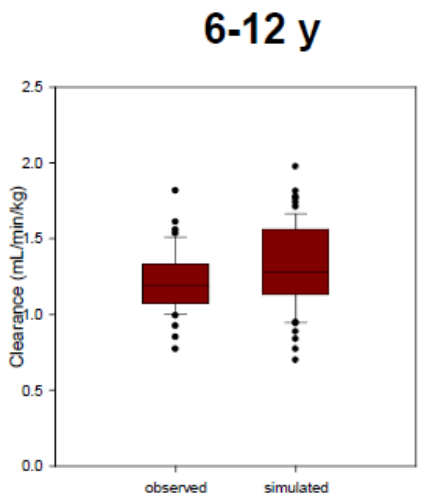
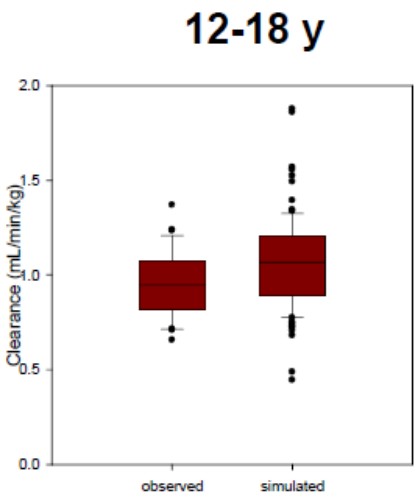
Work-flow

2. Extend adult Levetiracetam PBPK model to children (3 months-18 years)
3. Compare with observations









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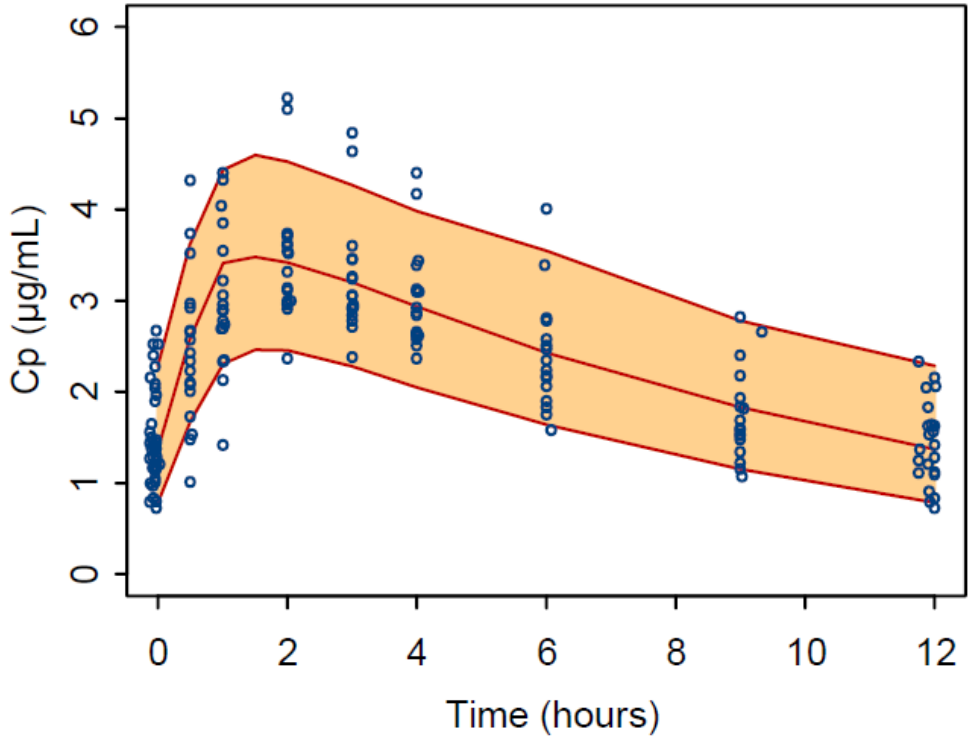
Work-flow

4. Develop adult Brivaracetam Pop-PBPK model



Brochot et al. 2010. Basic & Clinical Pharmacology & Toxicology, 106, 256–262.

