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

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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

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Disclosures

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

Meet Lucy in 1997

https://www.medpagetoday.com/endocrinology/generalendocrinology/43708

Long, long ago, right?

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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

Hoon D, Taylor MT, Kapadia P, et al. Trends in Off- Label Drug Use in Ambulatory Settings: 2006–2015. Pediatrics. 2019;144(4):e20190896
The Indian Journal of Pediatrics (December 2019) 86(12):1149 722
J Okla State Med Assoc. 2018 Oct; 111(8): 776–783.

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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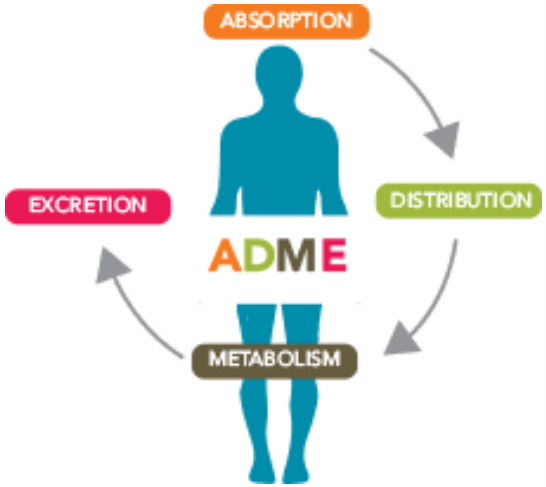
NIH U.S. National Library of Medicine

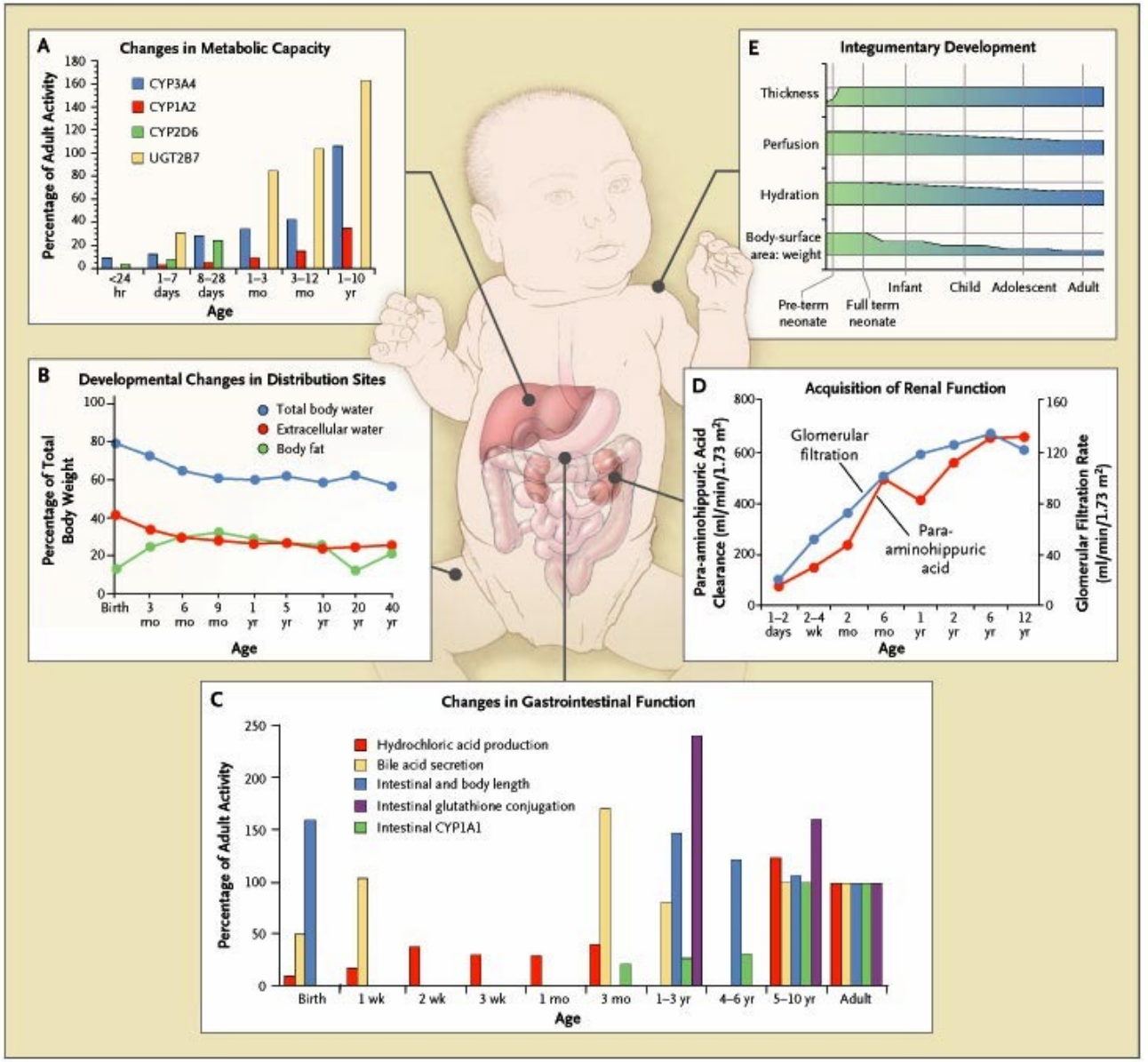
ClinicalTrials.gov

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

https://clinicaltrials.gov/ct2/show/NCT02559817

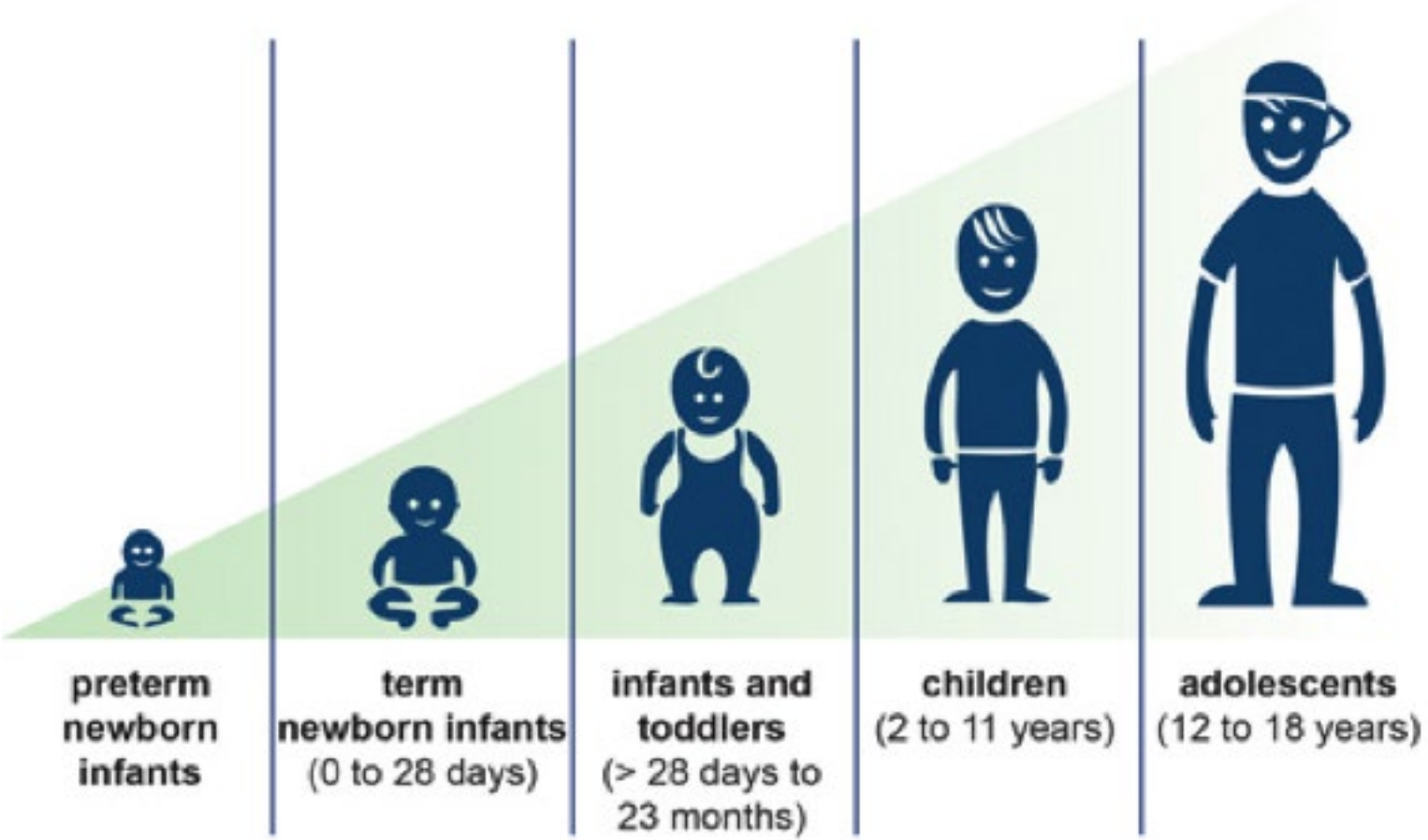




N Engl J Med 2003;349:1157-67.

