



## NIH (409I) Best Pharmaceuticals for Children Act: Pediatric Trials Network (PTN)

“Creating an infrastructure for investigators to conduct trials that improve pediatric labeling and child health.”

–Sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

–Success defined by improving dosing, safety information, labeling, and ultimately child health

–Focus on off-patent therapeutics

- For more information on the BPCA Program visit:  
<https://www.nichd.nih.gov/research/supported/bpca>
- For more information on the Pediatric Trials Network visit:  
<https://pediatrictrials.org/>

# FOOD AND DRUG ADMINISTRATION (FDA) AND MARLAND CENTER FOR EXCELLENCE IN REGULATORY SCIENCE INNOVATION (M-CERSI) PUBLIC WORKSHOP:

## PEDIATRIC DOSE SELECTION

- October 22, 2020 10:00 a.m. to 3:00 p.m.
- October 23, 2020 10:00 a.m. to 12:35 p.m.



# What information does the pediatric clinician need, and how is dosage “drift” over time handled clinically?

Jill A. Morgan, PharmD, BCPS, BCPPS, FNAP

Professor and Chair

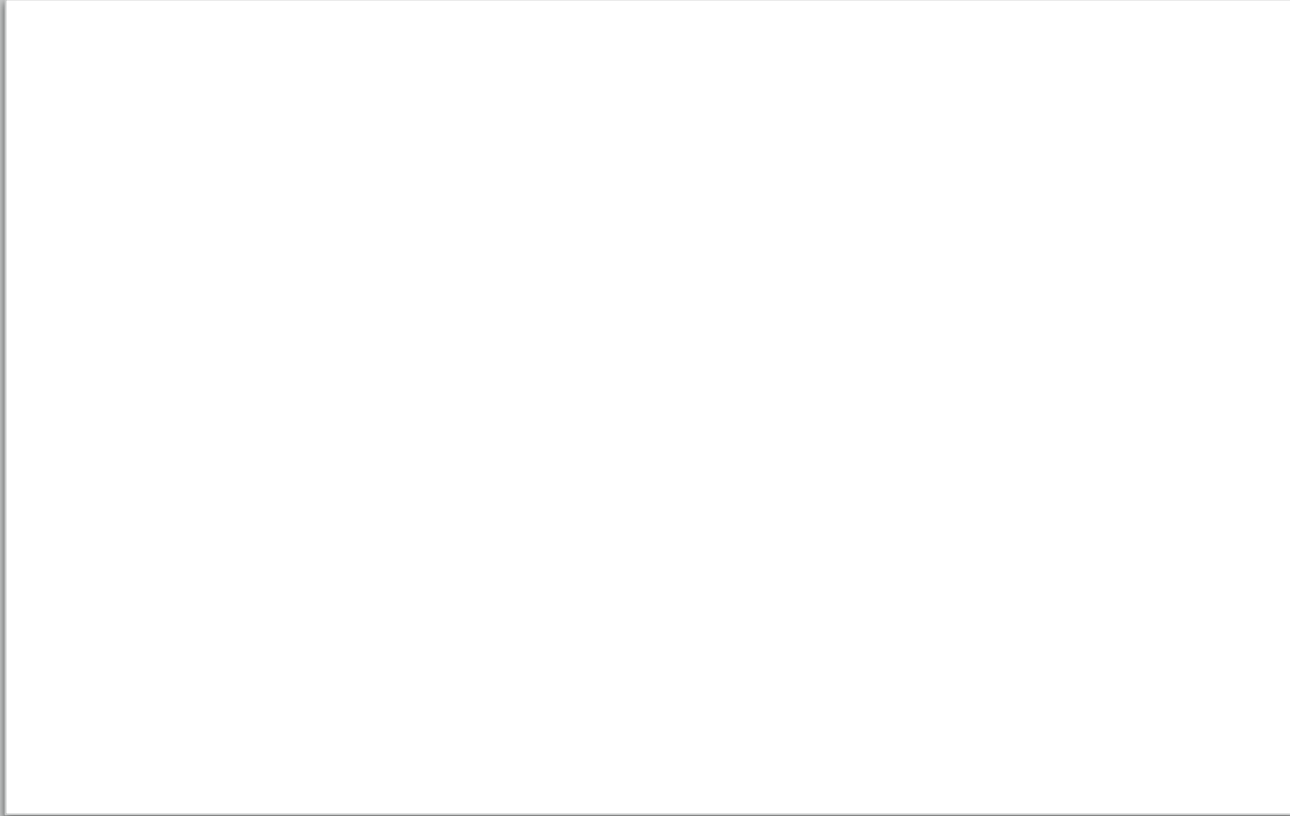
CERSI Pediatric Dose Selection Meeting

October 2020



# Disclosures

- I have no financial disclosures.
- I will discuss some off-label information.



# Meet Lucy in 1997



ONCE  
UPON  
A  
TIME

*Long, long  
ago, right?*



# Off-Label Medication Use in Pediatrics

## Ambulatory Care

- 2006-2015 in US
- 41.2 million orders/year
- Higher in adolescents

## Inpatient Care

- 2014, 76 medications reviewed
- 28.1%
- Higher rates in neonates and infants

## Systemic Review

- 2007-2017 (31 studies included)
- 3.2%-95%
- Reasons: 48.3% dose

# How much Linzess should a 9-year old 72 kg autistic patient receive?

- **WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS**
- LINZESS is contraindicated in patients less than 6 years of age. In nonclinical studies in neonatal mice, administration of a single, clinically relevant adult oral dose of linaclotide caused deaths due to dehydration. **Use of LINZESS should be avoided in patients 6 years to less than 18 years of age.** The safety and effectiveness of LINZESS have not been established in patients less than 18 years of age.





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SCHOOL OF PHARMACY



*ClinicalTrials.gov*

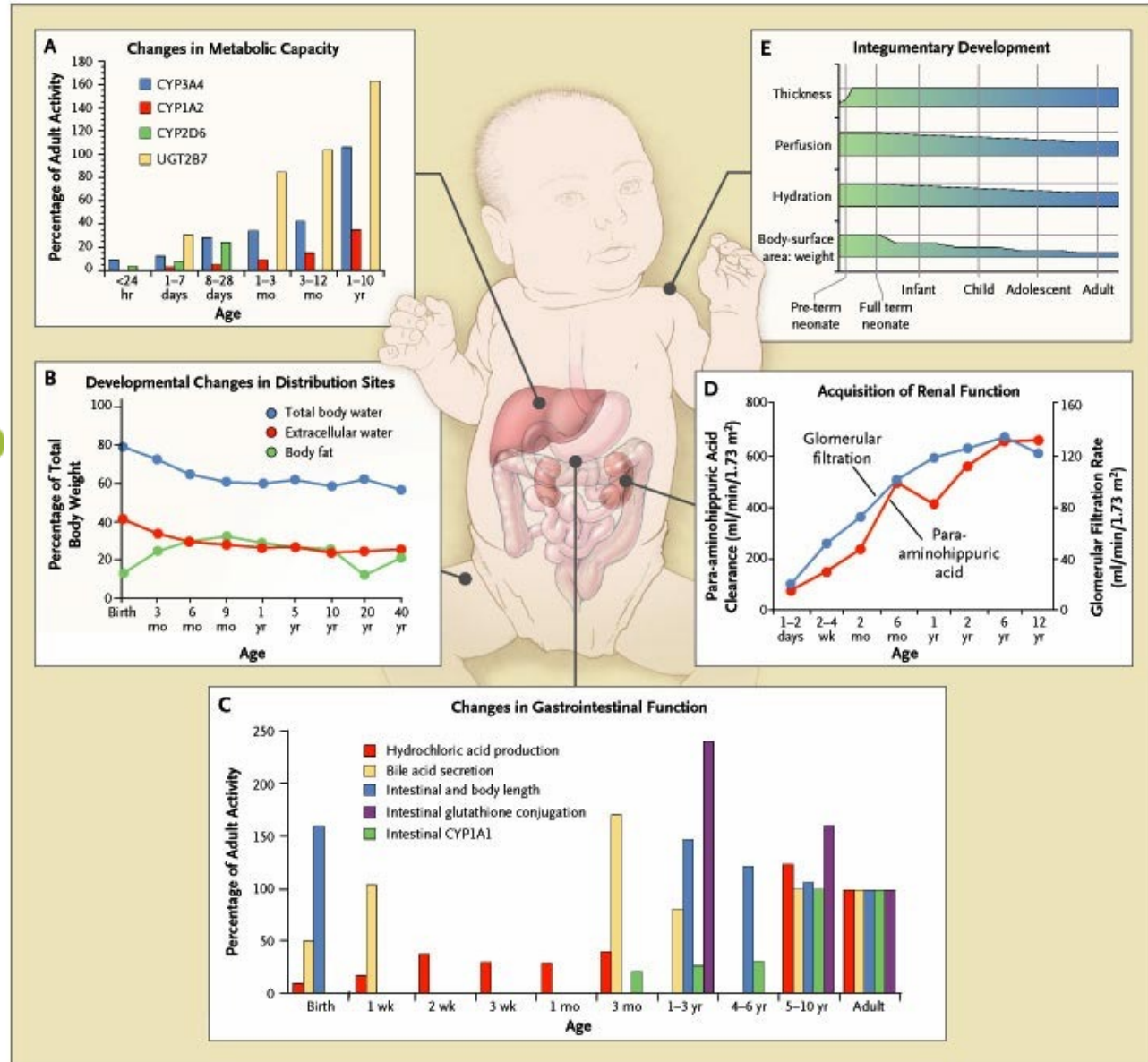
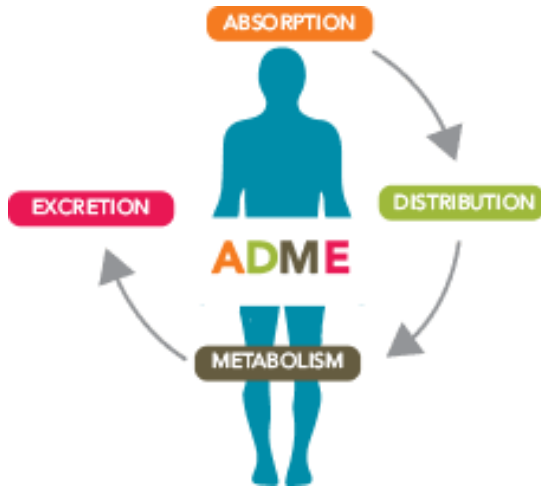
# **A Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to Children Ages 7-17 Years, With Irritable Bowel Syndrome With Constipation (LIN-MD-63)**

Included children 6-17 years

Doses studied – 18mg, 36mg, 72 mg, and 145mg

Study completed August 30, 2019





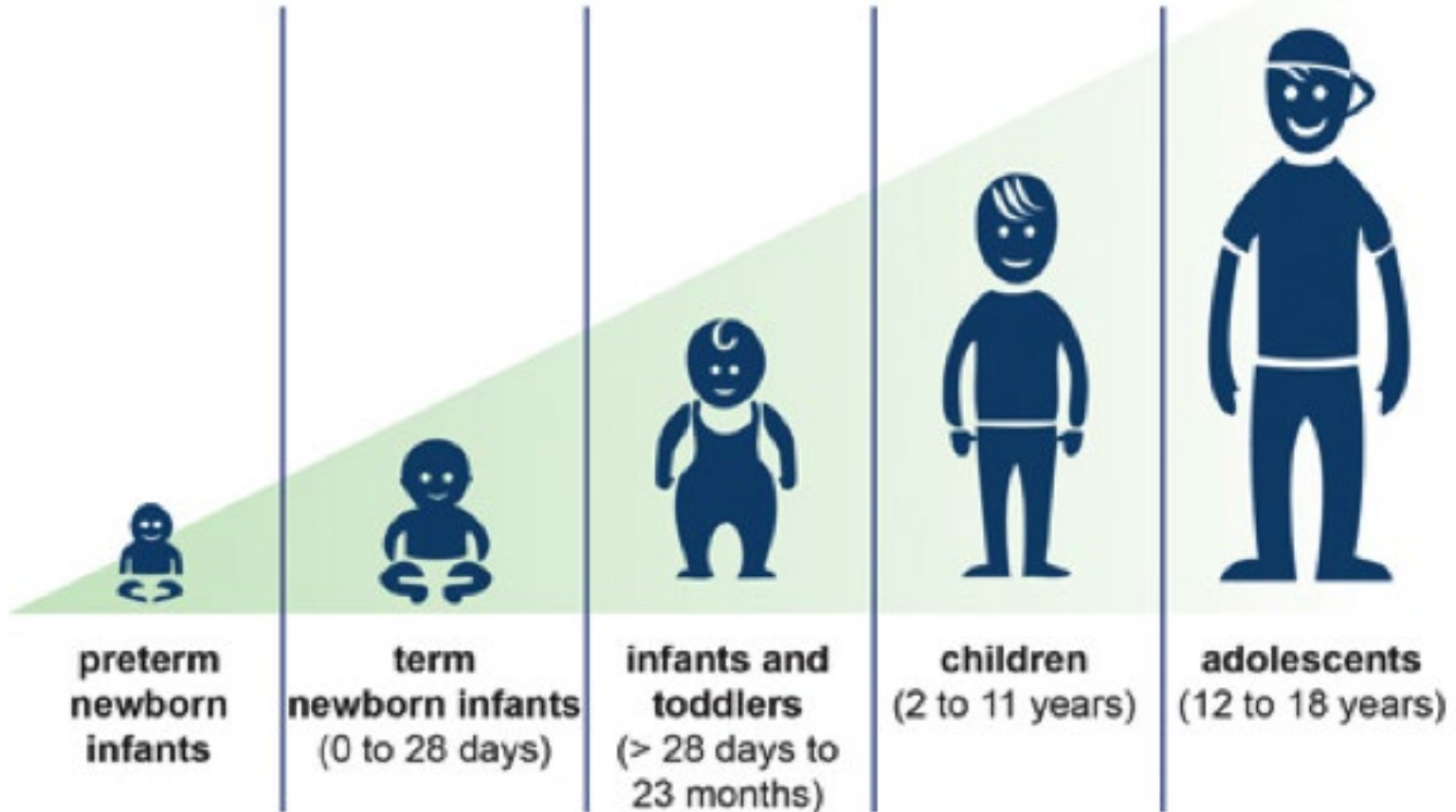
What  
information  
does a  
clinical  
pharmacist  
need?