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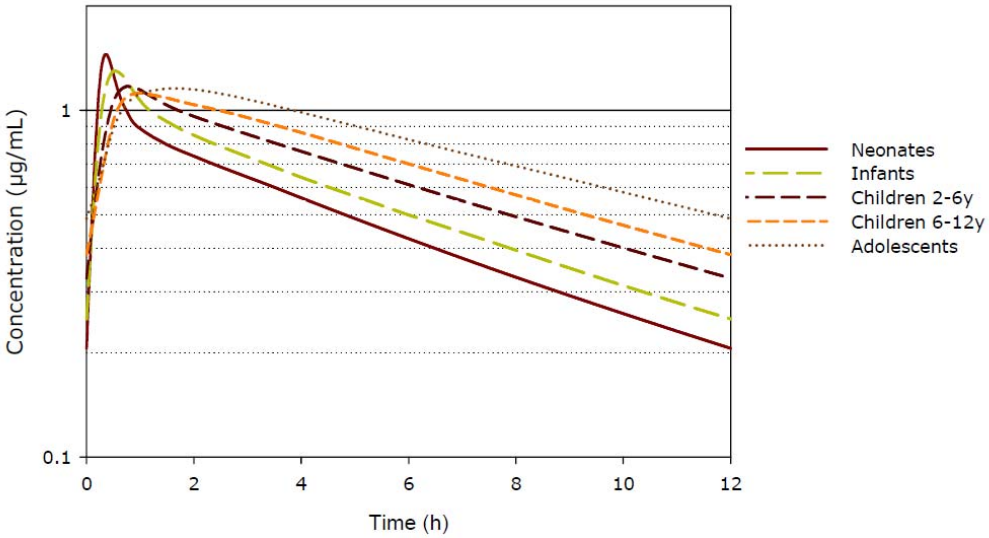
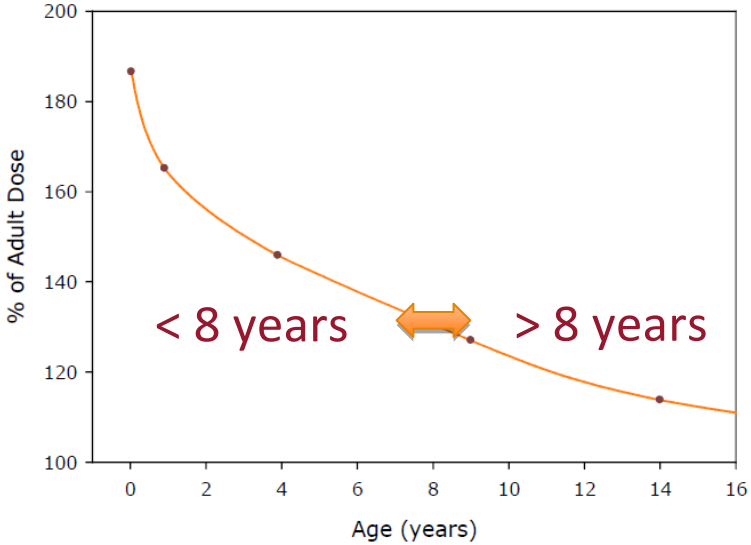
Output

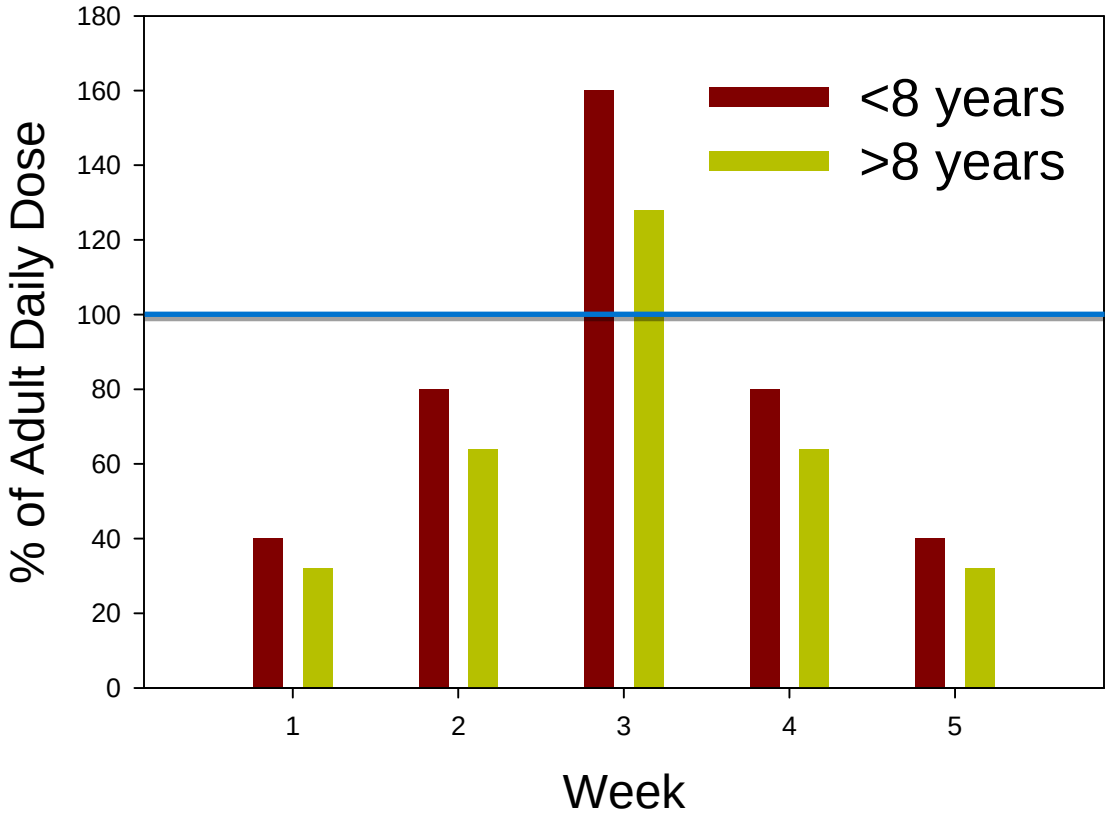
5. Age-dependent PK prediction



6. Dose (mg/kg) prediction to generate same exposure as adults



Trial recruiting as of July 2011 – planned doses for 1 mo-16 yrs (*n*=100)



Primary endpoint: PK
Secondary endpoints: safety, efficacy, compliance

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Are PBPK models being used for pediatric submissions?