What information does a clinical pharmacist need?

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?

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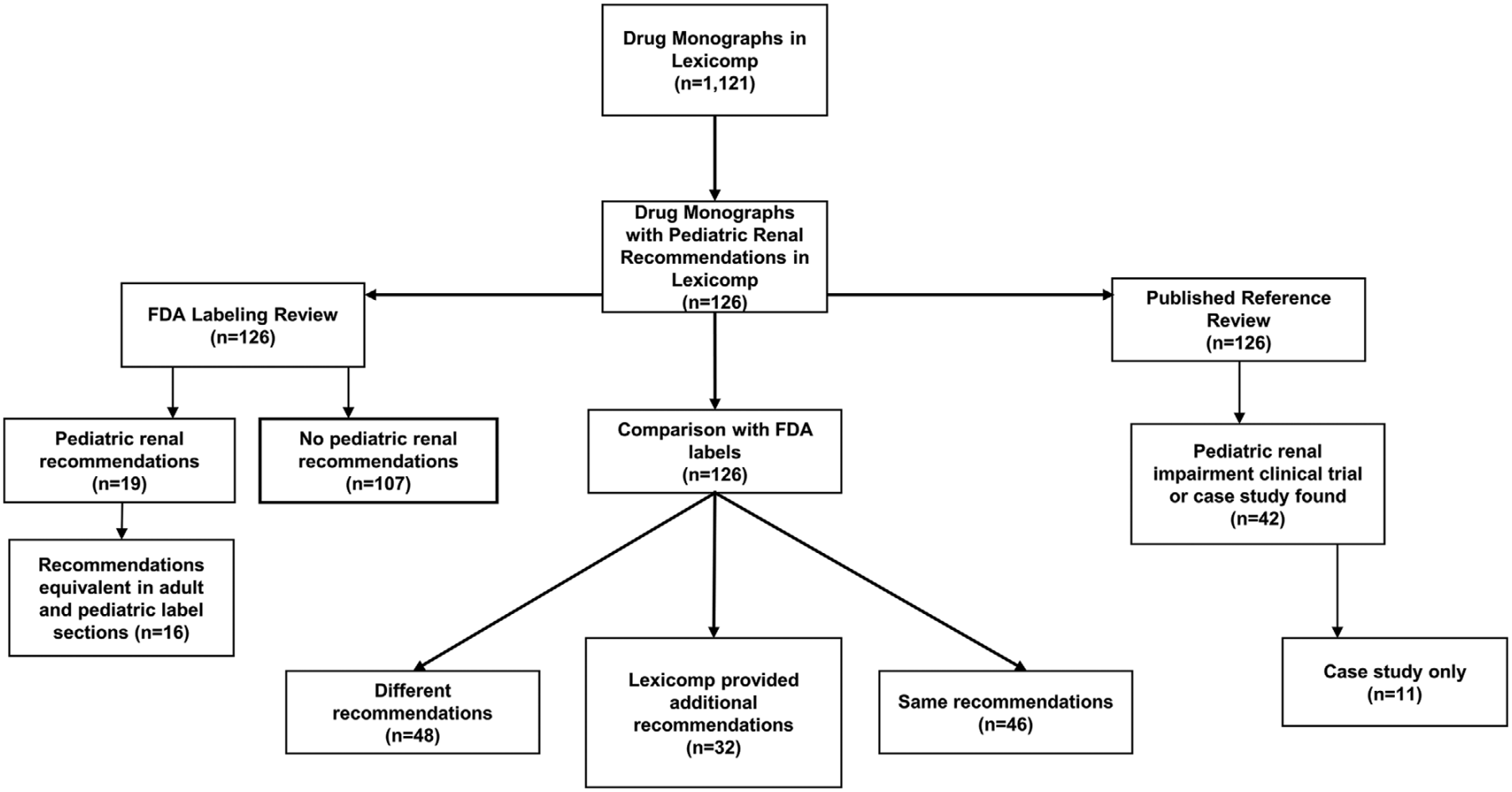
Dosing in Renal Dysfunction



Journal of clinical pharmacology. 2020 Jun 15. *Date of Electronic Publication:* 2020 Jun 15.

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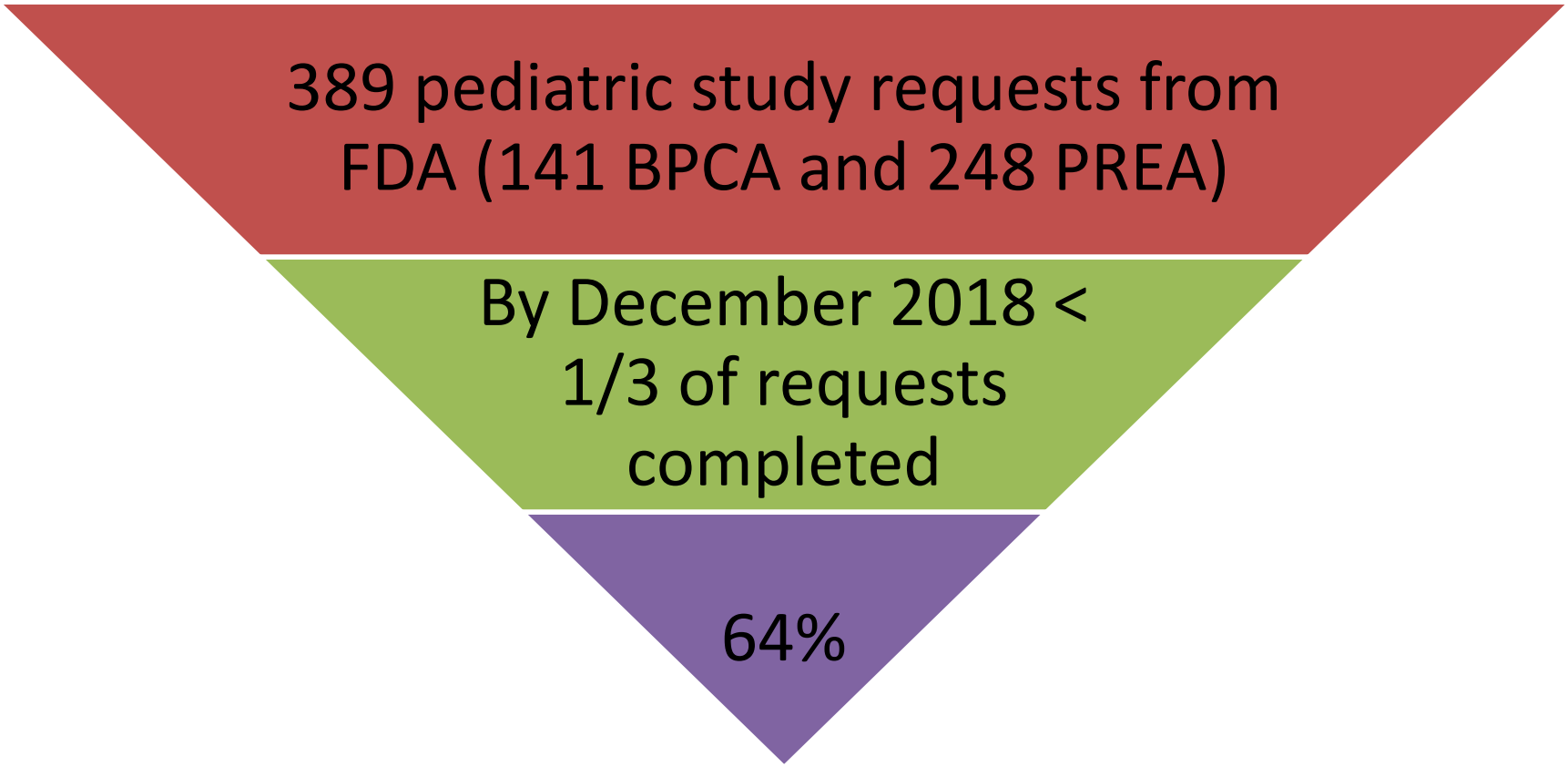
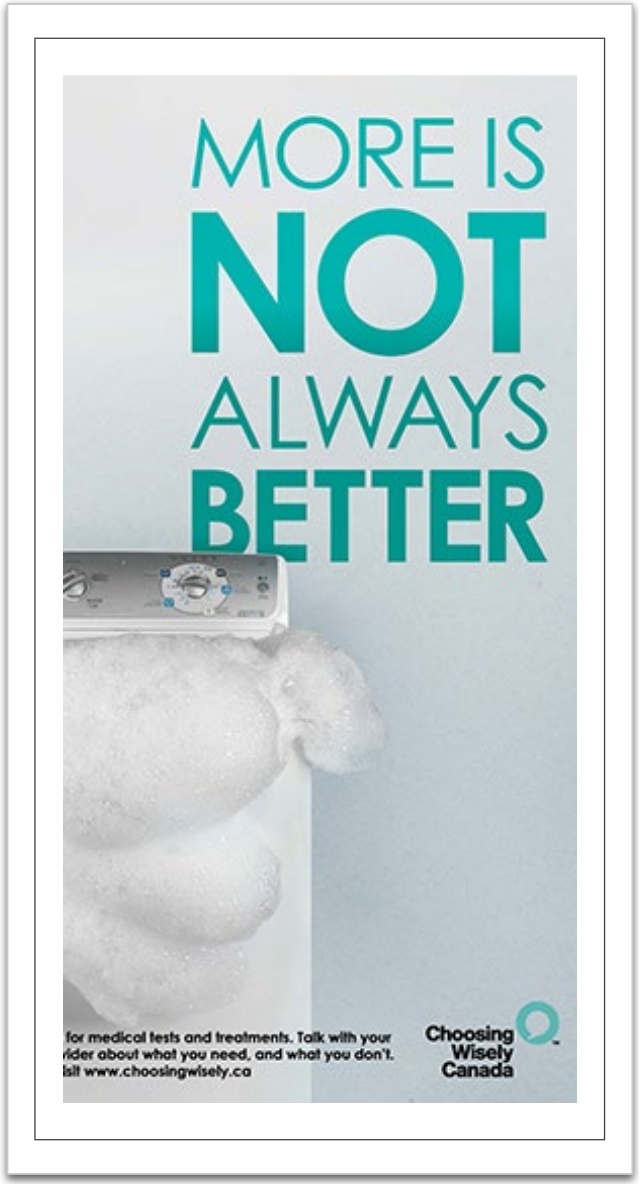
2002-2018 New Drug Indications