I WANT  
IT ALL



# Can I have a dose for each?



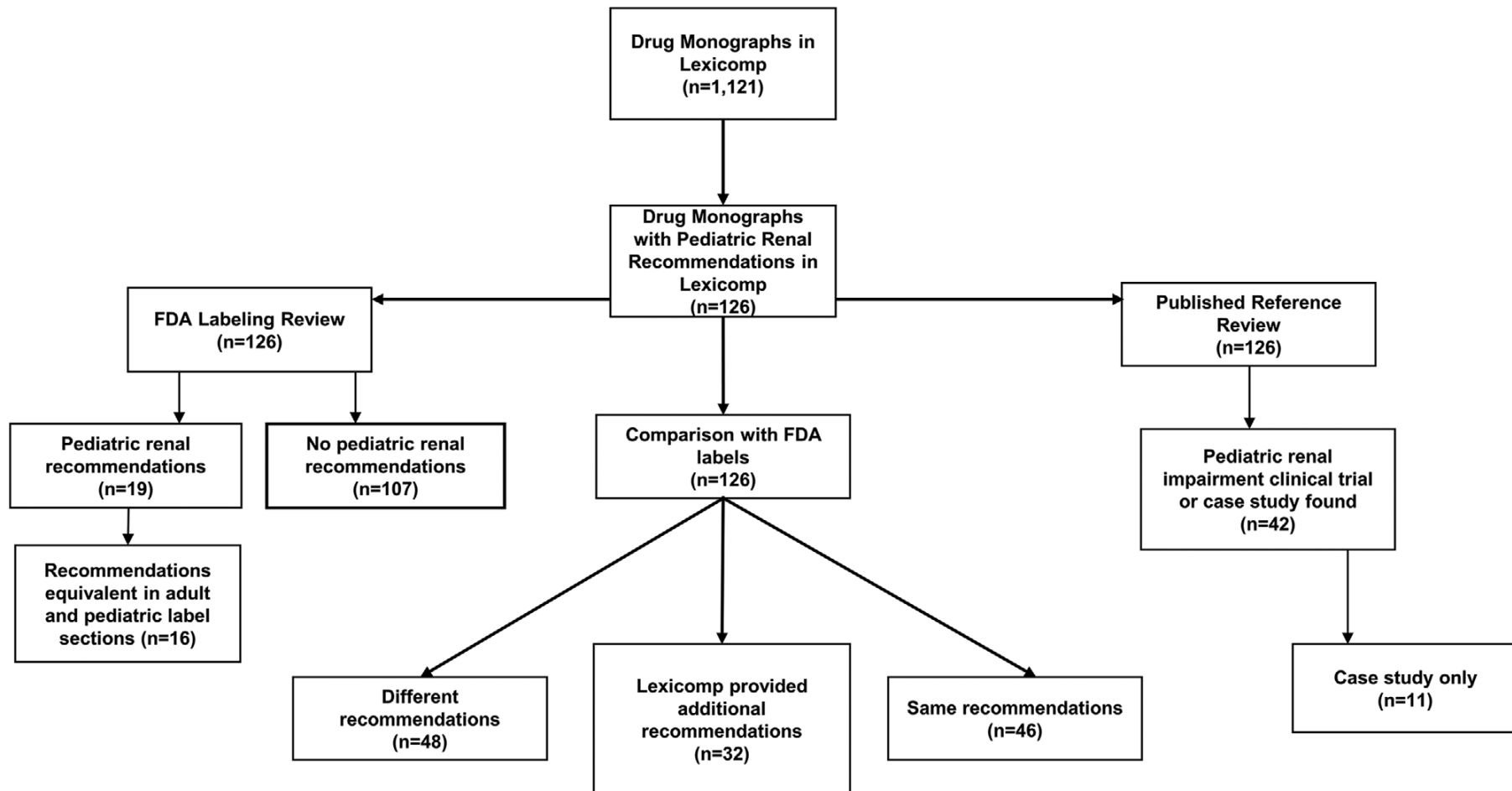


# Data

- Dosing information
  - What is the maximum for efficacy?
- Pharmacokinetic and dynamic data
  - Absorption site (G-tubes and J-tubes)
  - Onset of action time
  - Distribution sites (antibiotics)
  - Half-life
  - Elimination data
    - Renal adjustments
    - CRRT adjustments
    - Hemo/PD Dialysis
- Pharmacogenomic data
  - Who needs a test and how should doses be adjusted with results?



# Dosing in Renal Dysfunction





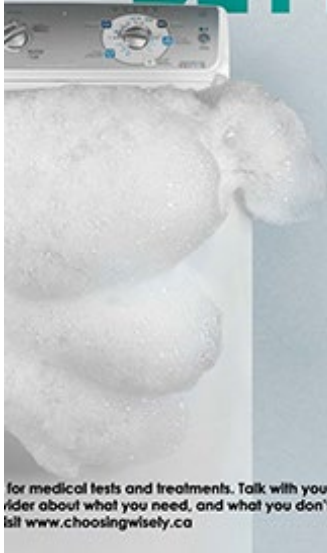
# 2002-2018 New Drug Indications

389 pediatric study requests from  
FDA (141 BPCA and 248 PREA)

By December 2018 <  
1/3 of requests  
completed

64%

MORE IS  
**NOT**  
ALWAYS  
**BETTER**



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Choosing  
Wisely  
Canada

Dealing with  
Dosage Drifts  
as Clinician -  
Ask Why and  
Do a Study



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# Evaluation of polyethylene glycol (PEG) for use in pediatric bowel clean out and maintenance of chronic constipation

Amy Kruger Howard, PharmD  
University of Maryland School of Pharmacy  
Pediatric Pharmacy Fellow  
May 1, 2020





# Doses for PEG

## Functional Constipation

▪ 1 - 1.5 g/kg/day for home cleanout

0.2 - 0.8 g/kg/day for maintenance therapy

## Colonoscopy Prep

4 g/kg/day for 1-day cleanout

▪ 2 g/kg/day for 2-day cleanout

## UMMS Study

N=78

Median weight-based dose was 4.58g/kg/day (IQR 3.02,5.8) 1-day cleanout

Median weight-based dose was 4.6g/kg/day (IQR 3.95,5.56) 2-day cleanout

Median maintenance dose was 0.74g/kg/day



Increase compliance with FDA study requests  
Study database for pediatrics for clinicians  
Promote multiple institution data sharing /research (use EPIC?)



# What information does the pediatric clinician need, and how is dosage “drift” over time handled clinically?

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CERSI Pediatric Dose Selection Meeting

October 2020



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Review of the Adult Dose Selection EMA Workshop & application to paediatrics

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Efthymios Manolis, EMA

Oct. 22-23, 2020, Pediatric Dose Selection

*Disclaimer: The views expressed in this presentation are the personal views of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.*

An agency of the European Union





## Key learning from EMA dose selection workshop

Dose selection is a shared risk

Dose Exposure Response (DER) is a key component of the development and evaluation of medicinal products. Especially for children, elderly and ethnic groups this is the mainstay of drug development

Traditional pairwise comparisons in Ph2 are suboptimal

Dose ranging studies should be designed for estimating dose response characteristics. As many as 4-7 active doses across a >10-fold range

Mathematical, statistical and pharmacological **methodologies** to characterise DER and optimal dose selection are scientifically well developed, available for application and welcomed by regulators



## Dose selection toolbox

### **Data analysis**

Quantitative Systems  
pharmacology

Modelling and Simulation

MCP-Mod

Empirical regression models

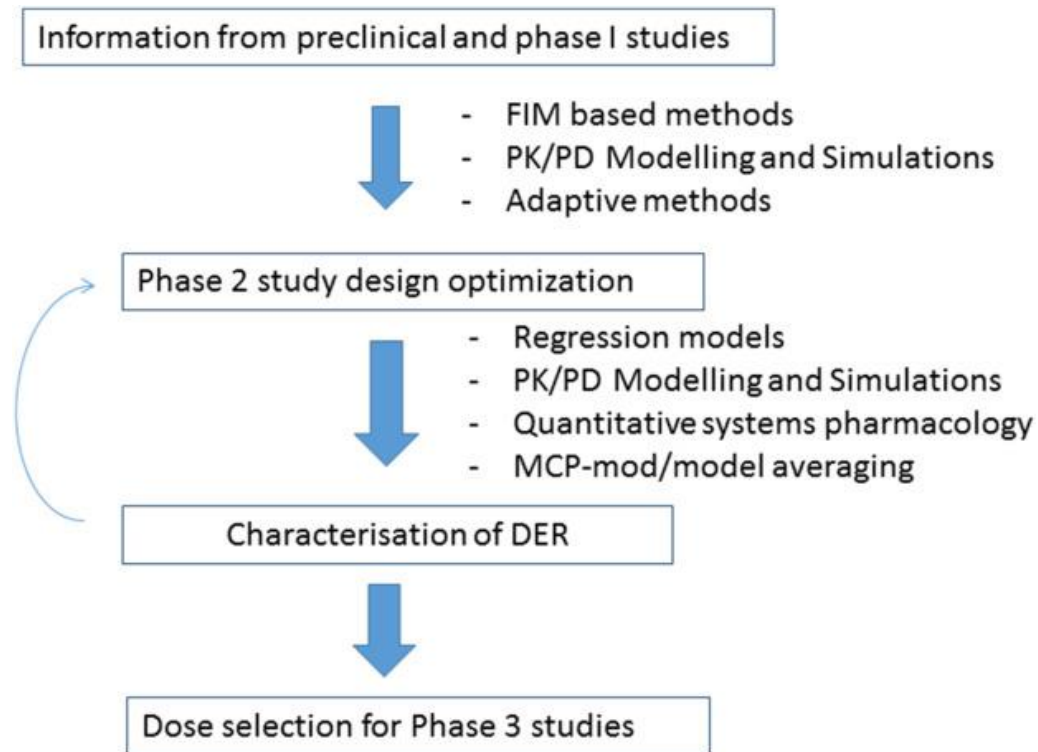
Model averaging

### **Study design optimization**

Fisher information matrix  
(FIM)-based methods

Clinical trial simulations

Adaptive studies





## Dose selection toolbox in children

Same tools, **similar** objectives

Most of the times data in adults are available:

- Phase 1
- Phase 2 dose ranging studies
- Efficacy and safety studies

*or/and off label paediatric use*

Methods focus shifts to:

Reduce and Mitigate uncertainty *from*

Disease, growth and maturation, formulations effects

⇒ Bridging to the DER information in adults







## Dose selection in children under the assumption of similar ER with adults

Objective: Define a dose that matches the exposure considered as efficacious and safe in adults

Prerequisite: exposure metric linked to efficacy and safety in adults

DER characterisation in adults key, both for definition of exposure metrics but also for the acceptance criteria

No dose ranging studies in children are needed

No possibility to check the assumption of ER similarity on the basis of the data generated in children



## Dose selection in children (assuming similar ER with adults)

Use Pop PK model established in adults including allometry to predict matching exposure and associated dose in different paediatric age groups

Often useful to use fixed allometric exponents

Include maturation functions for younger children

PBPK model predictions useful, but if they are used in lieu of clinical data they should be qualified

Iterative circles of learning and confirming as moving down to younger age groups to be weighted against drug availability in children and risk of off-label use



## Dose selection in children (cannot assume similar ER with adults)

Dose ranging studies in children needed in theory to define DER

Alternative, PK/PD modelling to select a single dose in children predicting potential changes in PK/PD due to growth and maturation

Prerequisite is the availability of a PD marker that is predictive of clinical response and that systems data are available to account for effects of maturation and growth in the specific pharmacological pathway

Requirement for a clinical trial in children to confirm benefit risk, model assumptions and the suitability of dose



## Dose selection in children (special attention)

Neonates, dose adjustments and TDM should be considered

Formulation effects



# Conclusions



CARTOONSTOCK  
Search ID: pknn805

Thank you!

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## Useful Links

**EMA dose finding workshop 2014** <https://www.ema.europa.eu/en/events/european-medicines-agencyeuropean-federation-pharmaceutical-industries-associations-workshop-0>

**FT Musuamba et al, CPT 2017** <https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1002/psp4.12196>

**EMA M&S Q&As** <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers#paediatrics-section>

**EMA Scientific advice and protocol assistance** <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance>

### **Qualification of novel methodologies for medicine development**

<https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development-0>

# Review of the Methods Used for Dose Selection in US Pediatric Drug Development Programs

Gilbert J. Burckart, Pharm.D.  
Associate Director for Pediatrics  
Office of Clinical Pharmacology  
OTS, CDER, FDA

Disclaimer: The comments and concepts presented are those of the speaker and should not necessarily be interpreted as the position of the US FDA

# Objectives

- Review traditional methods of pediatric dosing and allometric scaling
- Discuss the methods used in pediatric submissions to the FDA



# Classical Pediatric Dosing Formulas

## – Weight-based

- Clark's Rule ( $\text{wt [lbs]} \times \text{adult dose} / 150$ )
- Salisbury Rule (adjustments for weights  $>$  and  $<$  30 kg.)

## – Age-based

- Fried's Rule 0-24 months ( $\text{age [mos]} \times \text{adult dose} / 150$ )
- Young's Rule 2-12 yrs ( $(\text{age [yrs]} / \text{age} + 12) \times \text{adult dose}$ )

# Allometric Scaling

- The term “allometry” was coined in 1936, as a means of inter and intra-species scaling; where:  $Y = bM^k$
- Y is the physiologic parameter, M is the body mass, and b and k are constants;
- For pediatric dosing, this usually converts to:

$$\text{Pediatric dose} = \left( \frac{\text{weight (kg)}}{70} \right)^{0.75} \times \text{adult dose}$$

# The Science of Allometric Scaling

- The 0.75 exponent has been the source of considerable discussion;
  - Dr. Iftekhar Mahmood (formerly of CBER) has discussed this extensively (see *J Pharm Sci* 2010; 99:2927-2933)
- The 0.75 exponent is supposed to represent clearance, and is derived from basal metabolic rate;
  - The two terms are not necessarily related, and BMR changes developmentally.
- Dr. Mahmood and others support using allometric exponents optimized using available drug-specific clinical data.
  - Requires adult data, which is commonly available in drug development programs.