- FDA: handful of PBPK examples, majority still using allometry

- EMEA: Pediatric Committee (PDCO) who review pediatric plans *strongly encourages* the use of physiological modeling to address age-dependencies

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Thank you

Andrea Edginton
aedginto@uwaterloo.ca

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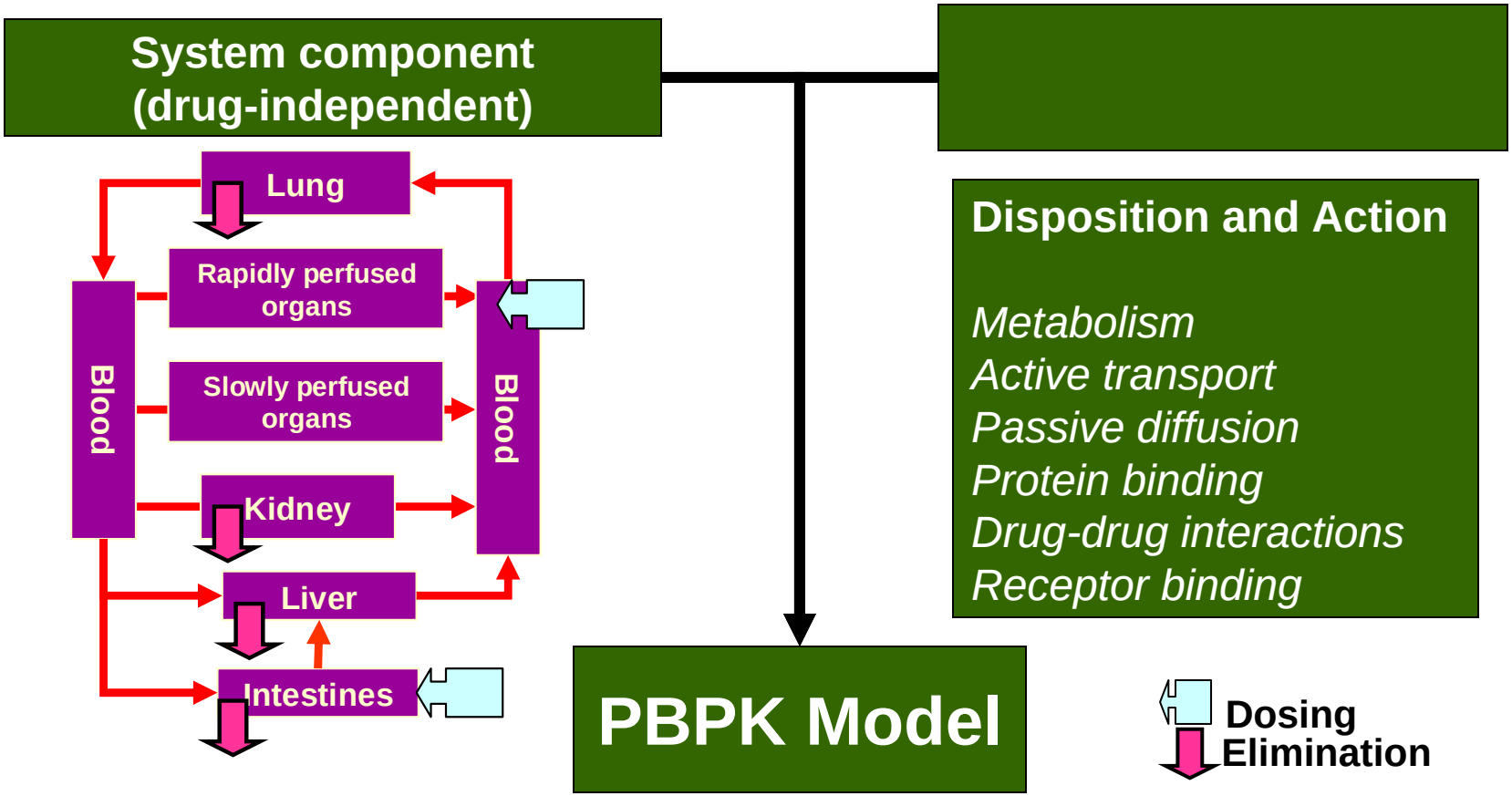
Regulatory Experience In Physiologically-based Pharmacokinetic (PBPK) Models In Pediatric Submissions

Ping Zhao, PhD

Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
Food and Drug Administration

PBPK Model Has System Component And Drug Component



Pediatric PBPK simultaneously evaluates parameters that may change with age

When Is PBPK Needed In Pediatric Drug Development?