HEALTH AFFAIRS. 2020: 1799–1805.



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

https://choosingwiselycanada.org/campaign/more-is-not-always-better/

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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

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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

J Pediatr Gastroenterol Nutr. 2014;59(3):409–16
J Pediatr Gastroenterol Nutr. 2014;58(2):258–74
J Pediatr Gastroenterol Nutr. 2019;68(4):595–606

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

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Efthymios Manolis, EMA

Oct. 22-23, 2020, Pediatric Dose Selection

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 charactertise 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

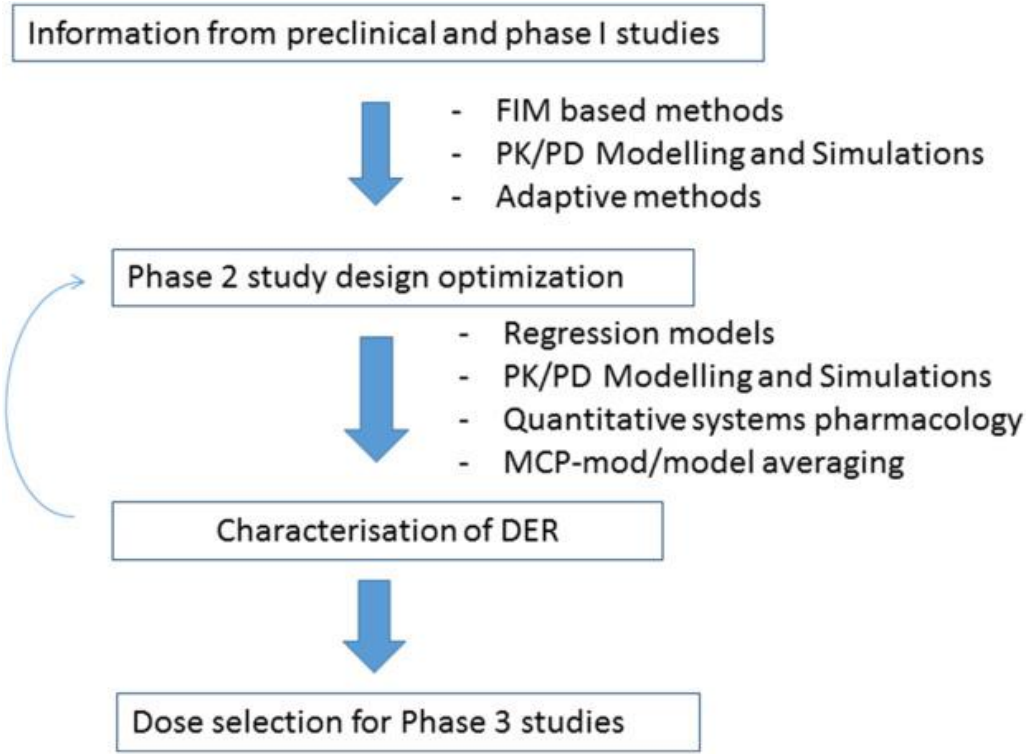
Study design optimization

Fisher information matrix (FIM)-based methods

Clinical trial simulations

Adaptive studies

Advanced Methods for Dose and Regimen Finding During Drug Development: Summary of the EMA/EFPIA Workshop on Dose Finding (London 4–5 December 2014)



CPT: Pharmacometrics & Systems Pharmacology, Volume: 6, Issue: 7, Pages: 418-429, First published: 19 July 2017, DOI: (10.1002/psp4.12196)

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

Thank you!

Efthymios.Manolis@ema.europa.eu

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 (wt [lbs] x adult dose / 150)
  - Salisbury Rule (adjustments for weights > and < 30 kg.)
- Age-based
  - Fried's Rule 0-24 months (age [mos] x adult dose / 150)
  - Young's Rule 2-12 yrs ((age [yrs]/age + 12) x 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 Dug 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

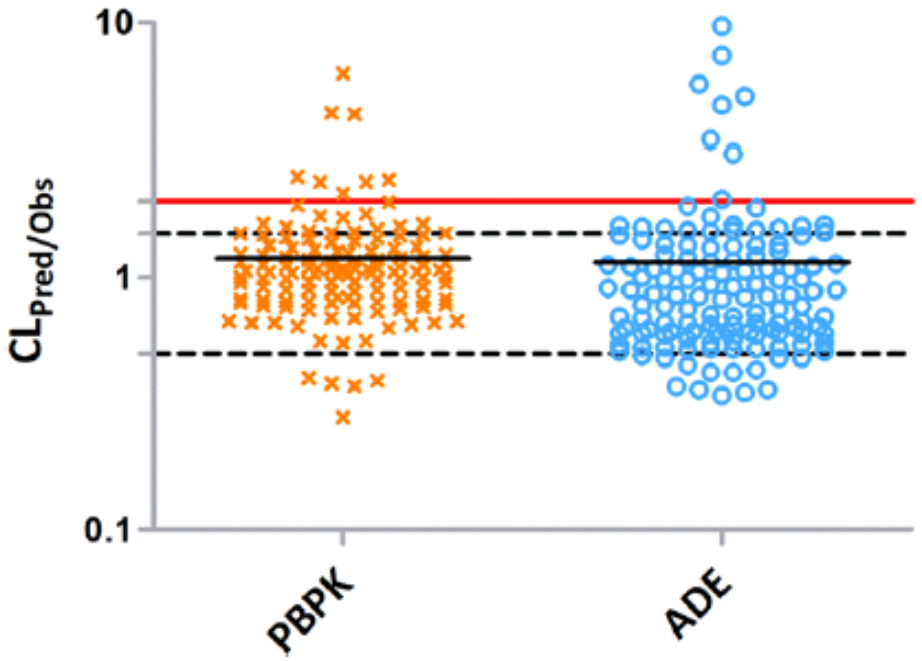
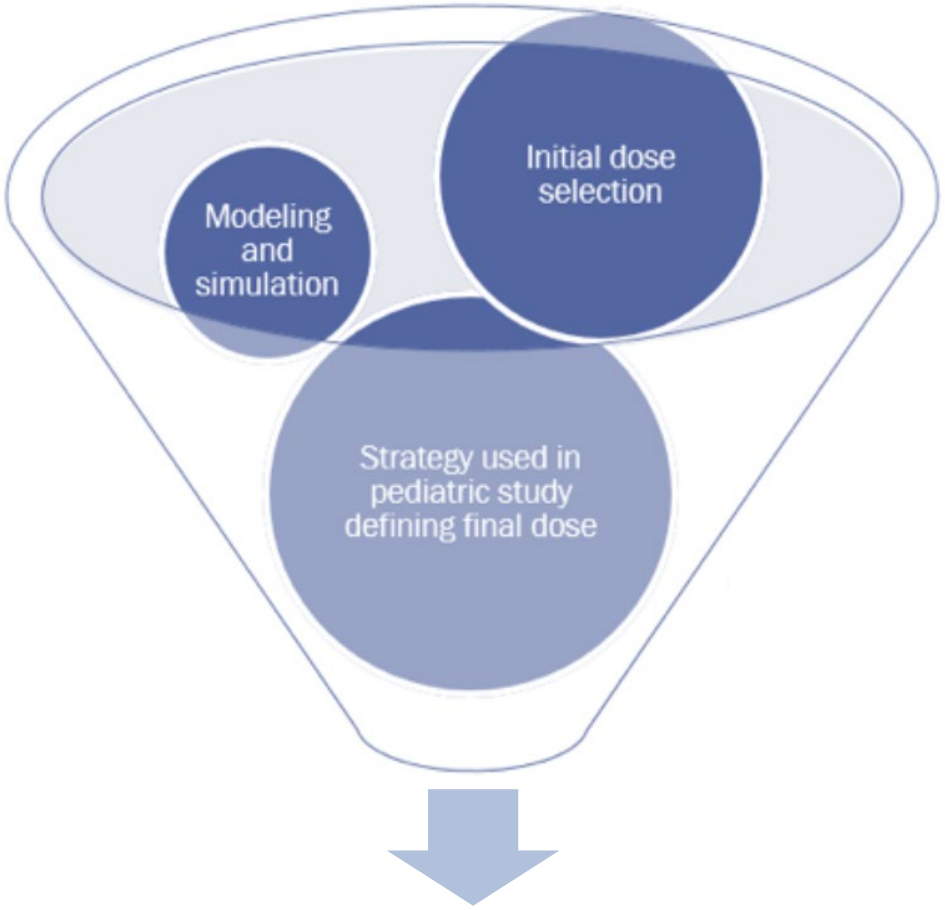