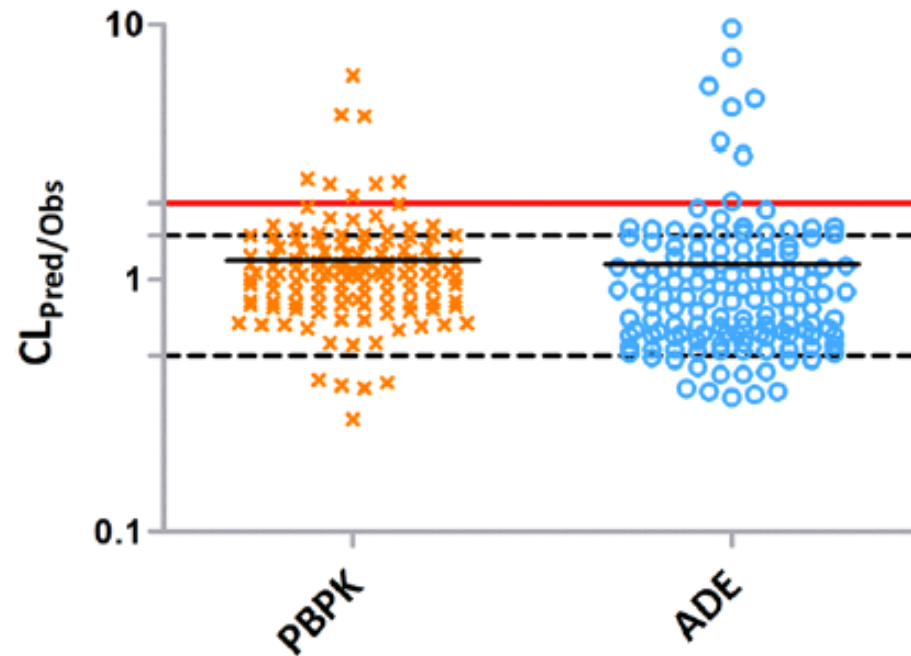
# Application of Allometry in Pediatric Drug Development

- Can be used to predict initial pediatric doses;
  - Usually supports >2 yrs of age, but adjustment to a multistep model may allow predictions down to birth (*J Clin Pharm* 2018; 58: 877-884)
- May also be useful for predictions in:
  - Pediatric obese population (*Clin Pharmacokinet* 2012;51:527)
  - Pediatric monoclonal antibodies (*J Clin Pharm* 2020; doi 10.1002/jcph.1677)
  - Pediatric drug-drug interactions (*Drugs R D* 2020;20:47)
  - Extremely low to low birth weight infants (*Eur J Drug Metab Pharmacokinet* 2017; 42:601-610)

# Allometric Scaling and PBPK

ADE= age dependent exponents. 1.2 for preterm and 1.1 for term neonates for age 0-3 months, and 1.0, 0.9, and 0.75 for >3 months-2 years, >2-5 years, and >5 years, respectively.

Mahmood I, Tegenge MA.  
J. Clin. Pharm. 2019; 59:189



**Figure 3.** The ratio of predicted (Pred) to observed (Obs) clearance values (CL) for children  $\leq 2$  years old. The broken lines denote prediction within 0.5- to 1.5-fold, and dark solid line shows the mean value for the fold error. The red solid line indicates the 2-fold prediction range. ADE indicates age-dependent exponent; BW, body weight; PBPK, physiologically based pharmacokinetic method.

# Pediatric Dosing Project

- So what strategies were used in pediatric submissions to the US FDA, and is there an opportunity to see if there can be a “structured approach”?
- Review of pediatric submissions under FDASIA (2012-present) initially using only publicly available information.
- Headed by Dr. Frank Green, ORISE fellow

# Components of Pediatric Dose Selection



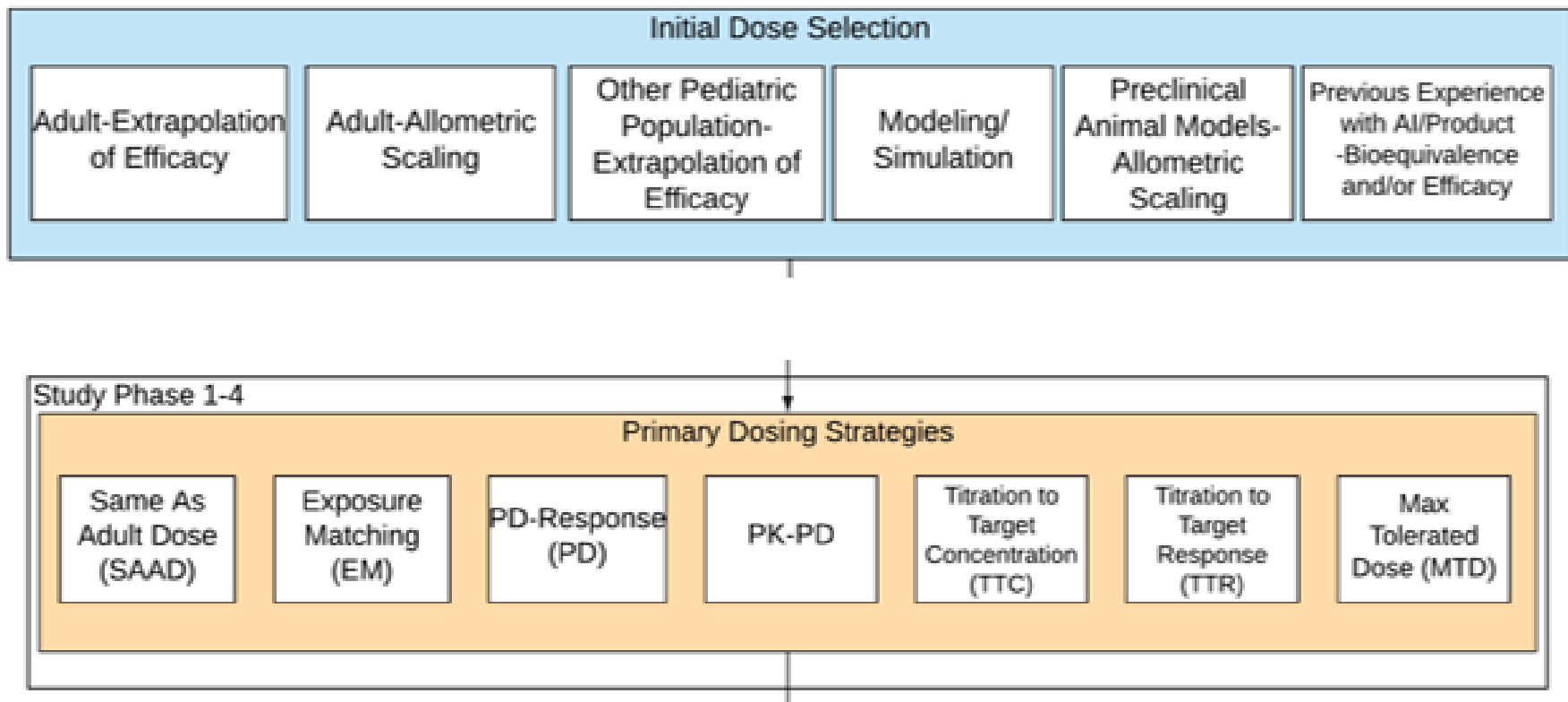
Aggregate dosing strategy

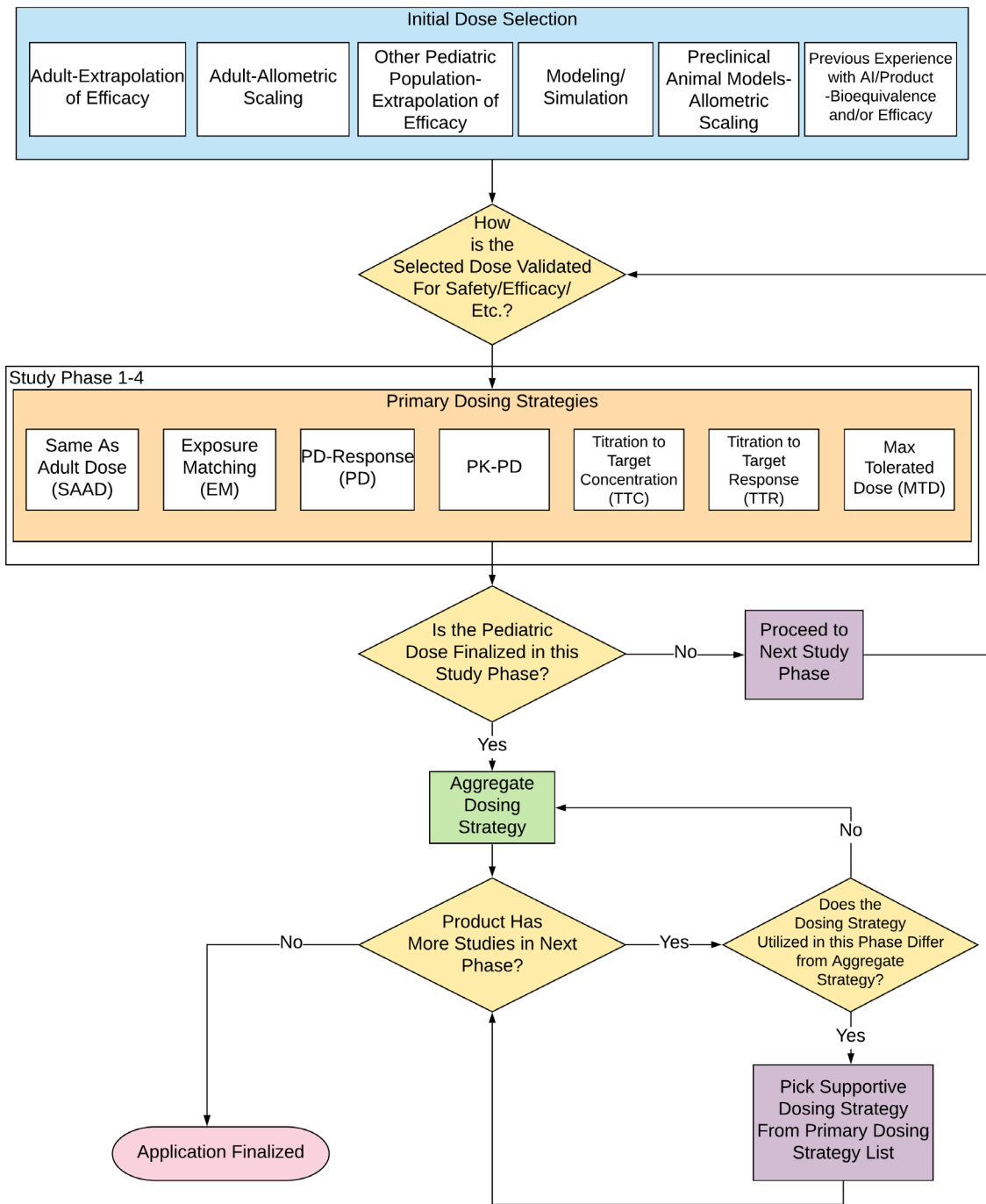
# Methods

- Reviewed publicly available pediatric clinical studies for products submitted to US FDA under FDASIA (7/9/2012 – present)
- Inclusion criteria:
  - Public documents available for review: medical review and/or clinical pharmacology review and product labels;
  - Include pediatric studies.
- Exclusion criteria
  - **Did not conduct pediatric studies**, instead relying on adult data or literature searches.
  - The application relied on **previously submitted pediatric data** from earlier INDs/NDAs/BLAs that were **not included as evidence in the review documents**