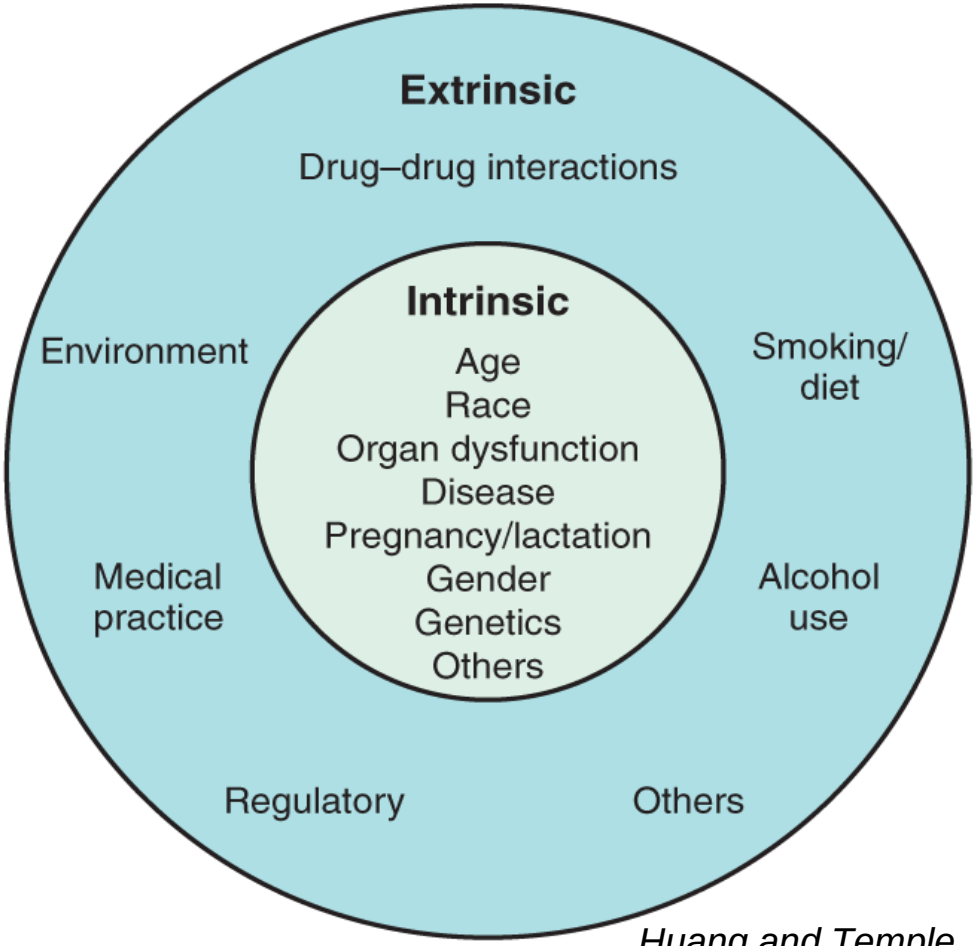
- **Can we predict the PK of an investigational drug in an age group that has NOT been exposed to the drug? (First in Pediatric PK Prediction)**

- **Can we predict whether the effect of specific patient factor(s) on pediatric drug PK be assumed to be the same as that in adults?**

- *Diseases (including organ impairments)*
- *Drug-drug interactions*
- *Pharmacogenetics*

In theory, all situations can be tested clinically. However, ethical and practical issues may limit the numbers of studies that can be conducted in pediatric patients

Patient Factors Routinely Studied In Adults



Huang and Temple, Clin Pharmcol Ther, 2008

Are these same factors important in children?

A. Patient Factors

Intrinsic factors

Extrinsic factors

Huang and Temple, 2008

B. PBPK Model components

System component (drug-independent)