Figure 3. The ratio of predicted (Pred) to observed (Obs) clearance values (CL) for children ≤2 years old. The broken lines denote prediction within 0.5- to 1.5-fold, and dark solid line shows the mean value for the fold error. The red solid line indicates the 2-fold prediction range. ADE indicates age-dependent 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

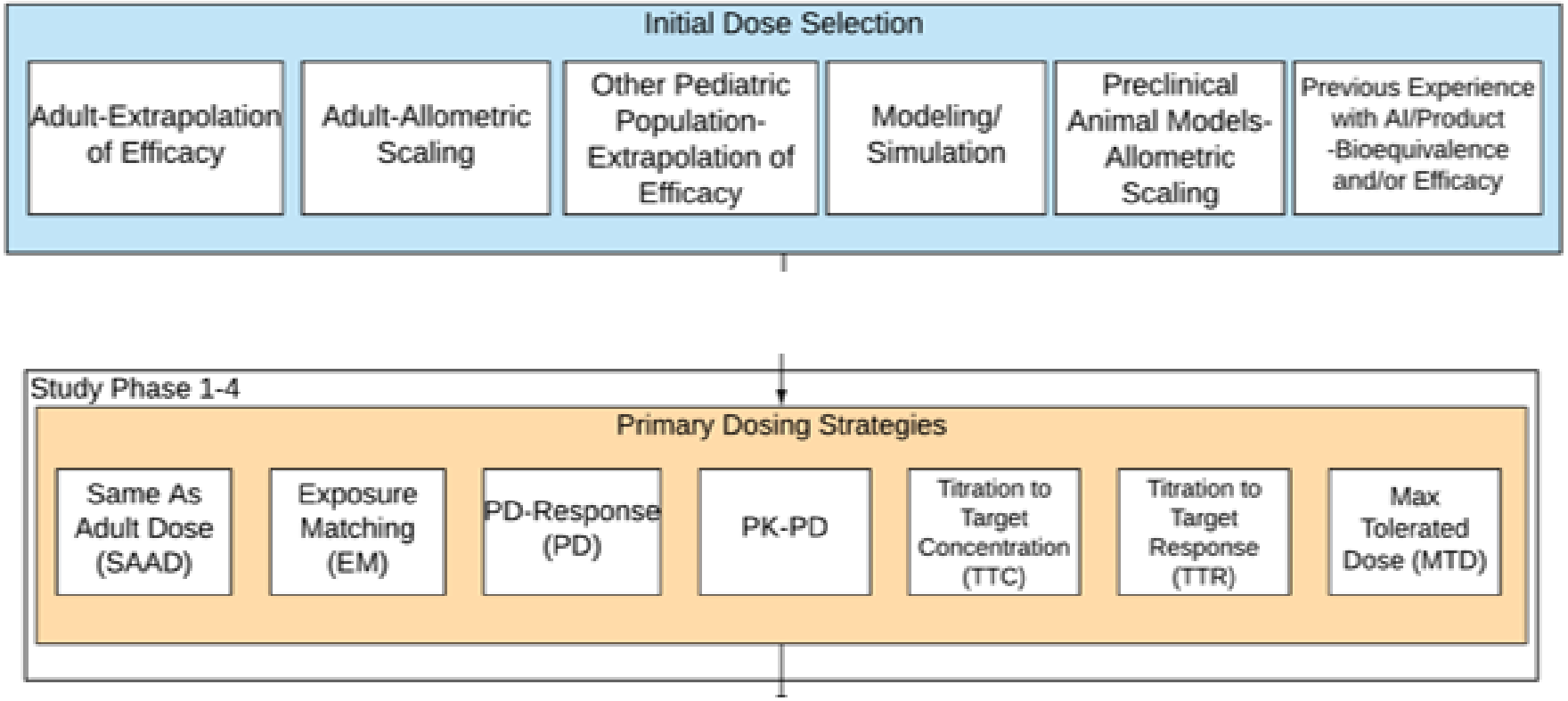


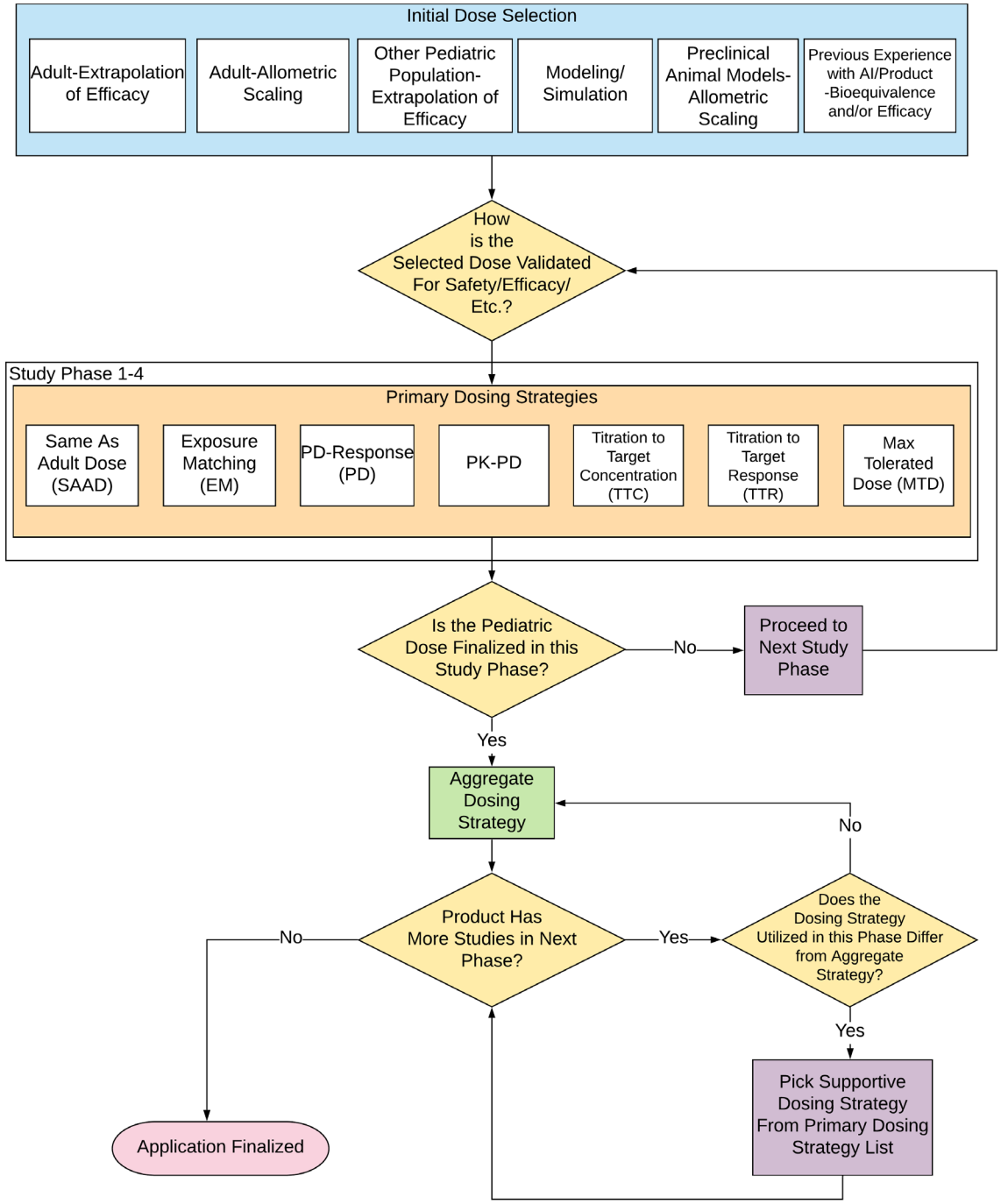
Aggregate dosing strategy

Methods

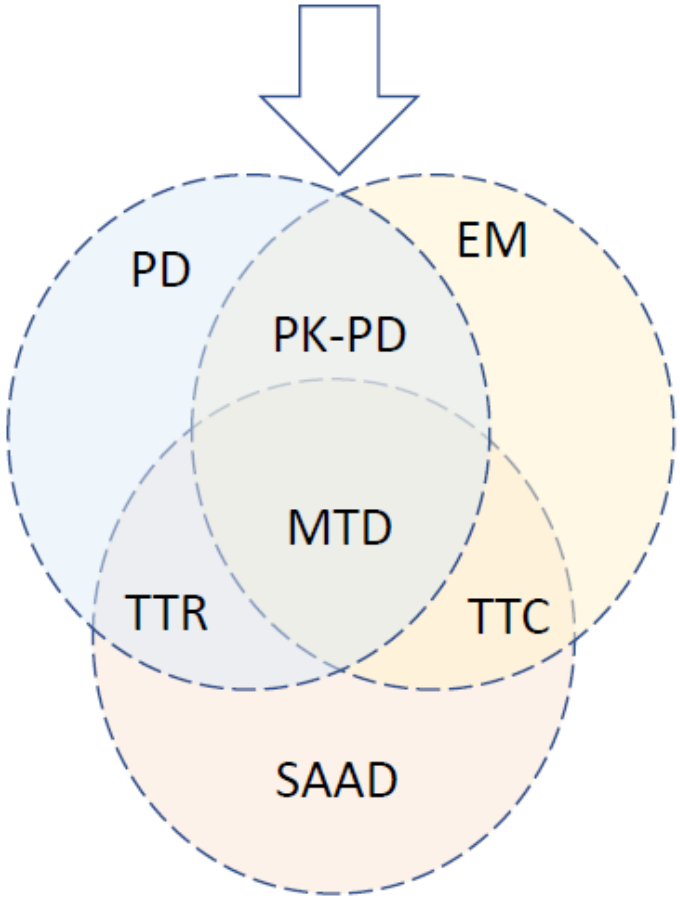
- Reviewed publicly available pediatric clinical studies for products submitted to US FDA under FDASIA (7/9/2012 – present)
- Inclusion criteria:
  - Public documents available for review: medical review and/or clinical pharmacology review and product labels;
  - Include pediatric studies.
- Exclusion 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

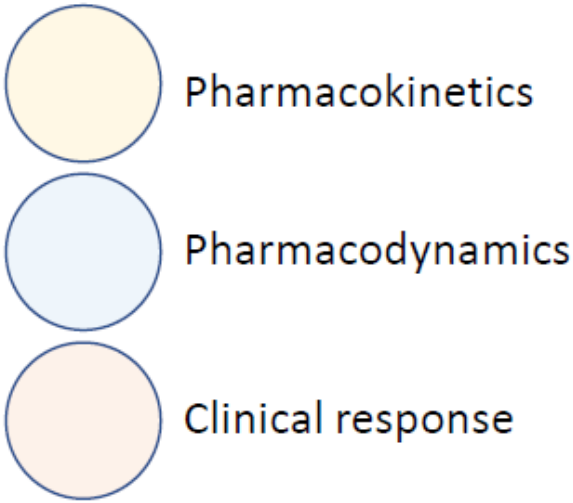



Initial Dose Selection
Adult-Extrapolation of Efficacy
Adult-Allometric Scaling
Other Pediatric Population-Extrapolation of Efficacy