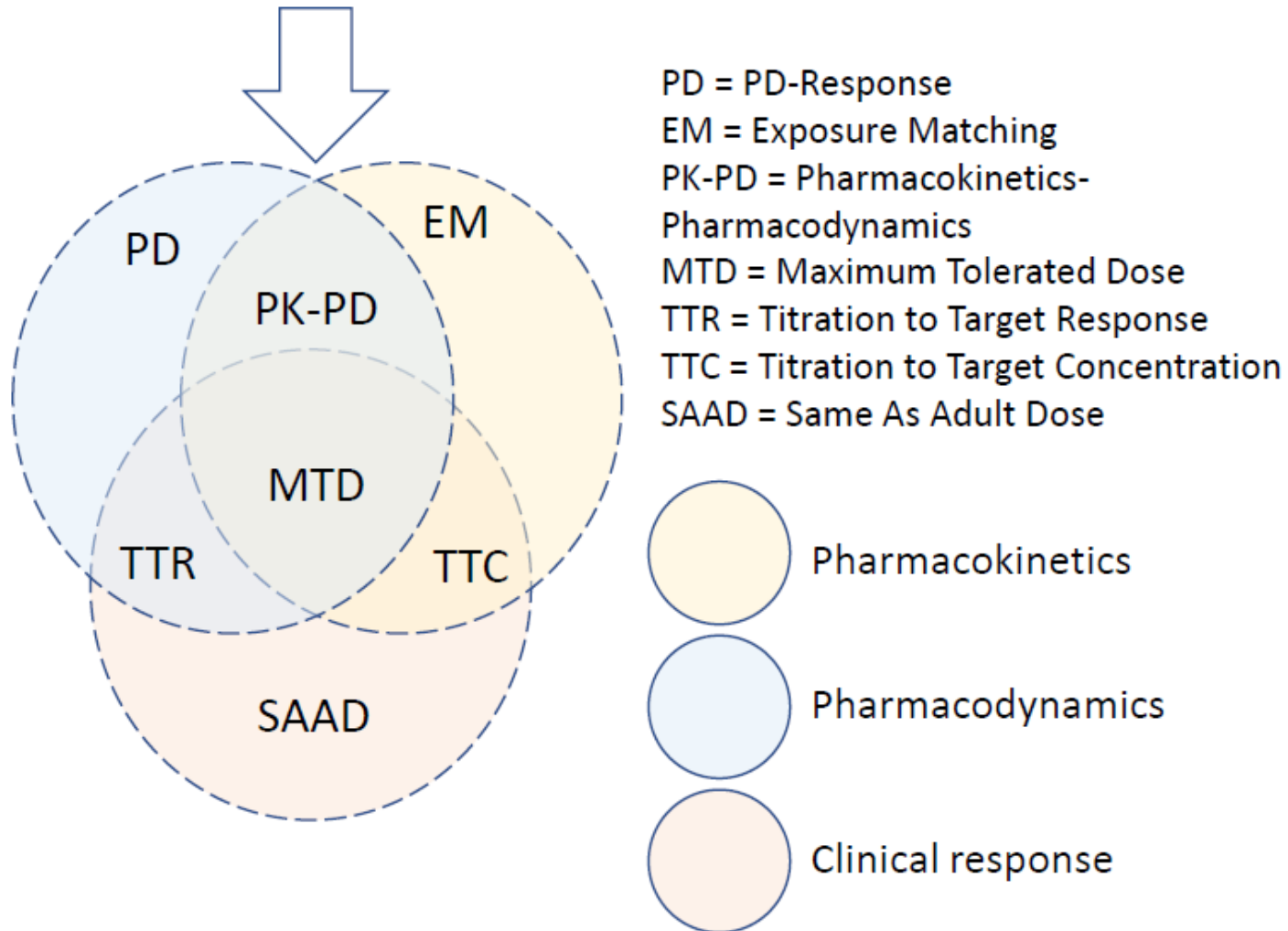


# Developing Categories





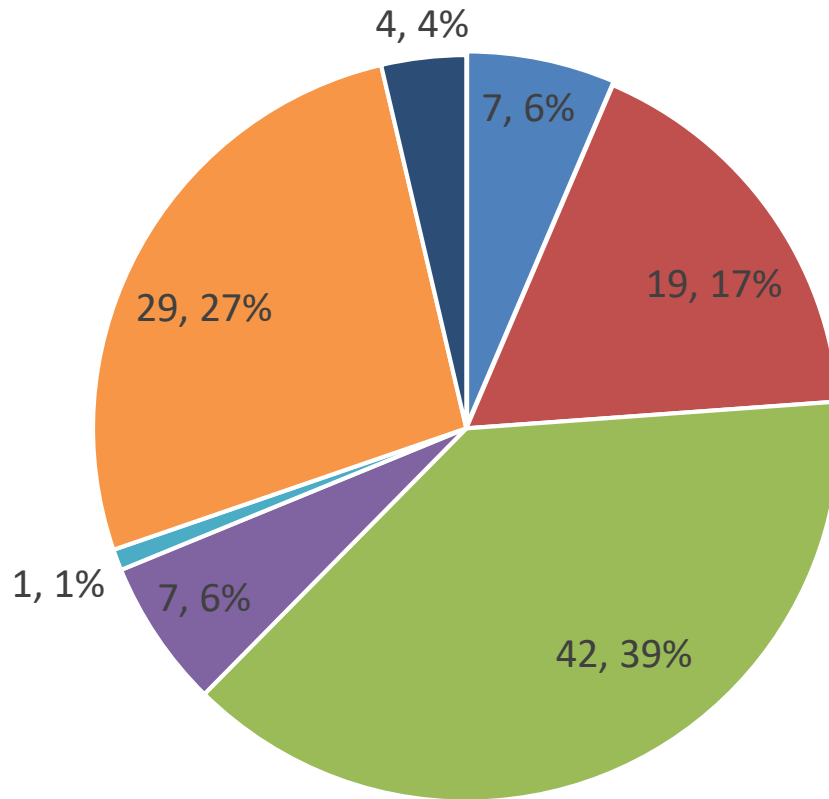
# Approaches to Pediatric Dose Selection



## Preliminary Results

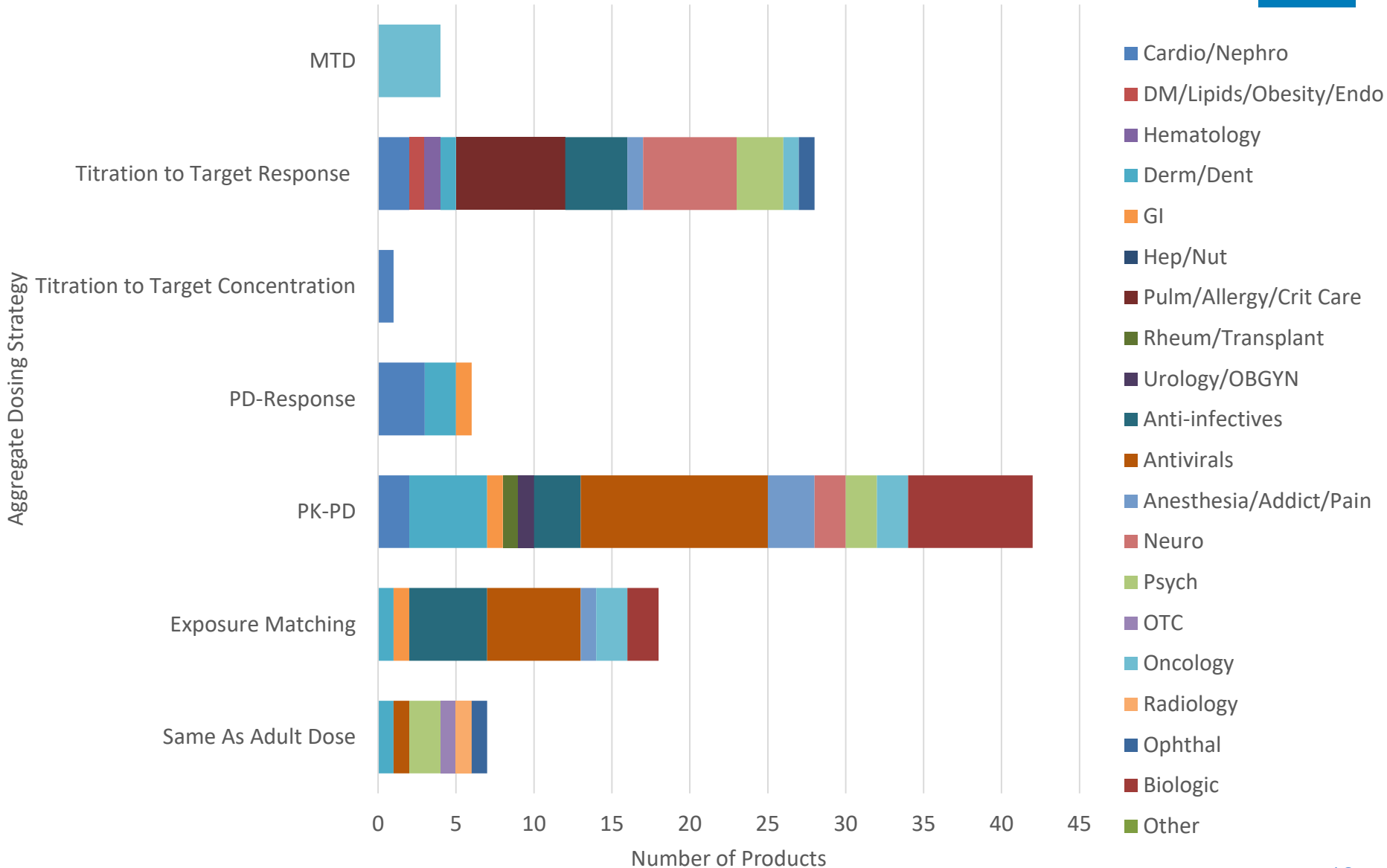
- 113 pediatric trials in present analysis.
- 21 (19%) pediatric trials included combined adult and pediatric studies.
- 17 (15%) pediatric trials saw a dose change from the initially selected pediatric dose over the R&D process.
- 43 (38%) pediatric trials employed a dose ranging study.
- 53 (47%) pediatric trials employed modeling and simulation.
  - 48 of these pediatric trials used population PK analysis.

# Aggregate Approach to Dose Selection



- Same As Adult Dose
- PK-PD
- Titration to Target Concentration
- MTD
- Exposure Matching
- PD-Response
- Titration to Target Response

# Dosing Strategy by Therapeutic Area



## Summary

- Traditional methods of pediatric dosing such as allometry provide one approach to initial pediatric dosing;
- Current programs rely heavily upon modeling and simulation;
- While PK/PD studies are utilized most frequently in pediatric drug development, dose titration to response and exposure matching are common approaches.
- It may be possible to build a more structured approach to developing pediatric doses during drug development.





# Drug Development Programs Where the Dose Was A Problem

Yaning Wang, Ph.D.

Division of Pharmacometrics

Office of Clinical Pharmacology

OTS/CDER/OMTP/FDA

*Disclaimer: This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.*

# Motivations for Dose Optimization

- **Efforts for dose selection/optimization**
  - Preclinical
  - Clinical: phase 1/2/3
  - Post-marketing
- **Risk/benefit balance**
- **Precision medicine**
- **Convenience**
- **Marketing competitiveness**

# Challenges

- **Disease specific risk/benefit judgment**
- **Availability of other treatments**
- **Optimal regimen not required by law**
- **Development cost/time**
- **Difficulty to differentiate active doses with reasonable sample size**

# Doses for Different Disease Areas



Therapeutic area	Phase 2	Phase 3	Label dose	Derived dose
Anti-Infective	2	1	1	Yes (Peds)
Antiviral	3	1	1	Yes (Peds)
Transplant	2	1	1 (therapeutic window)	
CadioRenal	3	1-2	>=1 (titration)	Yes
Neurology	3	2	>=1 (titration)	Yes (Peds)
Psychiatry	3	2	>=2 (titration)	Yes
Anesthesia	3	>1	>1 (titration)	
Metabolism	3	>1	1 (titration)	Yes
Pulmonary	3	2	1 (>1 initial dose)	Yes (Peds)
Rheumatology	3	1-2	1 (rare ↑dose)	Yes (Peds)
Dermatology	2	1-2	1-2	Yes (Peds)
Gastroenterology	3	1-2	1-2	Yes (Peds)
Bone	2	1	1 (>1 regimen)	
Reproductive	3	1-2	1	
Urology	2	1-2	1 (titration)	
Oncology	<=2	1	1 (>1 regimen)	
Hematology	3	1-2	>1 (titration)	Yes (Peds)

# Dose Related Approval



- **Formoterol (asthma)**
  - Only the low dose was approved even though both low and high doses were superior to placebo on efficacy
- **Mirabegron (overactive bladder)**
  - Only the low dose (studied in one trial) with optional up-titration was approved even though the high dose was repeated in three phase 3 trials and superior to placebo on efficacy
- **Dabigatran (stroke)**
  - Only the high dose (superior to low dose and warfarin on efficacy) was approved even though both doses showed non-inferiority relative to warfarin

# Dose Related Approval



- **Cariprazine (schizophrenia and bipolar disorder)**
  - FDA acknowledged that cariprazine clearly demonstrated efficacy
  - Complete response letter (not approval) to optimize dosing regimen
  - Approval in the 2<sup>nd</sup> cycle with PMR studies to study lower dose
- **Baricitinib (rheumatoid arthritis)**
  - FDA acknowledged that both low and high doses clearly demonstrated efficacy
  - Complete response letter (not approval) to optimize dosing regimen
  - Approval in the 2<sup>nd</sup> cycle with PMR study to study lower dose
- **Indacaterol (chronic obstructive pulmonary disease, COPD)**
  - FDA acknowledged that both low and high doses clearly demonstrated efficacy
  - Complete response letter (not approval) to optimize dosing regimen
  - Low dose was approved in the 2<sup>nd</sup> cycle after new dose-ranging trials with lower doses
- ...

# Dose Related PMC/PMR Studies



<b>Drug</b>	<b>Indication</b>	<b>PMC/PMR</b>	<b>Goal</b>
<b>Ponatinib</b>	<b>Chronic myeloid leukemia</b>	<b>PMR</b>	<b>Lower dose</b>
<b>Vandetanib</b>	<b>Medullary thyroid cancer</b>	<b>PMR</b>	<b>Lower dose</b>
<b>Cabozantinib</b>	<b>Medullary thyroid cancer</b>	<b>PMR</b>	<b>Lower dose</b>
<b>Lenvatinib</b>	<b>Multiple cancers</b>	<b>PMR</b>	<b>Lower dose</b>
<b>Adalimumab</b>	<b>Ulcerative colitis</b>	<b>PMR</b>	<b>Higher dose</b>
<b>Mozobil</b>	<b>Mobilize hematopoietic stem cells</b>	<b>PMC</b>	<b>Higher dose in low body weight patients</b>
<b>Herceptin</b>	<b>GI cancer</b>	<b>PMR</b>	<b>Higher dose</b>
<b>Ado-trastuzumab emtansine</b>	<b>Metastatic breast cancer</b>	<b>PMC</b>	<b>Higher dose</b>
<b>Ipilimumab</b>	<b>Melanoma</b>	<b>PMR</b>	<b>Higher dose</b>
<b>Omace taxine mepesuccinate</b>	<b>Chronic myeloid leukemia</b>	<b>PMR</b>	<b>Higher dose</b>
<b>Radium Ra 223 dichloride</b>	<b>Prostate cancer</b>	<b>PMC</b>	<b>Higher dose</b>

# PMC/PMR Studies for Lower Dose



Year approved	Drug name (brand name)	Indications	Approved highest maintenance dose in adults <sup>a</sup>	Comments <sup>b</sup>
2011	Gabapentin enacarbil (Horizart)	Restless legs syndrome (RLS)	600 mg	PMR: additional dose–response studies that include lower doses (300, 450 mg/day) are needed to define the maximally effective, lowest dose to relieve moderate to severe symptoms of RLS
2011	Vilazodone (Viibryd)	Major depressive disorder (MDD)	40 mg	PMC: some important adverse reactions are dose related; request to further characterize the efficacy and safety to evaluate 20- and 40-mg fixed doses in MDD
2010	Dalfampridine (Ampyra)	Multiple sclerosis (MS)	10 mg twice daily	PMC: to evaluate the efficacy of 5-mg twice-daily dose in MS
2010	Cabazitaxel (Jevtana)	Hormone-refractory metastatic prostate cancer (mHRPC)	25 mg/m <sup>2</sup> every 3 weeks	PMR: to compare a lower dose (20 mg/ m <sup>2</sup> ) with 25 mg/m <sup>2</sup> in mHRPC
2010	Fingolimod (Gilenya)	Multiple sclerosis	0.5 mg daily	PMC: to evaluate a lower dose, 0.25 mg. The similarity in effectiveness of 0.5- and 1.25-mg doses suggests that a lower dose might be equally effective. The clinical findings of concern are clearly dose related
2010	Lurasidone (Latuda)	Schizophrenia	160 mg	PMC: to identify the lowest effective dose; to evaluate with a dose lower than 40 mg (e.g., 20 mg daily)
2009	Asenapine (Saphris)	Schizophrenia and bipolar mania	10 mg twice daily	PMC: to identify the lowest effective dose; to study a dose <10 mg twice daily (e.g., 5 mg twice daily) in bipolar mania and to study a dose <5 mg twice daily (e.g., 2.5 mg twice daily) in schizophrenia
2008	Riloncept (Arcalyst)	Cryopyrin-associated periodic syndrome	160 mg weekly	PMC: to assess whether either lower maintenance doses or a longer interval between doses could be equally effective but potentially safer than the approved dose
2008	Desvenlafaxine (Pristiq)	MDD	50 mg	PMC: to evaluate efficacy at 10, 25, and 50 mg/day. The available data suggest a flat dose–response curve for efficacy between 50 and 400 mg/day. There is a clear dose response for adverse events as the dose increases from 50 to 400 mg/day
2006	Paliperidone (Invega)	Schizophrenia	12 mg	PMC: to conduct a study to explore for a minimal effective dose