Drug-dependent component

Physiology

Anatomy

Biology

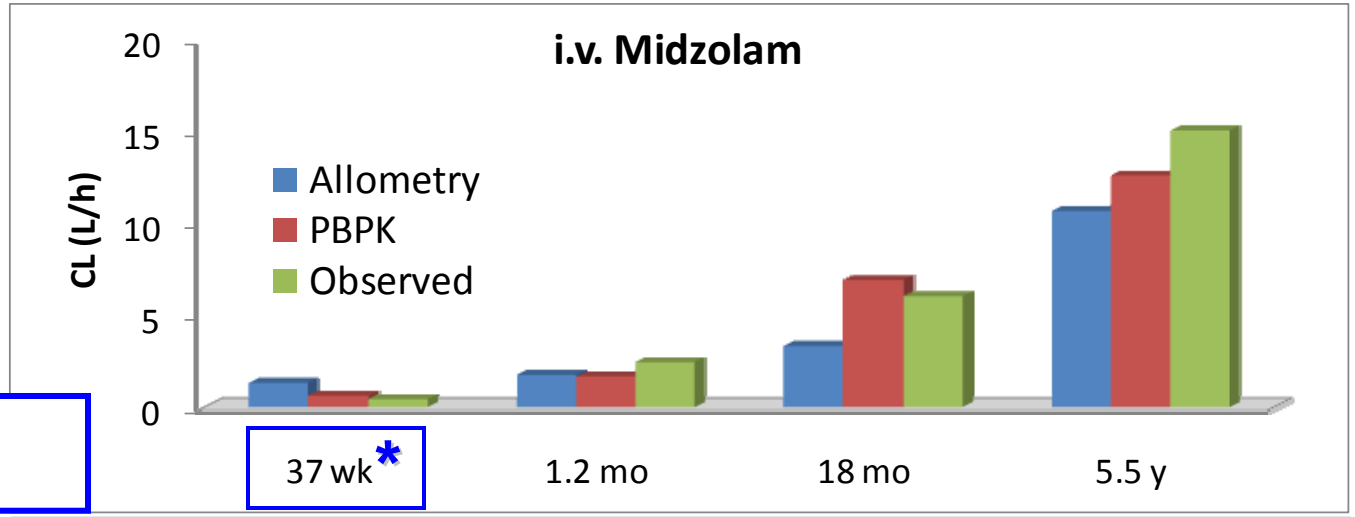
Drug disposition

PBPK Model

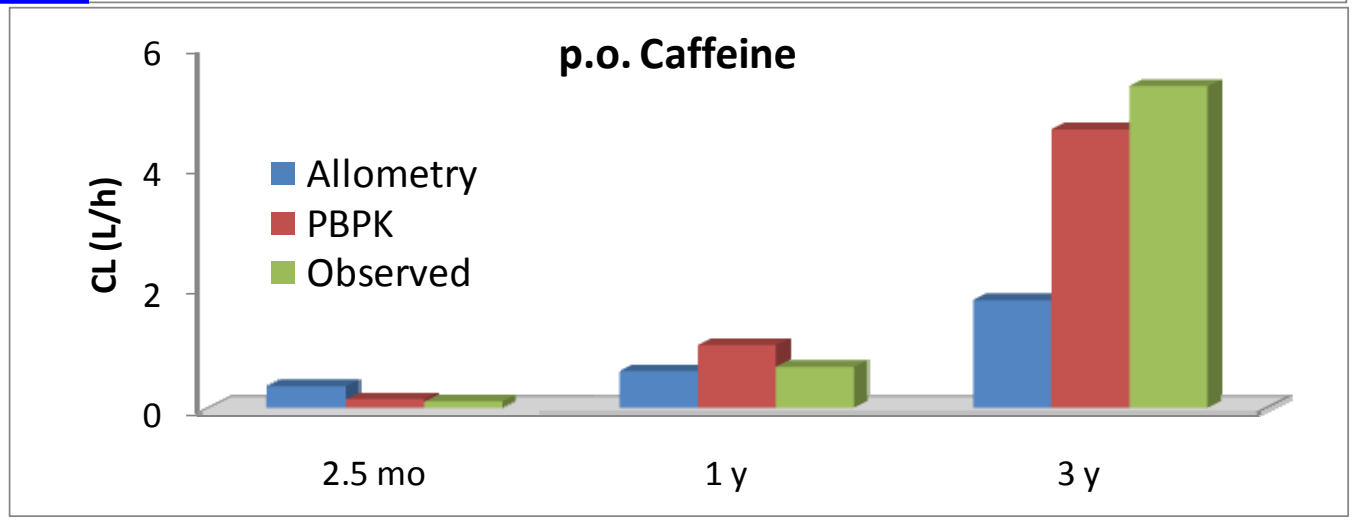
Predict, Learn, Confirm

Adapted from Zhao, et al Clin Pharmacol Ther 2011

Clearance Prediction Needs To Be Tailored To Individual Drug



* Post-conceptio

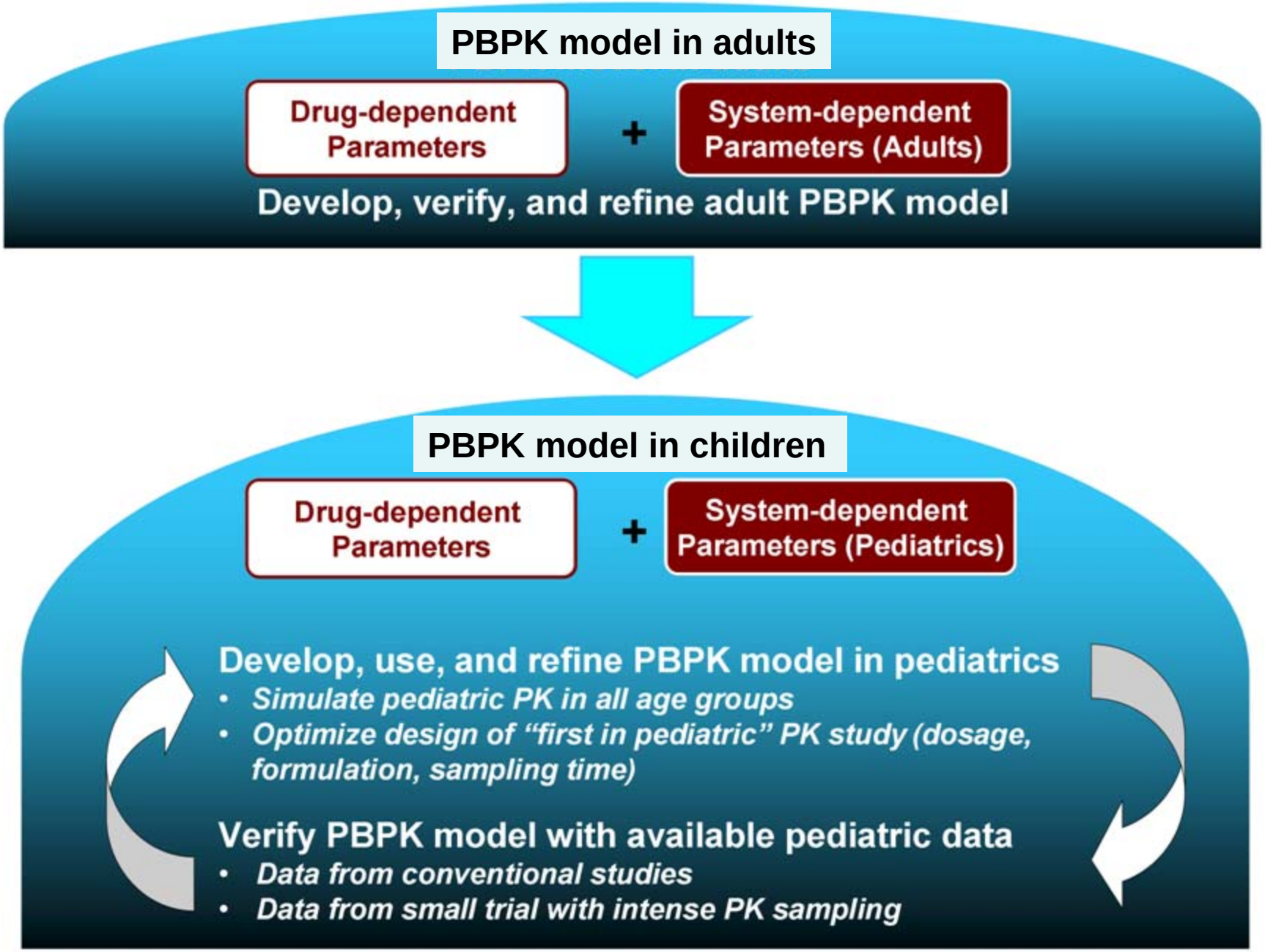


Modified from Johnson et al, Clin Pharmacokinet, 2006

Pediatric Submissions Containing PBPK (2009-2011)

	Drug A	Drug B	Drug C	Drug D	Drug E
Drug-specific data in adult PBPK model					
Integrate Physico-chemical data	√	√	√	√	√
Integrate ADME data	√	√	√	√	√
Pediatric PBPK model development					
Verify adult model using i.v. and p.o. data	√	√	√	√	√
Demonstrate adequacy of adult model	√	√	√	√	√
Justify age-dependent ADME processes	√	√	√	√	√
Application of the pediatric PBPK model					
Plan dedicated "first in pediatric" PK study	√	√		√	
Optimize study design	√	√		√	
Verify model of certain age groups	√		√		
Recommend starting dose by targeting appropriate steady-state exposure	√	√		√	
Inform enzyme ontogeny using bench-mark drug				√	
Facilitate covariate analysis			√		√

Updated from Leong et al, Clin Pharmacol Ther, In Press



Leong et al, Clin Pharmacol Ther, In Press

Summary

- PBPK model building requires knowledge of physiology (system) and drug disposition
- Application of a pediatric PBPK model should use existing adult model and integrate/update with current knowledge in ontogeny of physiological processes
- PBPK model should be continuously updated for enhanced model confidence in predicting unknown clinical situations

A Perspective From A Drug Sponsor on Pediatric Drug Development

Sam Maldonado, MD

Vice-President of Pediatric Drug Development

FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

March 14, 2012

janssen

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Disclaimer

- My remarks are personal and my sole responsibility
- Partly based on my testimony on behalf of PhRMA to the Institute of Medicine Committee on BPCA/PREA in 2011
- The PhRMA testimony to IOM was based on multiple consultations with PhRMA companies and PhRMA staff

BPCA and PREA – Tremendous Success

- AAP: “Pediatricians are now armed with more information about which medicines are safe and effective for pediatric patients and at what doses.”
- Senator Christopher Dodd: “The story of BPCA is one of huge success for children and their families…”