Modeling/ Simulation
Preclinical Animal Models-Allometric Scaling
Previous Experience with AI/Product -Bioequivalence and/or Efficacy
How is the Selected Dose Validated For Safety/Efficacy/ Etc.?
Study Phase 1-4
Primary Dosing Strategies
Same As Adult Dose (SAAD)
Exposure Matching (EM)
PD-Response (PD)
PK-PD
Titration to Target Concentration (TTC)
Titration to Target Response (TTR)
Max Tolerated Dose (MTD)
Is the Pediatric Dose Finalized in this Study Phase?
No
Proceed to Next Study Phase
Yes
Aggregate Dosing Strategy
No
Product Has More Studies in Next Phase?
No
Yes
Does the Dosing Strategy Utilized in this Phase Differ from Aggregate Strategy?
Yes
Pick Supportive Dosing Strategy From Primary Dosing Strategy List
Application Finalized

Approaches to Pediatric Dose Selection



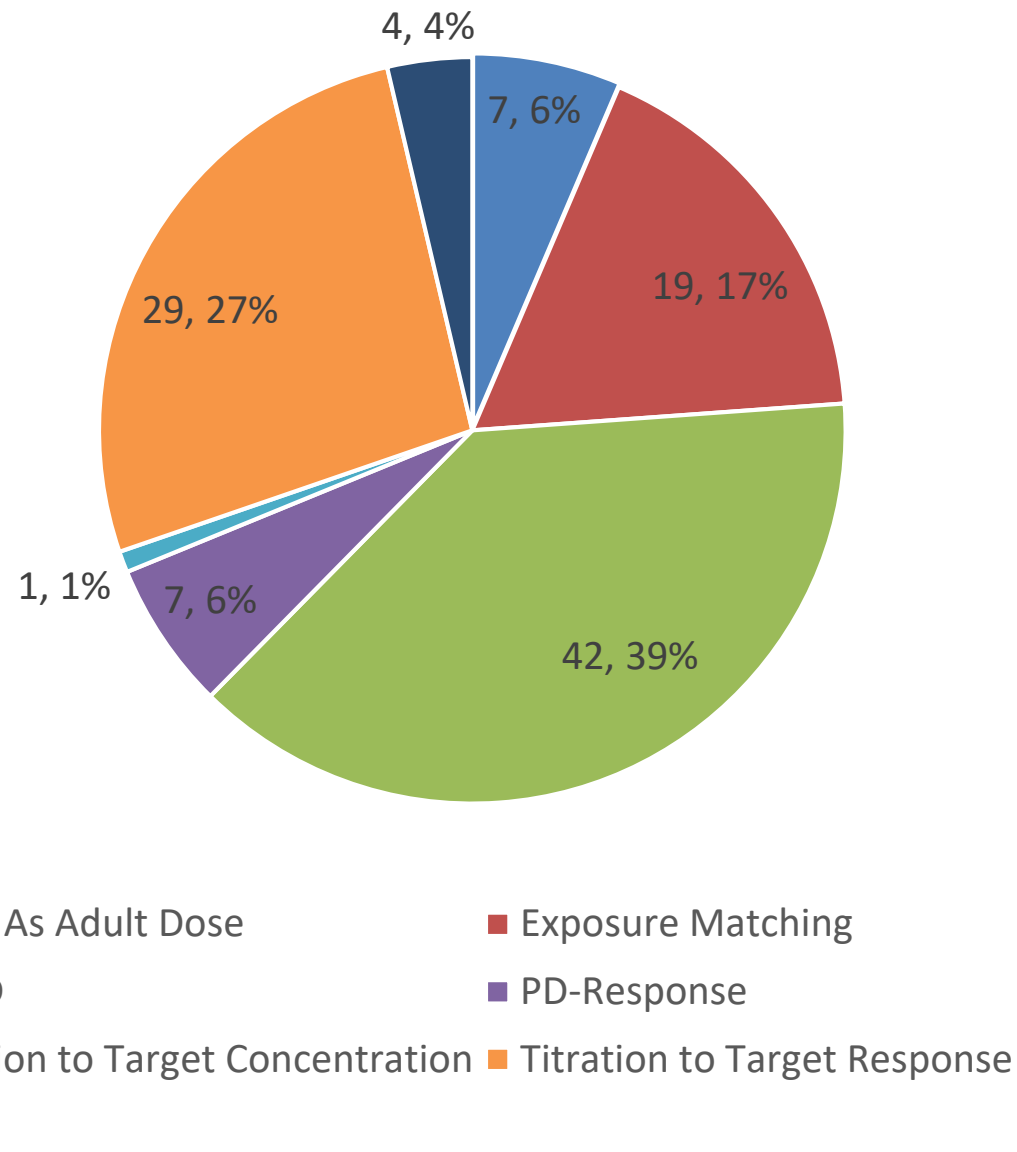
PD = PD-Response
EM = Exposure Matching
PK-PD = Pharmacokinetics-Pharmacodynamics
MTD = Maximum Tolerated Dose
TTR = Titration to Target Response
TTC = Titration to Target Concentration
SAAD = Same As Adult Dose