# Dose Selection Trend



- **More disease areas target the minimum dose with near maximum efficacy**
- **Individualized dosing regimen**
- **Fewer maximum tolerated dose**
- **Optimal dose**

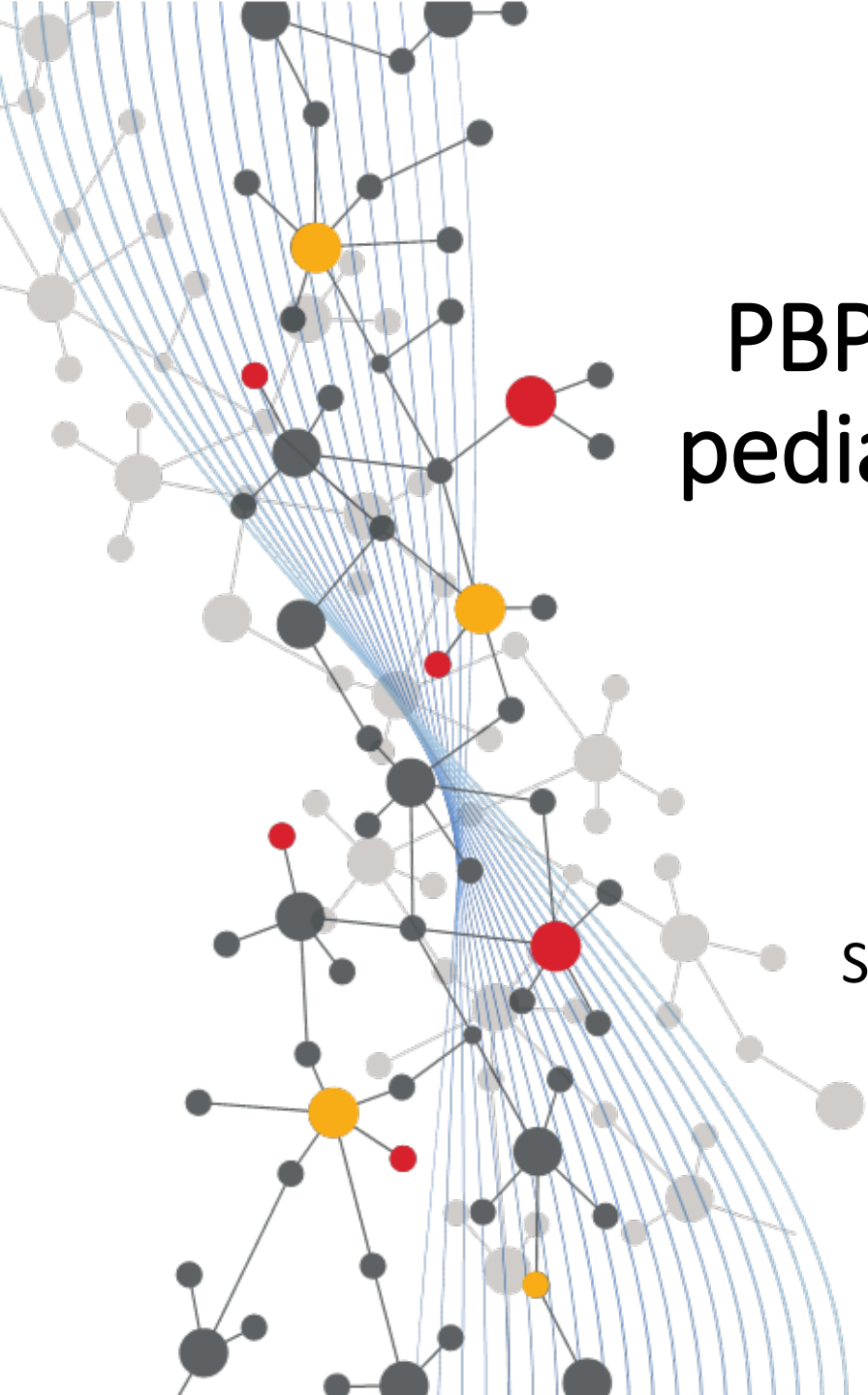
# Summary

- **Not sufficient to support the safety and efficacy of one dose relative to placebo/control**
- **Search for dosing regimen with optimal safety/efficacy profile or even individualized dose(s)**
- **Impact of dose-exposure-response information**
  - **Approval**
  - **PMC/PMR**



**THANK YOU**

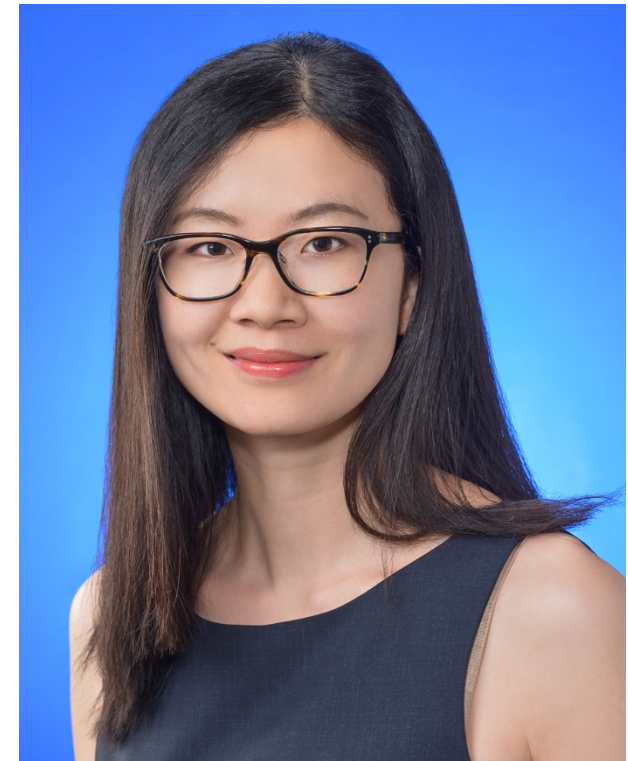
<b>FDA</b>	<b>U.S. FOOD &amp; DRUG ADMINISTRATION</b>
	<b>CENTER FOR DRUG EVALUATION &amp; RESEARCH OFFICE OF CLINICAL PHARMACOLOGY</b>



# PBPK modeling and allometric scaling in pediatric drug development: where do we draw the line?

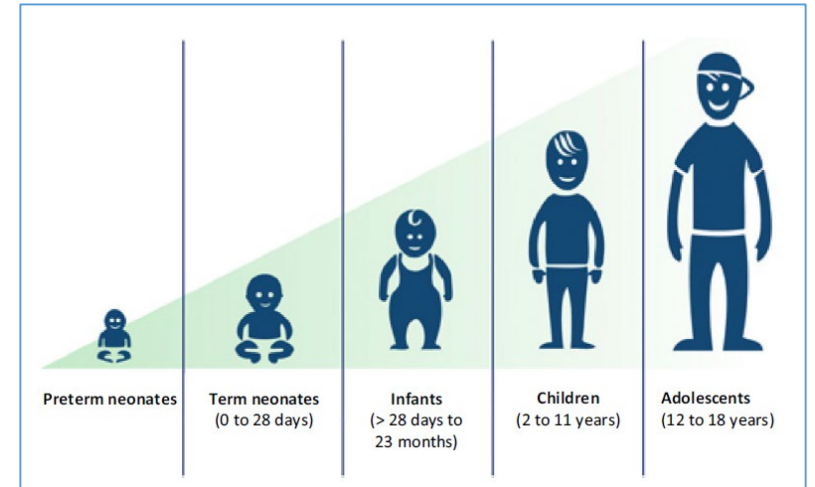
Alice Ke, Ph.D.

Senior Consultant & Scientific Advisor  
Certara



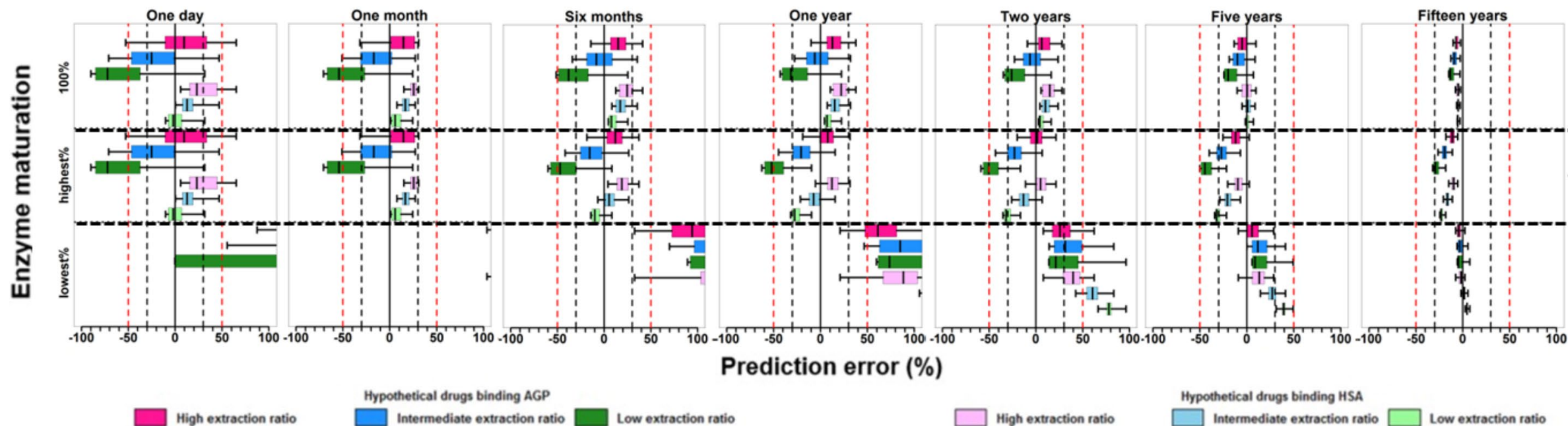
# Reviewing the Landscape

- Developing medicines for children is now established in legislation both in the US and Europe and unless waiver or deferral is sought, new drugs require pediatric studies as part of their marketing authorization.
- Children are not small adults and all children are not the same
- Children under the age of 2 are the most heterogeneous
  - Many developmental processes are not reflected by simple scalars such as body weight or body surface area
  - Projecting doses based on simple allometric scaling can lead to significant overdoses in certain age groups



# When might allometric scaling (AS) be adequate?

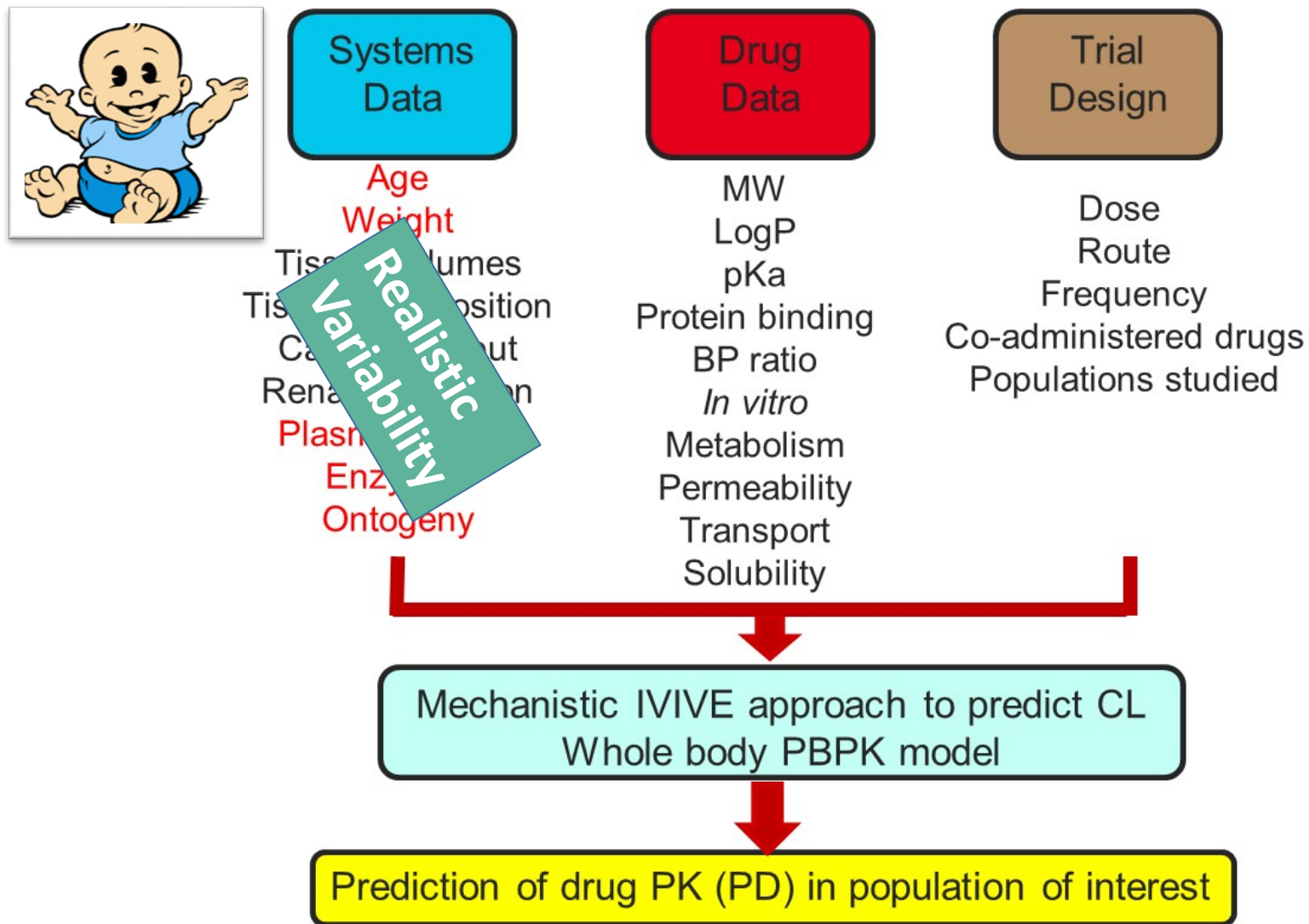
- Simple dose extrapolation in children >2y for drugs with linear PK