Laws but no Regulation or Guidance

- In spite of unprecedented success, these laws continue to sunset every 5 years
- The lack of regulation and/or current guidance from the FDA makes the applicability of the laws variable and unpredictable
- Every reviewing Division makes its own interpretation of the laws
- Eliminating the sunset clauses will allow the FDA to write regulation and guidance

Early Interactions between FDA and Sponsors

- It is important for FDA and Sponsors to have early interactions on Pediatric Programs
- As the European Pediatric Law has demonstrated, mandating by legislation the timing may not be very efficient
- FDA can regulate the timing of such interactions
- Around the time when the Sponsor is ready to begin phase III studies in adults has been suggested as an appropriate time

Pediatric Programs are Global

- There should be better harmonization between regulatory agencies on timing and scientific requirements for studies in children
- Efficiency would be maximized if there is harmony in the way studies are conducted globally
- It is imperative that countries outside EU and USA participate in “global” drug development

Extrapolation

- ICH E-11 states that if the disease is similar in both adult and children and the effects of the drug are similar, efficacy can be extrapolated from adults to children
- FDA allows appropriate data extrapolation in order to minimize exposure of children to unnecessary experimentation

Appropriate Use of Clinical Pharmacology Tools and Techniques

- Clinical pharmacology studies are key for dose determination
- Modeling and Simulation (M&S) is extremely important in providing a starting point and thereby minimizing trial and error
- In some cases, M&S may be sufficient in determining appropriate dosing information
- Pharmacometric techniques provide useful and reliable instruments that are still underutilized in pediatric drug development

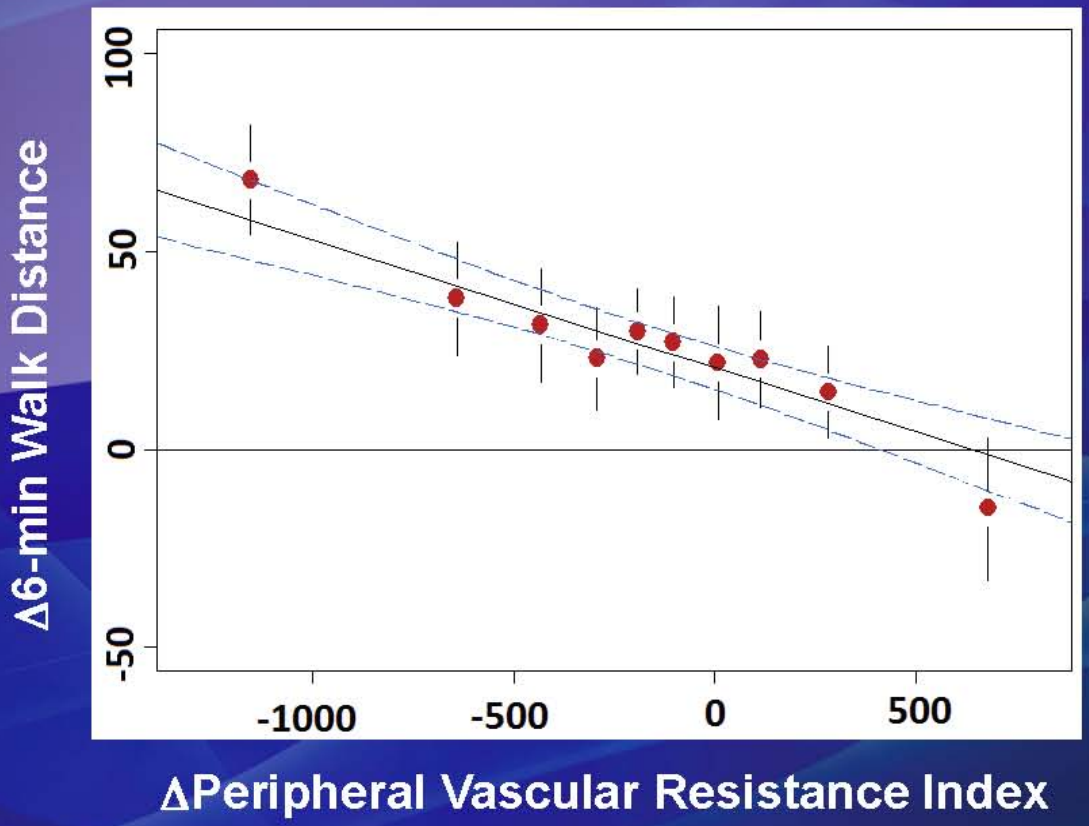
Alternative Endpoints in Pediatric Studies

- Similar or dissimilar adult and pediatric manifestations of the target indication
- Necessary when a pediatric patient cannot reliable perform a procedure
- Surrogate markers may be necessary especially for infants including neonates

Pulmonary Arterial Hypertension Approval Basis for Pediatrics

- Rare disease with a prevalence of about 15 cases per million in adults
- No approved treatment for children
- No suitable measures for assessing effectiveness (6-minute walk distance) for possible approval of drugs for PAH in children