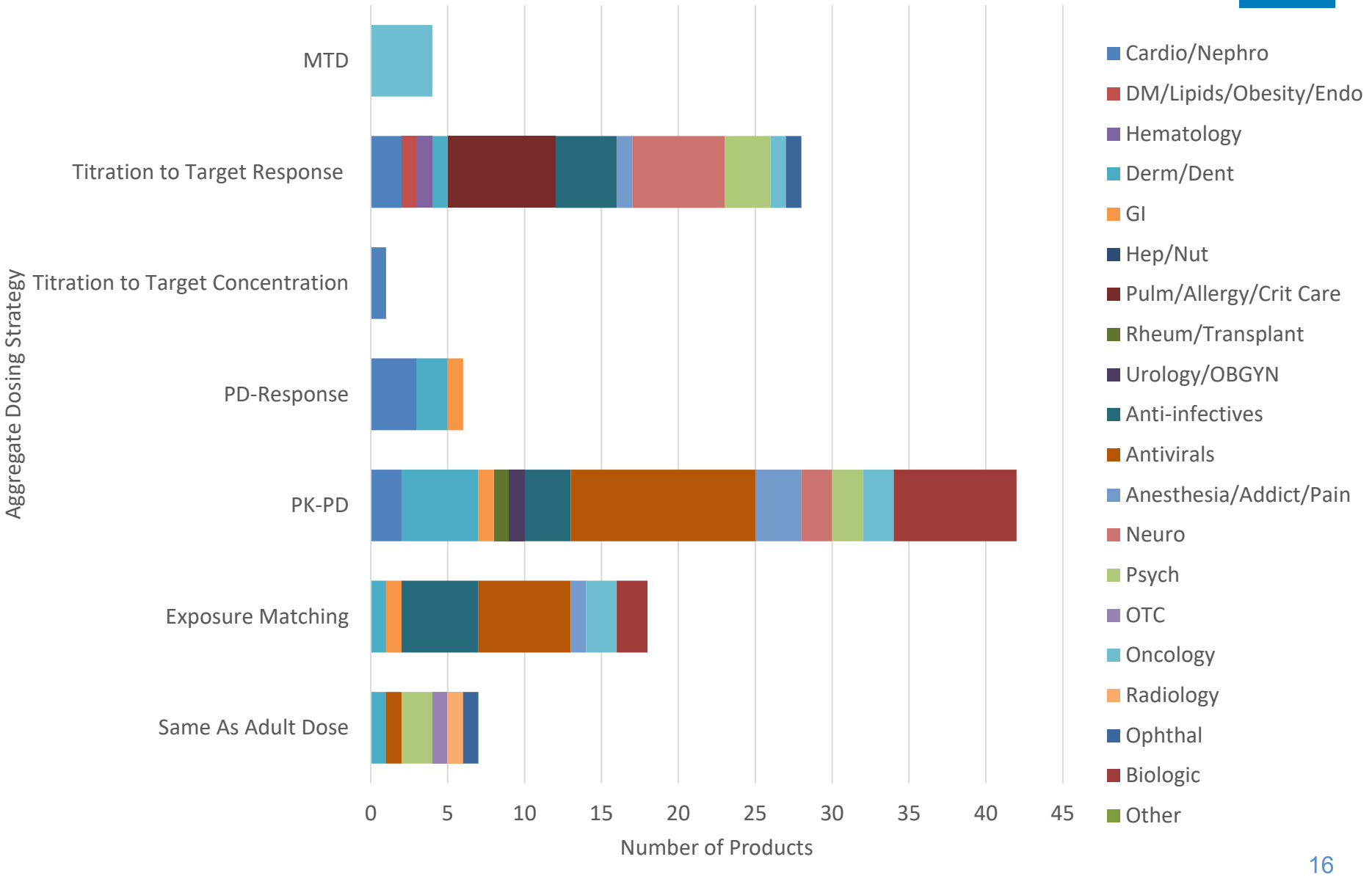
Preliminary Results

- 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



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.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Drug Development Programs Where the Dose Was A Problem

Yaning Wang, Ph.D.
Division of Pharmacometrics
Office of Clinical Pharmacology
OTS/CDER/OMTP/FDA

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 2nd 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 2nd 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 2nd cycle after new dose-ranging trials with lower doses
- …

Dose Related PMC/PMR Studies

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

Dan Lu, et al, A survey of new oncology drug approvals in the USA from 2010 to 2015: a focus on optimal dose and related postmarketing activities, Cancer Chemother Pharmacol (2016) 77:459–476

PMC/PMR Studies for Lower Dose

Year approved	Drug name (brand name)	Indications	Approved highest maintenance dose in adults[a]	Comments[b]
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^2 every 3 weeks	PMR: to compare a lower dose (20 mg/ m^2) with 25 mg/m^2 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	Rilonacept (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

Is This the Dose for You?: The Role of Modeling, S-M Huang, A Bhattaram, N Mehrotra and Y Wang, *Clinical Pharmacology & Therapeutics* (2013); 93 2, 159–162

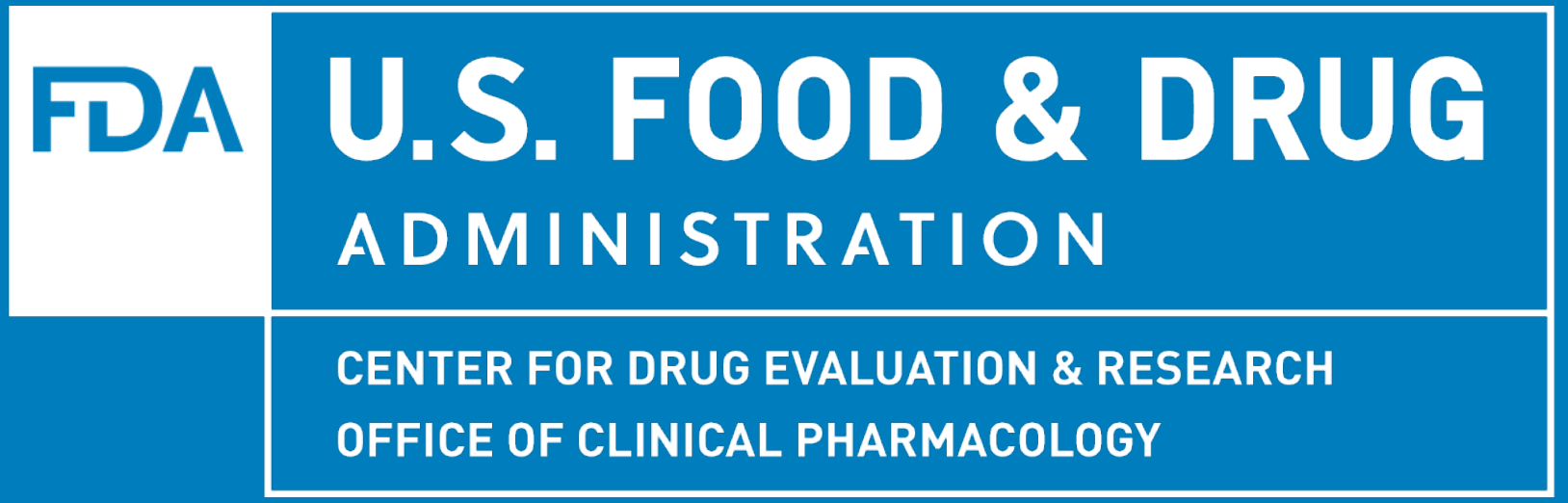
Dose Selection Trend

- 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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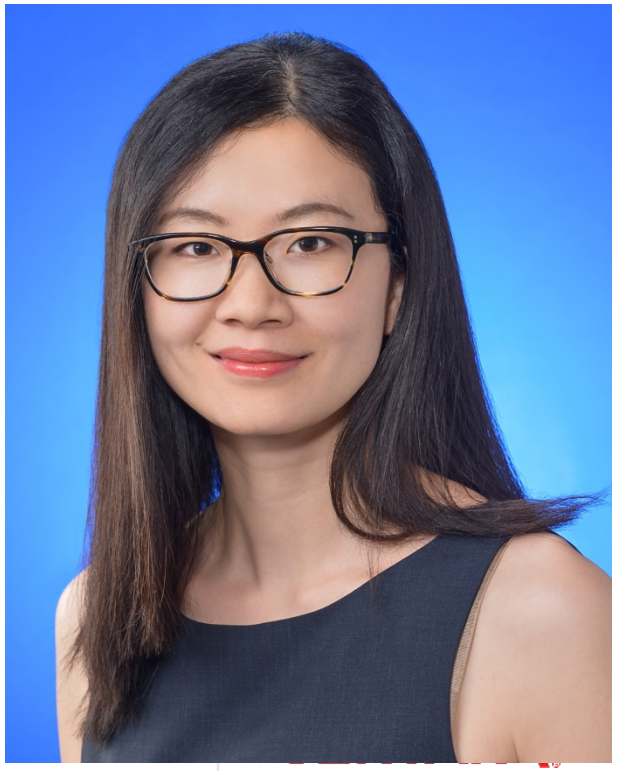
OFFICE OF CLINICAL PHARMACOLOGY

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

Alice Ke, Ph.D.