Krekels 2019 CPT:PSP

- Scaling for <2y when maturation function included (or exponent left to change with age e.g. as part of POPPK model)

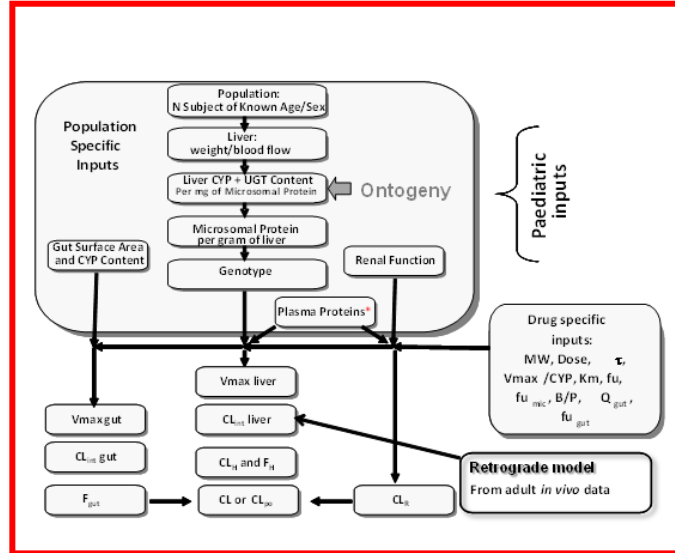
# PBPK- Integrating Systems & Drug Information



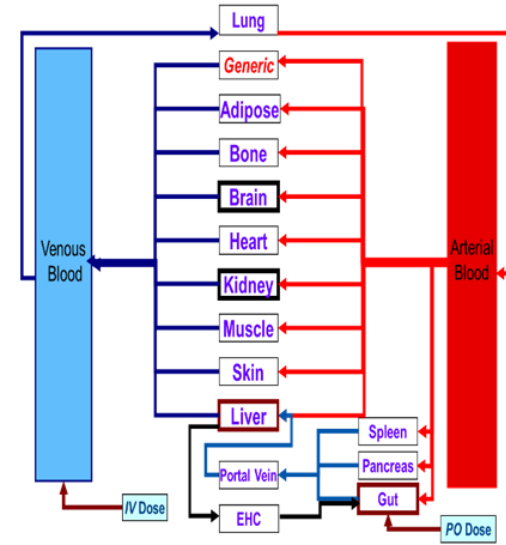


# PBPK- Integrating Systems & Drug Information

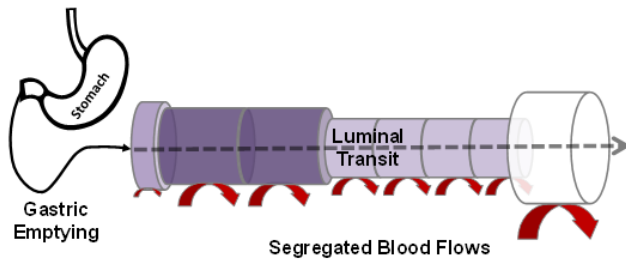
## Drug Elimination



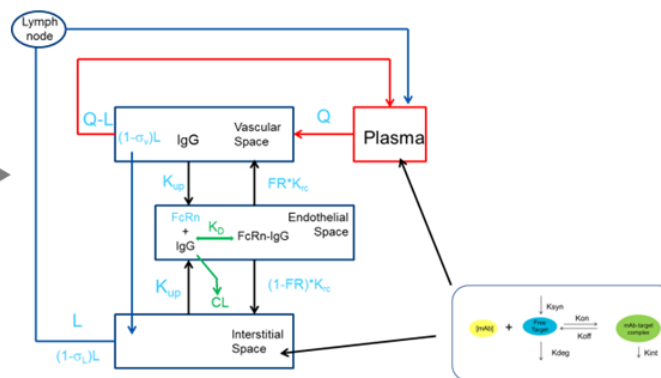
## Drug Distribution



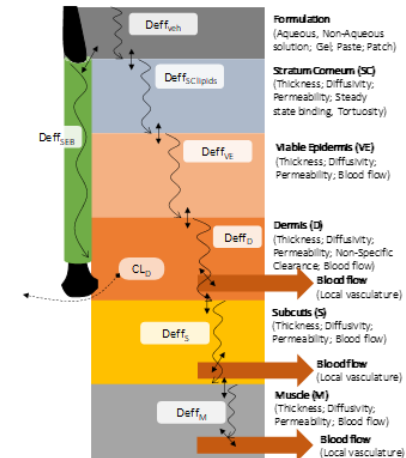
## Oral Absorption



## Biologics



## Dermal Absorption



# Examples of PBPK modeling being more mechanistically useful

- Dose projections in younger ages due to enzyme/transporter ontogeny and absorption differences for low-solubility drugs - Radiprodil (Johnson et al., BJCP 2020)
- **Bridging different formulations in children - Quetiapine (Johnson et al BDD 2014) and hydrocortisone**
- **Prediction of DDI in children – Deflazocort (NDA review)**
- **Disease differences between adults and children make scaling the dose difficult e.g. Sickle cell disease**
- Dose is predicted based on link to PD - Radiprodil (Johnson et al., BJCP 2020)
- PBPK model give better prediction of CL of therapeutic proteins compared to AS (Pan et al., AAPS J 2020)

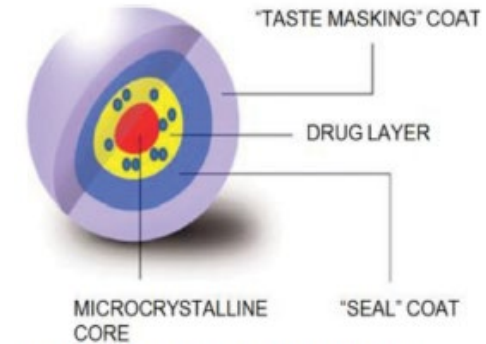
# New Hydrocortisone formulations

## 1) Infacort (Alkindi) granule formulation (Taste mask)

### Development and Testing in Healthy Adults of Oral Hydrocortisone Granules With Taste Masking for the Treatment of Neonates and Infants With Adrenal Insufficiency

J Clin Endocrinol Metab, April 2015, 100(4):1681-1688

Martin J. Whitaker,\* Sarah Spielmann,\* Dena Digweed, Hiep Huatan, David Eckland, Trevor N. Johnson, Geoffrey Tucker, Heiko Krude, Oliver Blankenstein, and Richard J. Ross



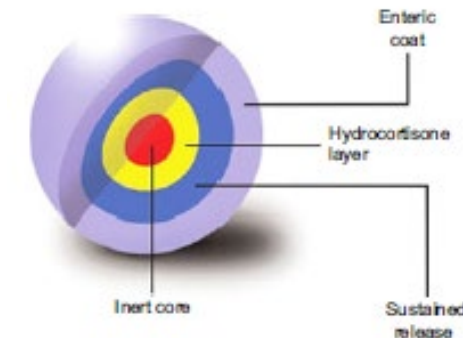
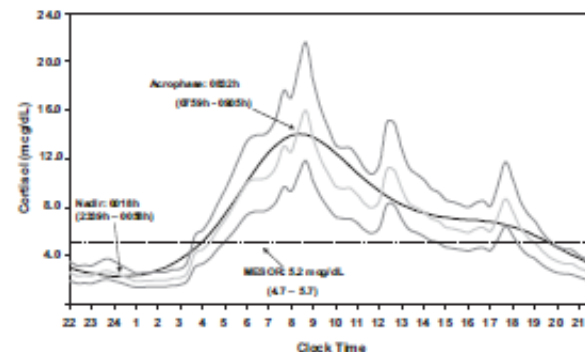
0.5, 1, 2, and 5 mg capsules

## 2) Chronocort EC granule formulation (Diurnal variation)

### A Phase 2 Study of Chronocort, a Modified-Release Formulation of Hydrocortisone, in the Treatment of Adults With Classic Congenital Adrenal Hyperplasia

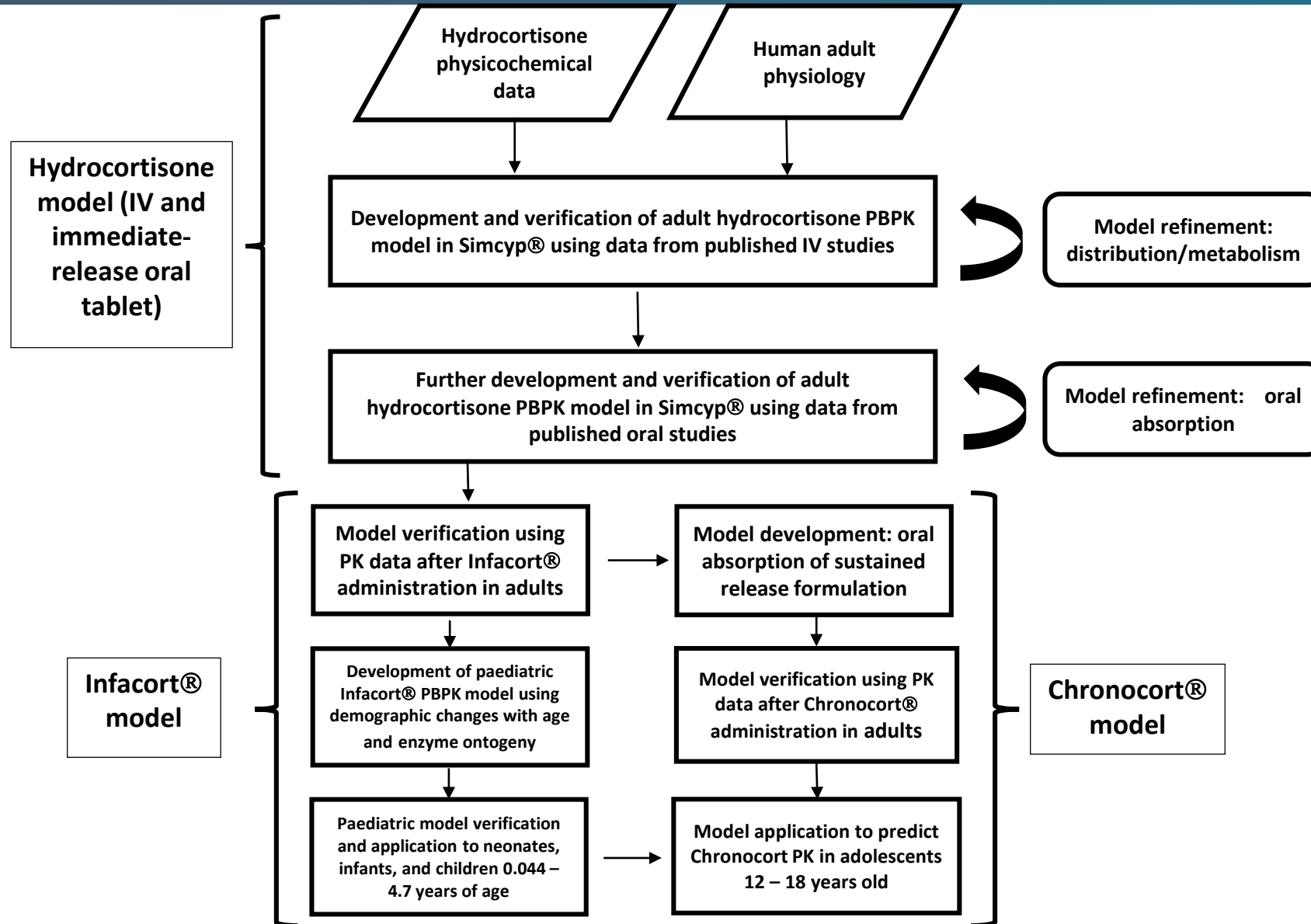
J Clin Endocrinol Metab, March 2015, 100(3):1137-1145

Ashwini Mallappa, Ninet Sinaii, Parag Kumar, Martin J. Whitaker, Lori-Ann Daley, Dena Digweed, David J. A. Eckland, Carol Van Ryzin, Lynnette K. Nieman, Wiebke Arlt, Richard J. Ross, and Deborah P. Merke