ΔPVRI is Significant Predictor of Δ6MWD in 13 Adult Trials



FDA CRDAC Meeting, July 29, 2010

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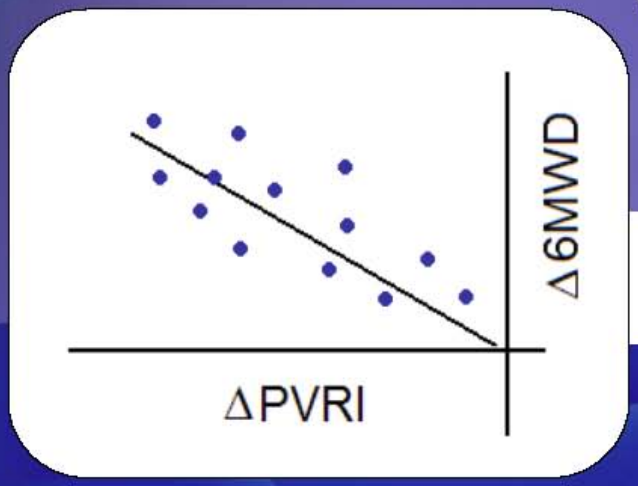
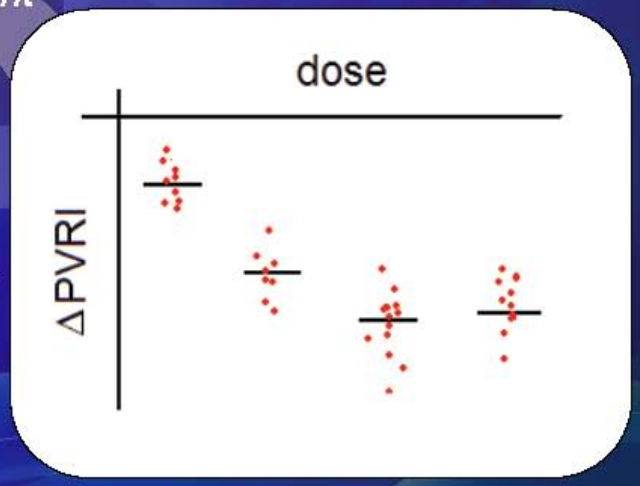
Pulmonary Arterial Hypertension
APPROVAL BASIS FOR PEDIATRICS

Derive dosing based on the desired benefit in exercise capacity





Adults: Establish relationship between ΔPVRI and Δ6MWD to specify target for pediatrics.

Pediatrics: Placebo controlled, dose ranging studies to be performed to achieve different degrees of hemodynamic benefit.

FDA CRDAC Meeting, July 29, 2010

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Conclusion

- Clinical pharmacology studies, including M&S, make pediatric drug development more efficient
- Appropriate extrapolation avoids unnecessary experimentation in children
- Alternative endpoints, including surrogates, should be explored as alternative

“Information that can be obtained in a less vulnerable population should not be obtained in a more vulnerable population”

Steve Spielberg

Committee Questions

Question 1

Should modeling and simulation methods be considered in all pediatric drug development programs? (VOTE)

In addressing this question, please comment on the following: (DISCUSSION)

a) **The gaps in knowledge that might limit the application of modeling and simulation approaches to pediatric drug development programs (e.g., neonates, critically-ill children, specific disease states, biologics/small molecules).**

b) **The barriers and incentives for industry to perform modeling and simulation (M&S) for these programs.**

c) **How regulatory agencies can serve as change agents to foster M&S in these programs.**

d) **The scope of guidelines developed by FDA for the efficient use of modeling and simulation in these programs.**

Question 2

The FDA Office of Clinical Pharmacology has proposed a framework to derive sample size in pediatric pharmacokinetic (PK) studies to ensure the quality of pediatric PK data. Is the quality standard based on this framework reasonable? (VOTE)

a) **Please discuss other available methods to ensure precise estimation of important PK parameters. (DISCUSSION)**

Question 3

Can dose(s) for the adolescent (>12 years) population be derived using adult data without the need for a dedicated PK study? (VOTE)

In addressing this question, please comment on the following: (DISCUSSION)

a) **Whether sparse PK sampling from this population should be collected during safety/efficacy studies if there is no dedicated PK study.**

b) **Whether the drug would then be given as the adult dose or scaled. If scaled, comment on whether allometric scaling or other approaches should be used.**

Question 4

Should the routine use of PBPK in pediatric drug development, when possible, be recommended at the present time? (VOTE)

In addressing this question, please discuss the following: (DISCUSSION)

a) If PBPK modeling can be useful in pediatric drug development for:

- **(1) identifying the dose for first-in-pediatric studies, and**
- **(2) pediatric clinical trial design (e.g. sampling times)**

b) If the potential for a drug-drug interaction can be reasonably modeled from adult data, if available, for all pediatric age groups.

c) If dosage adjustments for renal and hepatic impairment in pediatric patients could be modeled from adult data using PBPK.