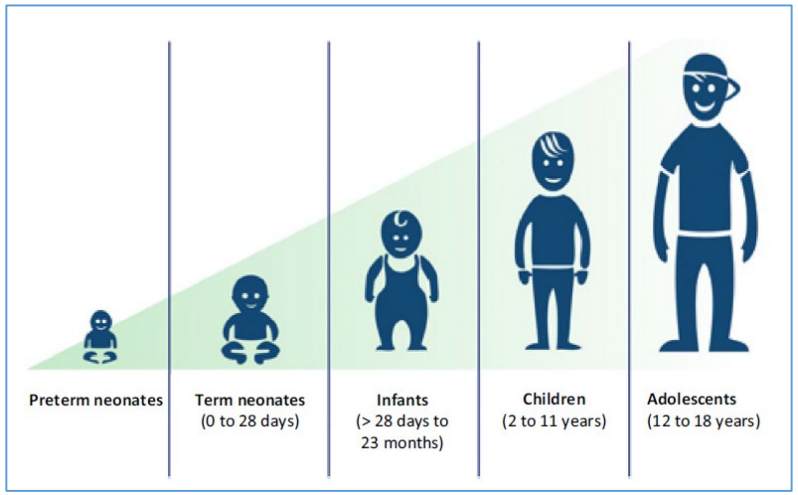
Senior Consultant & Scientific Advisor

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

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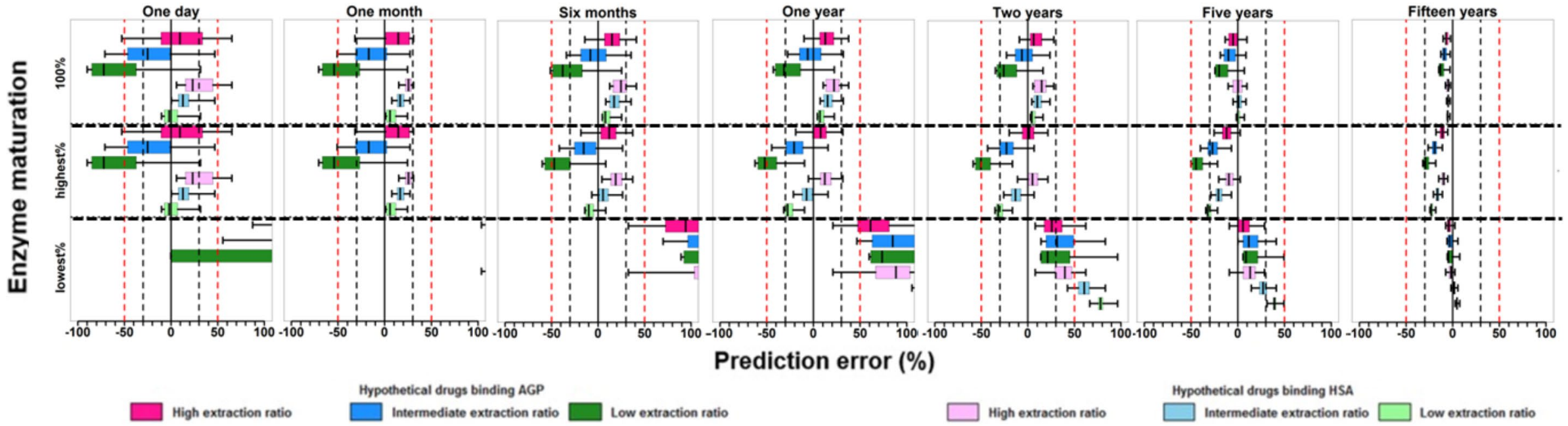
When might allometric scaling (AS) be adequate?

- 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

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PBPK- Integrating Systems & Drug Information

Systems Data

Age
Weight
Tiss lumes
Tis osition
C ut
Rena n
Plasm
Enz
Ontogeny

Realistic Variability

Drug Data

MW
LogP
pKa
Protein binding
BP ratio
In vitro
Metabolism
Permeability
Transport
Solubility

Trial Design

Dose
Route
Frequency
Co-administered drugs
Populations studied

Mechanistic IVIVE approach to predict CL
Whole body PBPK model

Prediction of drug PK (PD) in population of interest

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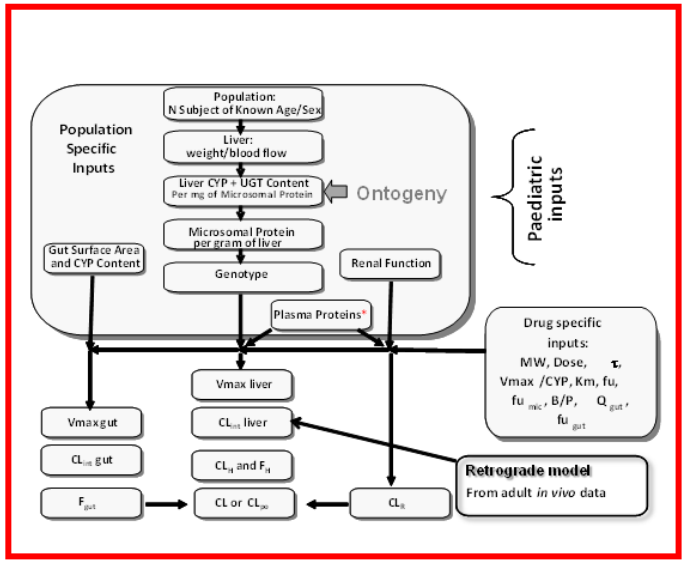
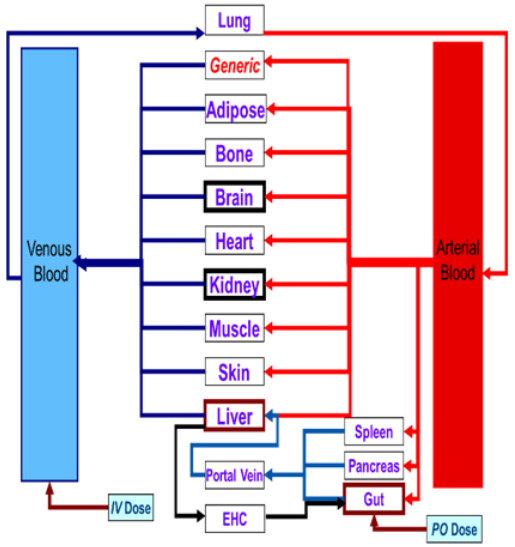
PBPK- Integrating Systems & Drug Information

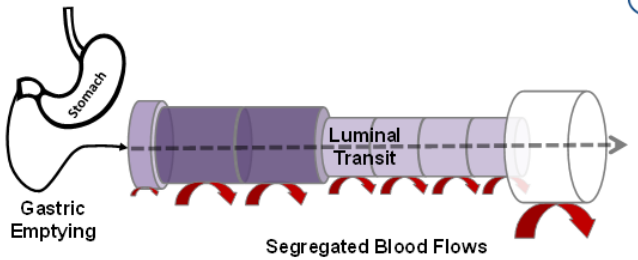
Drug Elimination



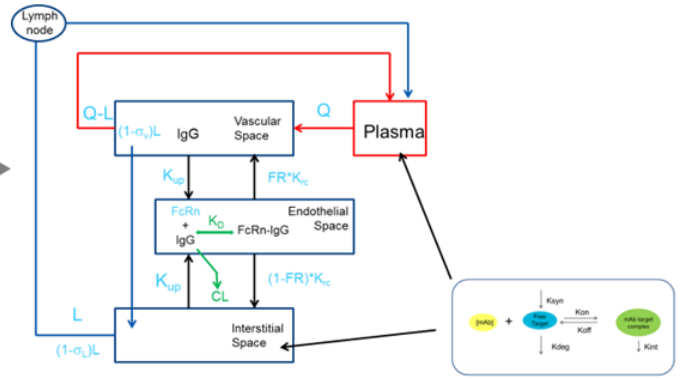
Drug Distribution



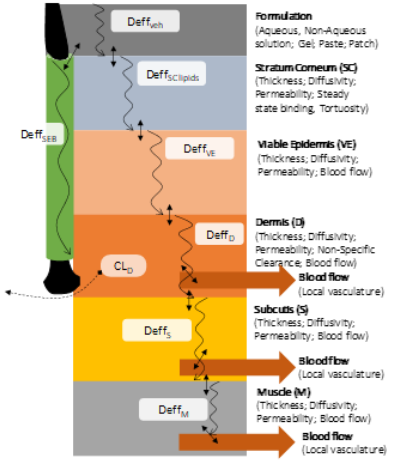
Oral Absorption



Biologics



Dermal Absorption



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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)

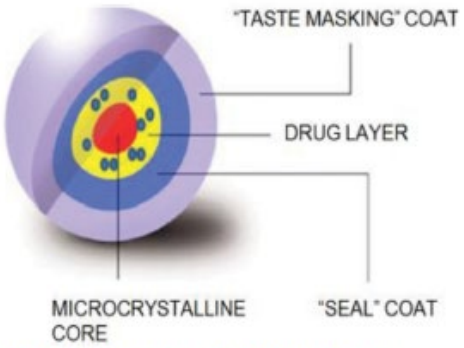
New Hydrocortisone formulations

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



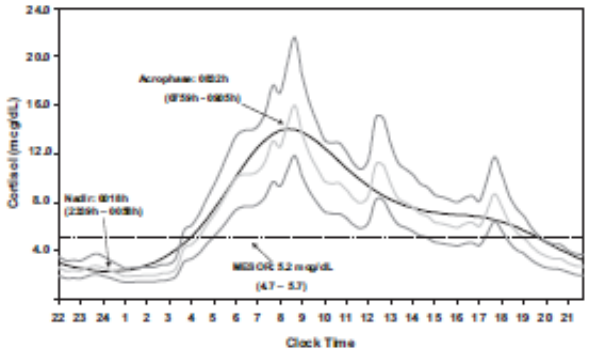
0.5, 1, 2, and 5 mg capsules

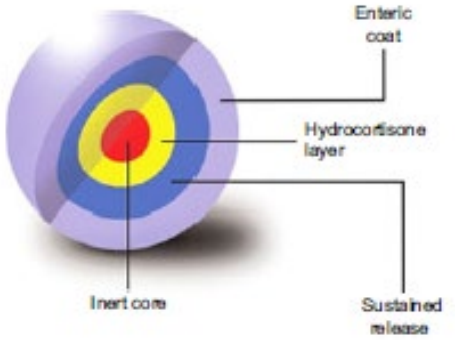
2) **Chronocort** EC granule formulation **(Diurnal variation)**