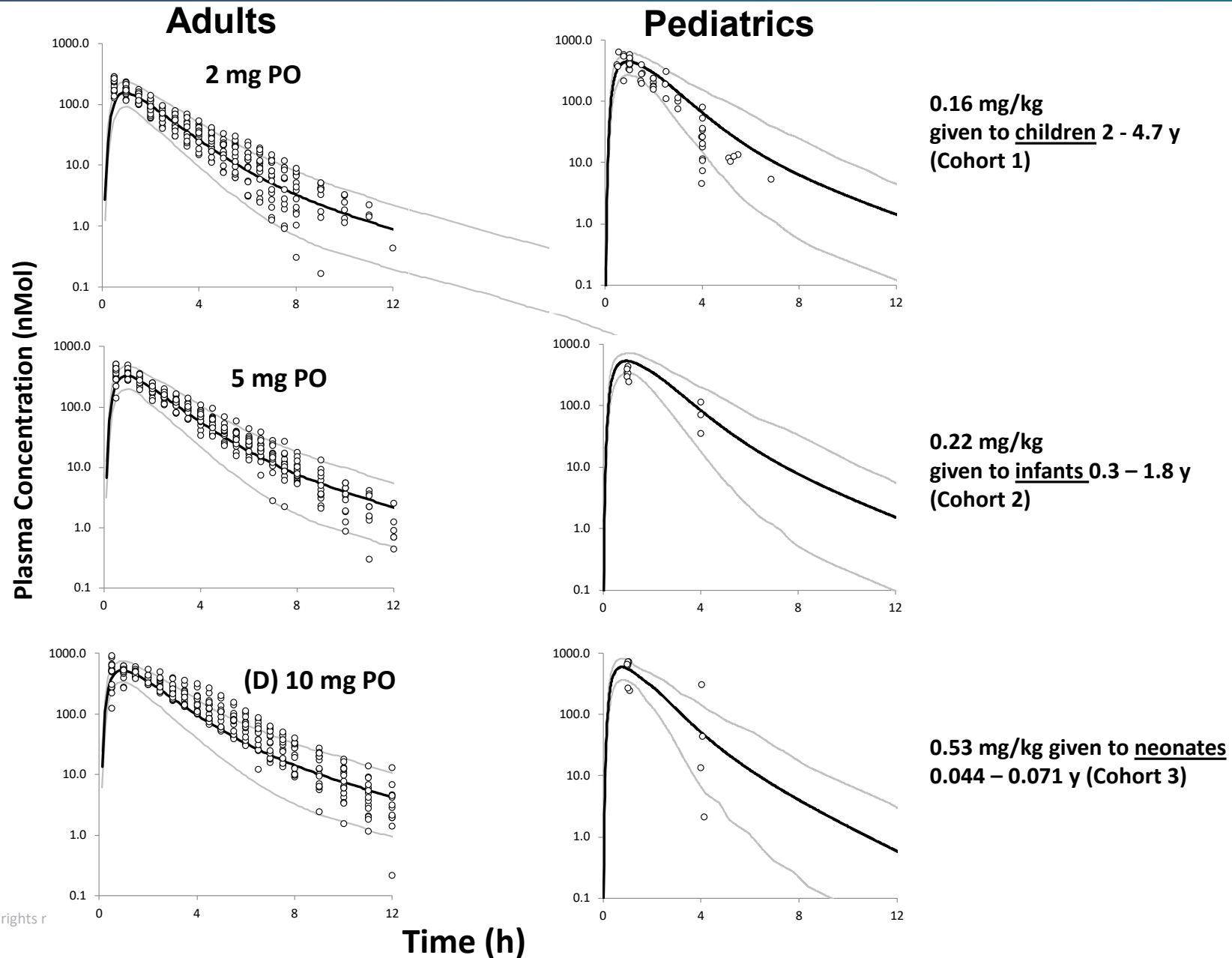


5, 10, and 20 mg capsules

# Hydrocortisone PBPK Modelling workflow

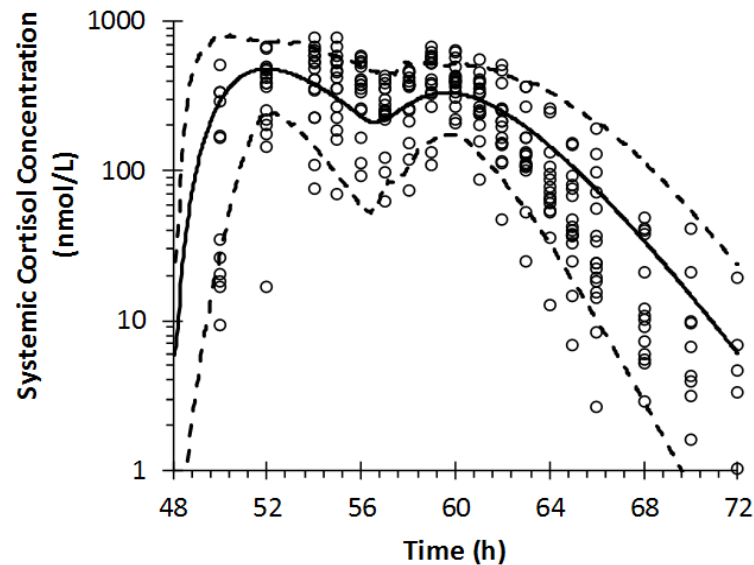


# Oral Infacort PK in adults and pediatrics

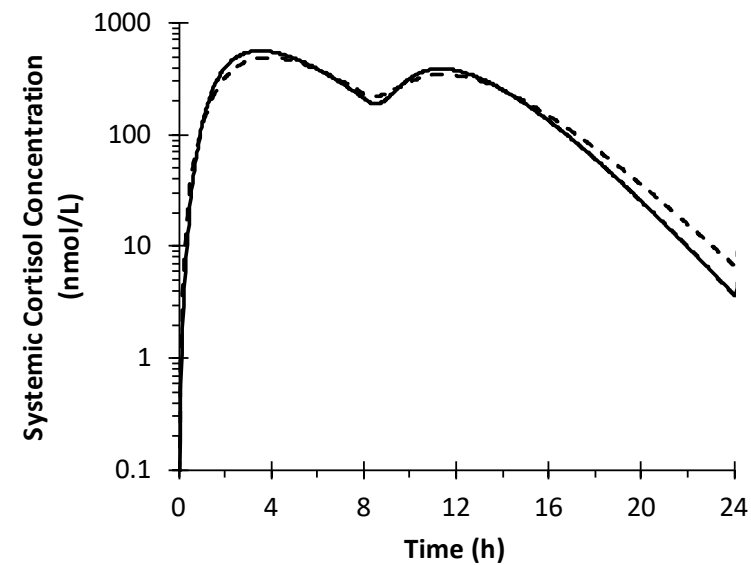


# Chronocort PK in adults, dose projections in adolescents

Modelled as EC formulation with trigger pH = 7.2

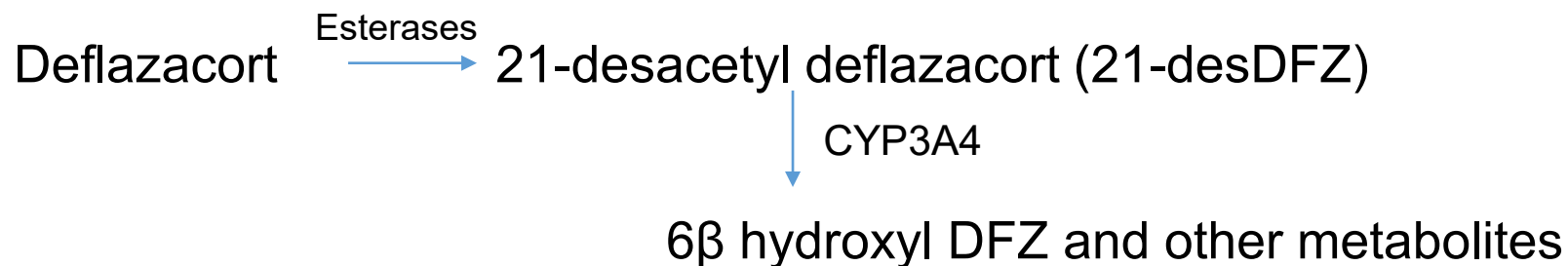


20mg evening, 10mg morning in adults



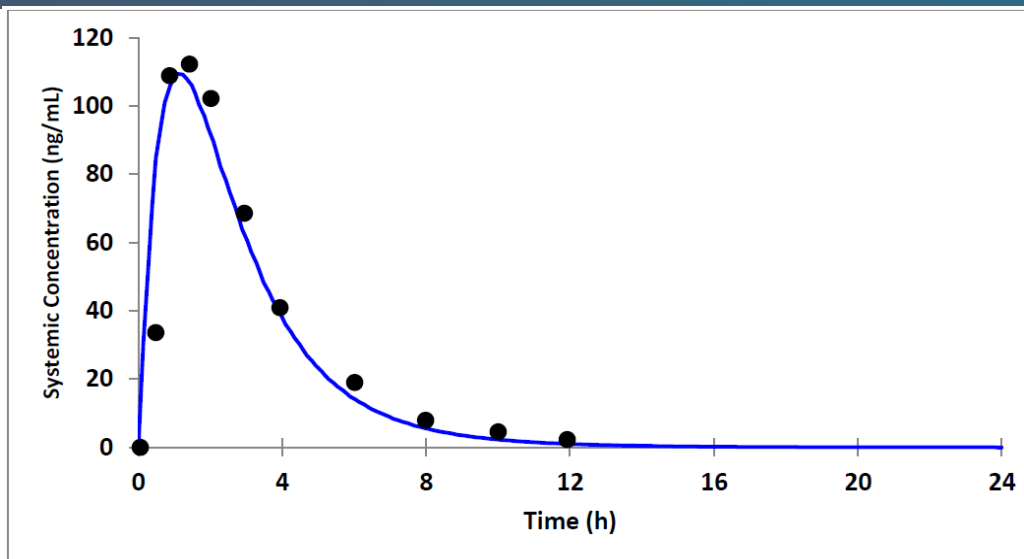
11.6 mg/m<sup>2</sup> evening, 5.8 mg/m<sup>2</sup> morning adolescents aged 12 to 18 years (solid line). Adults (dotted line).

# Case study 2: Deflazacort (Emflaza) example

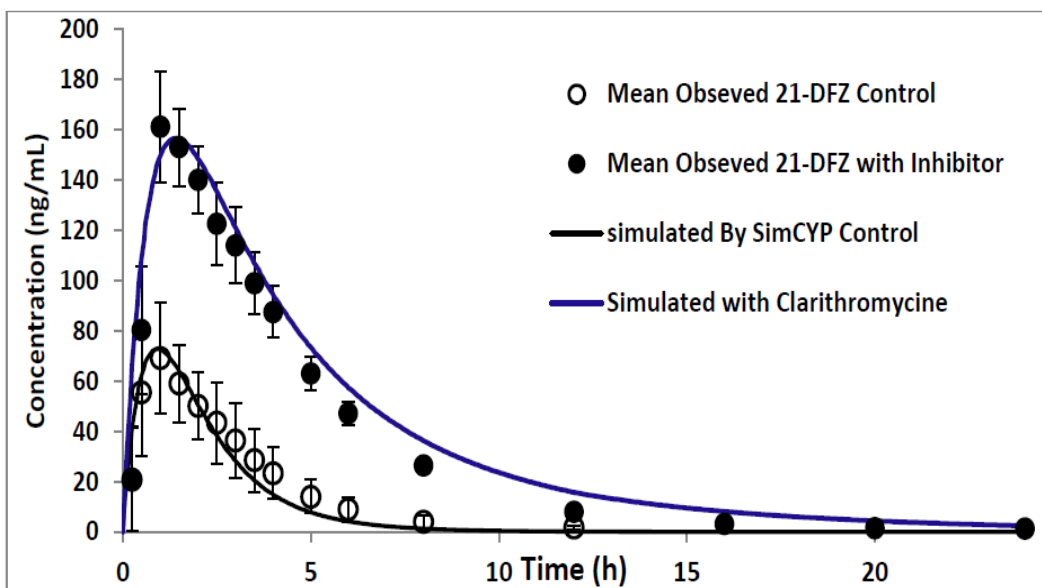


- PBPK model for 21-desDFZ
- Model verification
- Prediction of concentration-time profiles in adults
- Predicted DDI liability clarithromycin and rifampicin in adults
- Predicted exposure in children 4 to 11y and adolescents 12 to 16y
- Model application
- Predicted DDI liability in children (clarithromycin, fluconazole, rifampicin, efavirenz)

# Model Verification in Adults



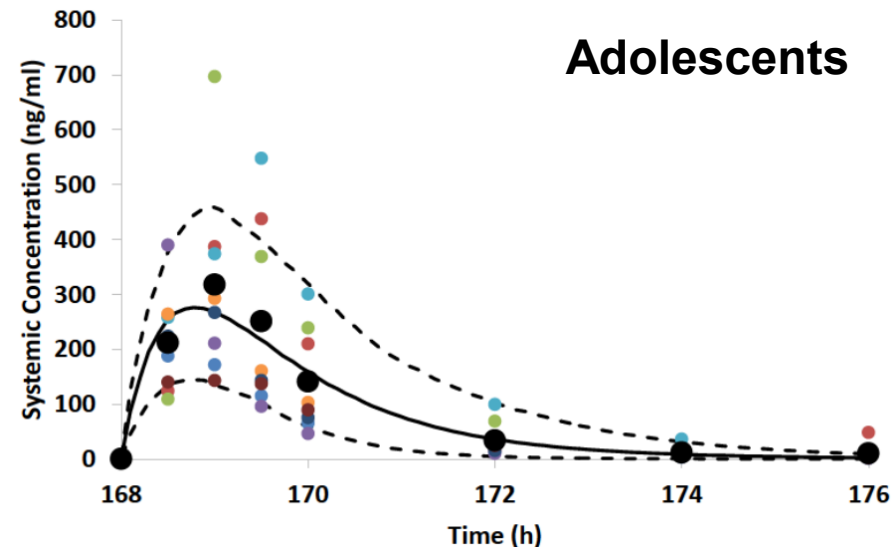
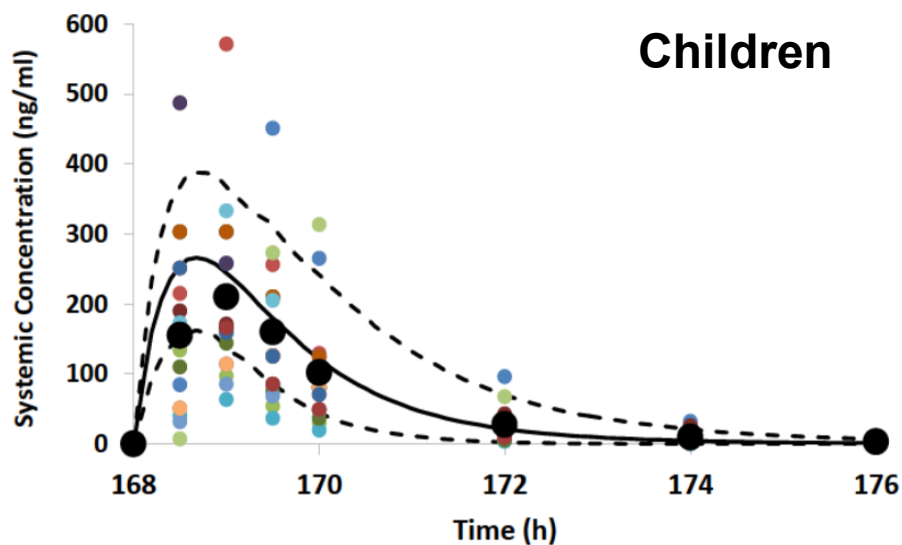
Source: FDA reviewer re-simulated under condition described by applicant (Figure 4, PBPK report [1]) using final PBPK model





# Model Verification in Paediatrics

	Children				Adolescents	
	0.8 mg/kg		0.9 mg/kg		0.9 mg/kg	
	$C_{max}$	$AUC_{(0,8)}$	$C_{max}$	$AUC_{(0,8)}$	$C_{max}$	$AUC_{(0,8)}$
	(ng/mL)	(ng/mL*h)	(ng/mL)	(ng/mL*h)	(ng/mL)	(ng/mL*h)
Simulated	261	499	294	562	268	587
Observed	214	374	214	374	329	567



# Model Application: DDI liability prediction

Predicted	Children		Adolescents	
	C <sub>max</sub> Ratio	AUC Ratio	C <sub>max</sub> Ratio	AUC Ratio
Clarithromycin (7.5 mg/kg)	1.97	3.85	2.14	4.31
Fluconazole (6 mg/kg)	1.96	3.61	2.10	3.97

Predicted	Children		Adolescents	
	C <sub>max</sub> Ratio	AUC Ratio	C <sub>max</sub> Ratio	AUC Ratio
Rifampicin (10 mg/kg)	0.31	0.22	0.24	0.17
Efavirenz (350/600 mg QD)	0.43	0.29	0.43	0.30

Adult		
Clarithromycin (500 mg)	C <sub>max</sub> Ratio	AUC Ratio
Observed	2.25	3.37
Predicted	2.1	4.2

Adult		
Rifampicin (600 mg)	C <sub>max</sub> Ratio	AUC Ratio
Observed	0.06	0.08
Predicted	0.22	0.15

# PBPK Informed the Label

## 7 DRUG INTERACTIONS

### 7.1 CYP3A4 Inhibitors and Inducers

#### Moderate or Strong CYP3A4 Inhibitors:

The active metabolite of deflazacort, 21-desDFZ, is a substrate of CYP3A4 [see *Clinical Pharmacology (12.3)*]. Co-administration of deflazacort with clarithromycin, a strong CYP3A4 inhibitor, increased total exposure to 21-desDFZ by about 3-fold. Therefore, give one third the recommended dosage of EMFLAZA when moderate or strong CYP3A4 inhibitors (e.g., clarithromycin, fluconazole, diltiazem, verapamil, grapefruit juice) are used concomitantly with EMFLAZA [see *Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)*].

#### Moderate or Strong CYP3A4 Inducers:

Co-administration of deflazacort with rifampin, a strong CYP3A4 inducer, significantly decreased the exposure of 21-desDFZ. Avoid concomitant use of strong (e.g., efavirenz) or moderate (e.g., carbamazepine, phenytoin) CYP3A4 inducers with EMFLAZA [see *Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)*].

	Recommended dose of DFZ in the presence of a	
	Based on $C_{max}$	Based on AUC
Clarithromycin	0.4 to 0.5	0.2 to 0.3
Fluconazole	0.4 to 0.5	0.2 to 0.3
Rifampicin	3.6	>5.4
Efavirenz	2.0	3.0

# Case study 3: Dose prediction accounting for age and disease

- GBT440 (Voxelotor) used for the treatment of Sickle Cell Disease (SCD)
- Low clearance drug (4-6 L/h)
- Half-life of 75 h in healthy subjects versus 36 hours in subjects with SCD
- Cleared by oxidation (74%), reduction (19%) and UGT-mediated metabolism (8%)
- Main oxidative enzyme – CYP3A4 (74% of oxidation)
- $F_u$  in plasma = 0.002; B:P ratio = 33
- Coagulation, platelet and adhesion markers are increased in patients with SCD.
- Changes in protein binding may occur due to lower albumin levels
- Sickled red blood cells are prone to haemolysis. Haematocrits are significantly lower in patients with SCD than in healthy subjects (typically, values are 21% *versus* 40%).

# PBPK modelling strategy: from adult to paediatric

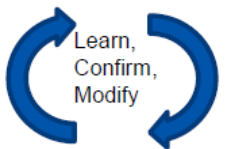
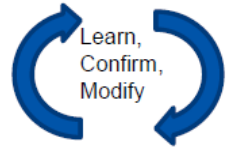
Review of *in vitro* and clinical data to develop PBPK model in healthy adults

Verify PBPK model in healthy adults using independent clinical data sets

Verify (and refine if necessary) PBPK model **in adults with SCD** using clinical data sets

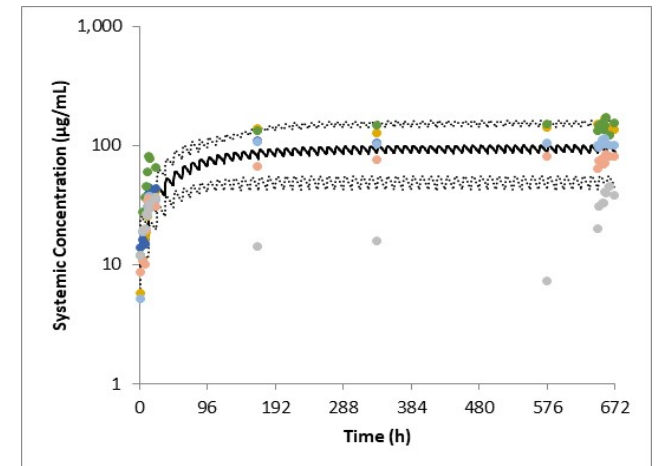
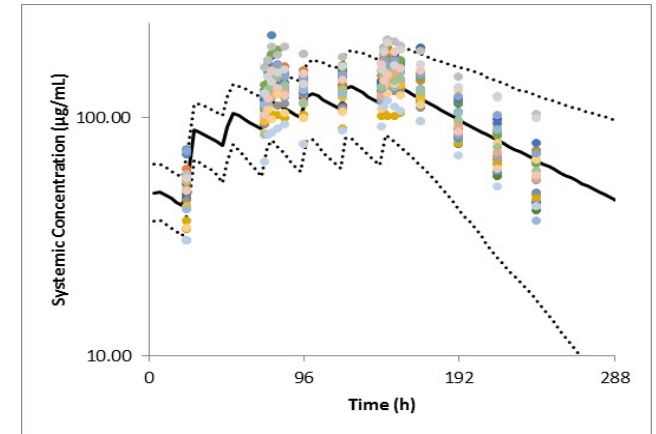
Verify PBPK model **in children and adolescents with SCD** using clinical data sets

Predict exposure and **DOSE** of GBT440 **in children aged 9 months up to 12 years of age**



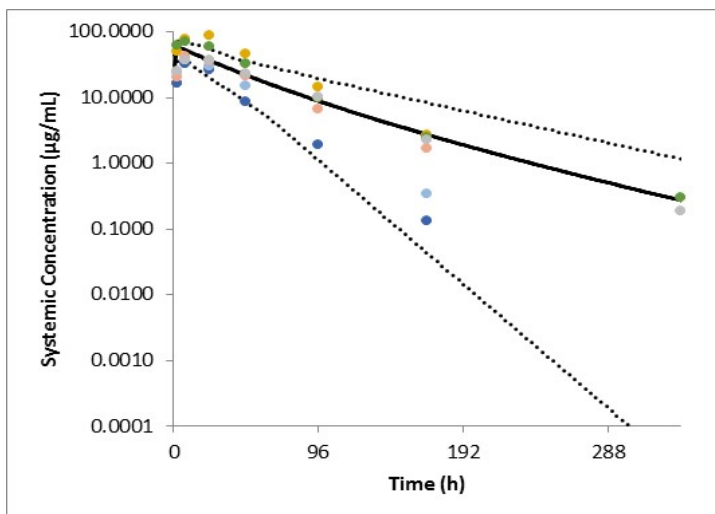
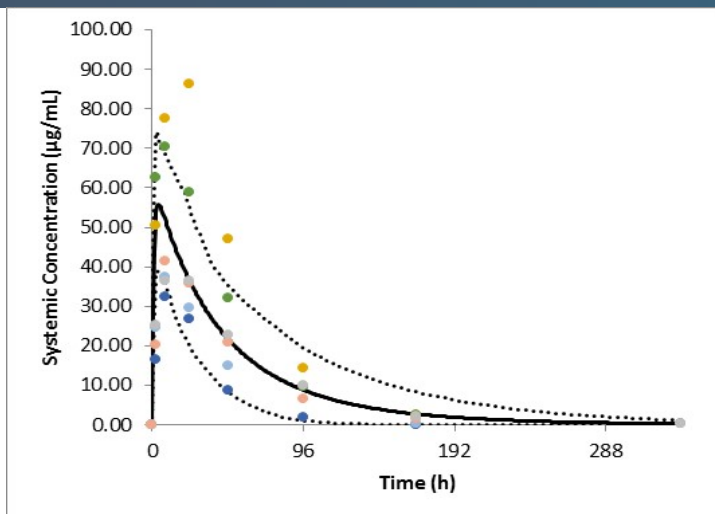
Integrate physiological changes related to SCD  
**DISEASE EFFECTS**

Integrate age-related changes  
**AGE EFFECTS**



Lower haematocrit for SCD in PBPK model led to reduced B:P ratio from 33.16 to 15.5 (consistent with observed data).

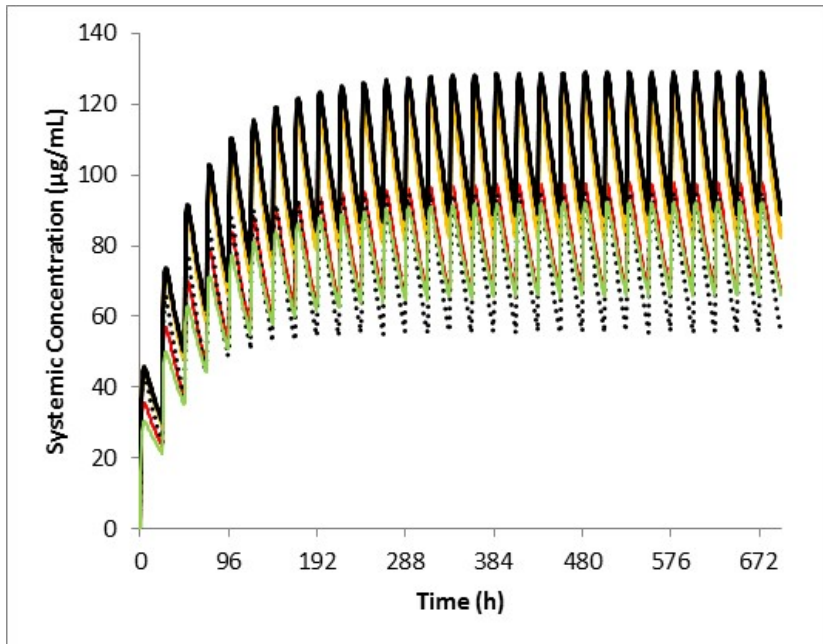
# GBT440: simulated blood exposures in children (6 to < 12 years) with SCD



A single oral dose of 600 mg GBT440 (linear and log-linear plots are on the top and bottom). Solid black line is the mean and dashed lines are the 5<sup>th</sup> and 95<sup>th</sup> percentiles of the simulated population. Circles are observed data.

	$C_{max}$	AUC
Trial (n=6)	( $\mu\text{g/mL}$ )	( $\mu\text{g/mL}\cdot\text{h}$ )
1	51.8	3344
2	55.9	2279
3	44.5	2560
4	61.0	3405
5	54.5	2693
6	51.6	3077
7	59.8	3666
8	61.9	2464
9	56.6	2185
10	59.0	2007
Population (n=60)	55.4	2716
Observed (n=6)	47.3	2785
S/O	1.17	0.98

# Dose projections in paediatrics with SCD



Predicted mean blood concentrations of GBT440 following administration of multiple oral doses of GBT440 (dose equivalent to **900 mg QD** in adults) in:

- infants aged 9 months to 2 years (**black**)
- children aged 2 to 5 years (**orange**)
- children aged 6 to 11 years (**red**)
- adults (**green**) with SCD

The solid and dashed black lines represent simulations using the CYP3A4 ontogeny profiles based on Simcyp and Upreti and Wahlstrom (2016), respectively.

	Dose equivalent	C <sub>min</sub>	C <sub>max</sub>	AUC(0,24)	C <sub>min</sub>	C <sub>max</sub>	AUC(0,24)
Populations (n=70)	(900 mg in adults)	(ng/mL)	(ng/mL)	(ng/mL.h)	Ratios (relative to adult)		
9 months to 2 years - Simcyp ontogeny	200	73.7	118	2330	1.25	1.34	1.31
9 months to 2 years - Upreti ontogeny	200	43.6	87.9	1590	0.74	1.00	0.89
2 to 5 years	300	67.7	112	2190	1.15	1.27	1.23
6 to 11 years	400	55.0	89.5	1754	0.93	1.02	0.99
12 to 17 years	900	70.0	109	2180	1.19	1.24	1.22
adults	900	58.9	87.9	1780	1.00	1.00	1.00

# Conclusions

- PBPK approach account for the age-specific physiological parameters, the ontogeny of enzymes and transporters and disease effect, as such it provides “the whole picture” and is ideal for dose projections in younger ages.
- PBPK approach can also be used support the development of complex pediatric formulation (oral formulation for low-solubility drugs, dermal formulation, etc) and is increasingly gaining regulatory acceptance in recent years.
- Allometric scaling as part of POPPK model and PBPK can be used synergistically together, e.g. middle-out agreement between POPPK with AS and PBPK to demonstrate that we understand the underlying biology, scaling certain biological parameters when no age information is available.



# Acknowledgements

- **Certara**
  - **Trevor Johnson**
  - **Karen Rowland Yeo**
  - **Howard Burt**
  - **Jennifer Bonner**
  
- **Diurnal**
  - **Richard Ross**
  - **Martin Whitaker**



# PBPK for Pediatrics: Really?

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*Center for Translational Medicine*

*Department of Pharmacy Practice & Science*

*University of Maryland, Baltimore*



# The Premise

Pediatric Development Program vs. Academic Research