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

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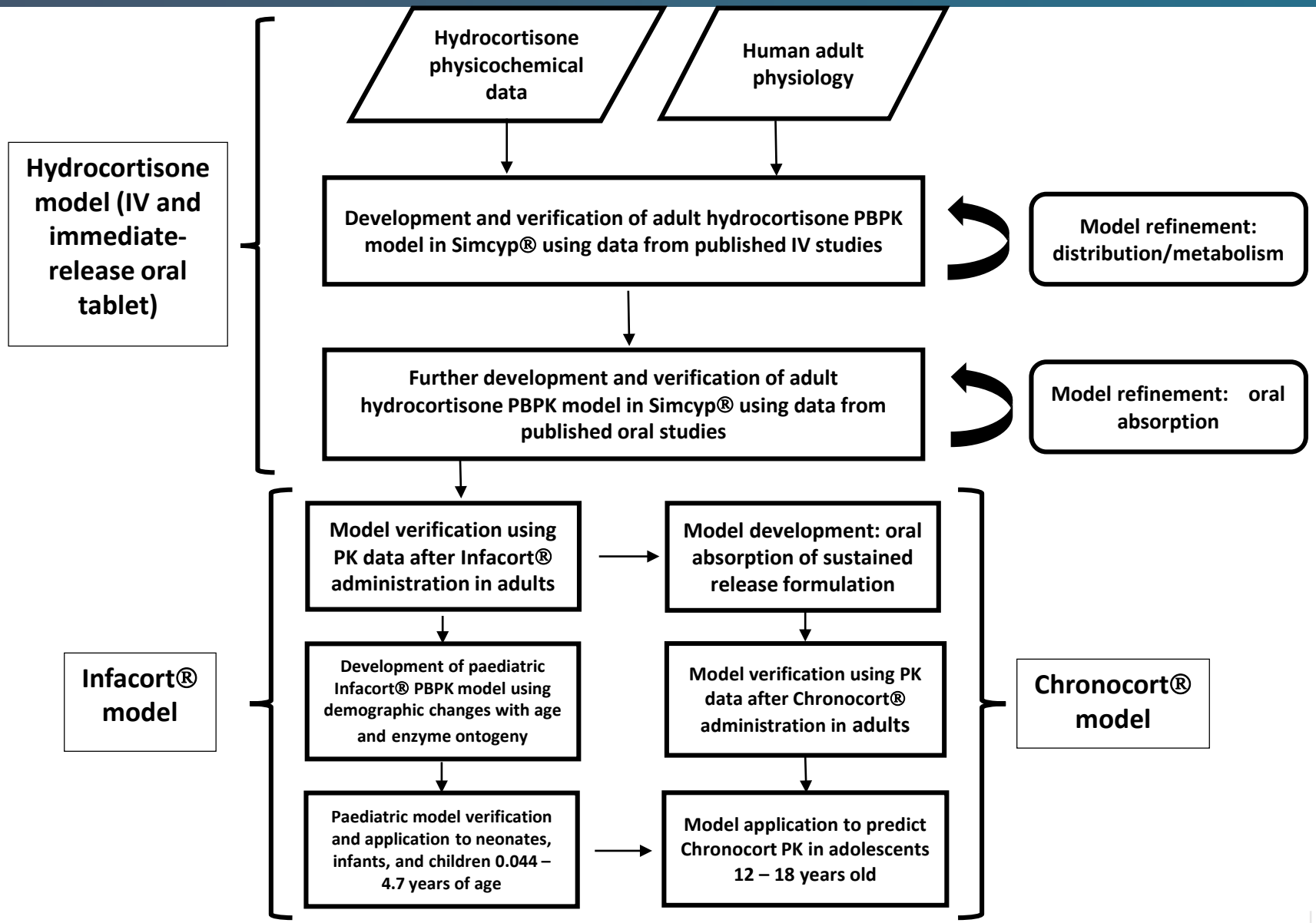
Hydrocortisone PBPK Modelling workflow



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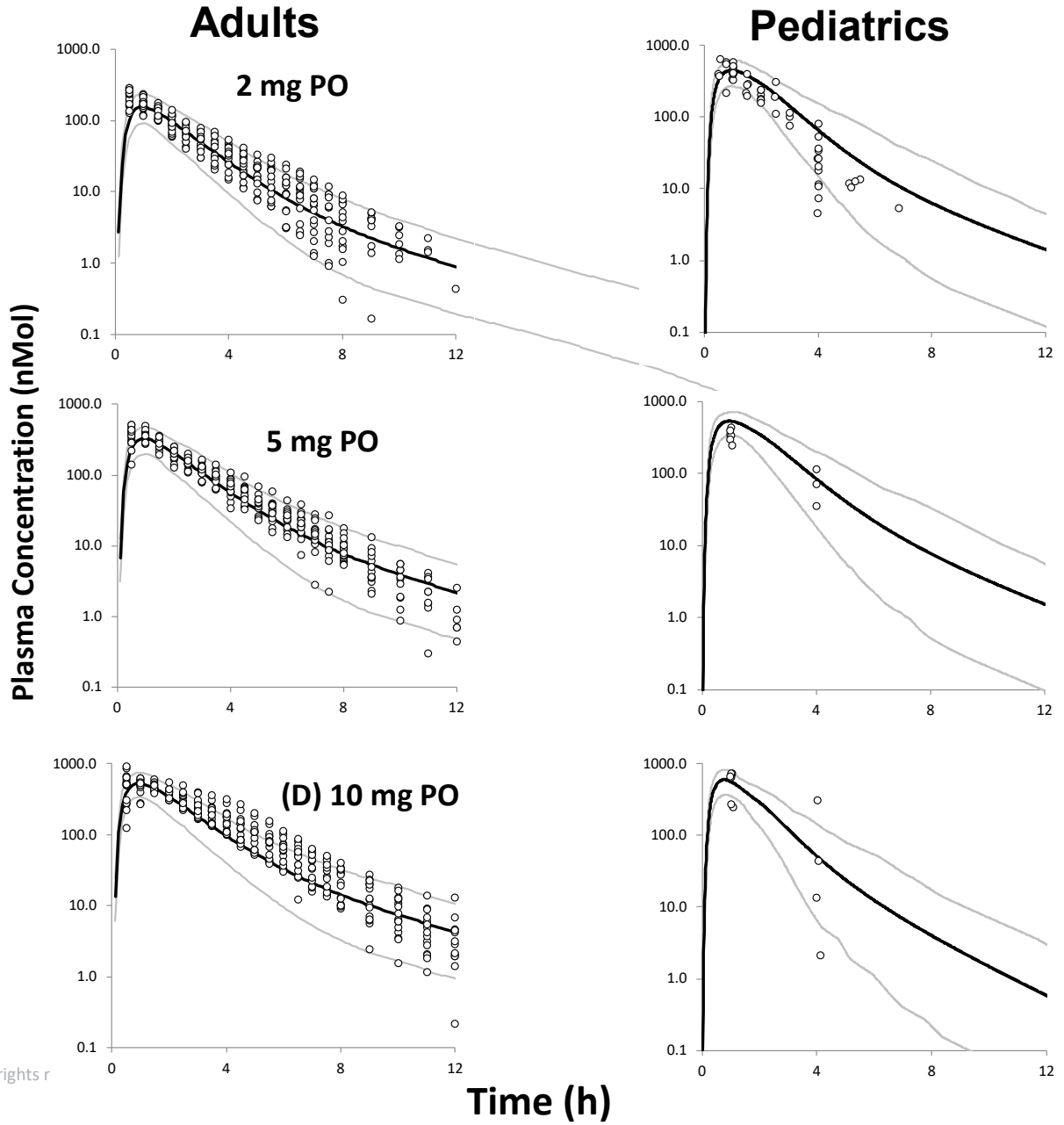
Oral Infacort PK in adults and pediatrics



0.16 mg/kg given to <u>children</u> 2 - 4.7 y (Cohort 1)

0.22 mg/kg given to <u>infants</u> 0.3 – 1.8 y (Cohort 2)

0.53 mg/kg given to <u>neonates</u> 0.044 – 0.071 y (Cohort 3)

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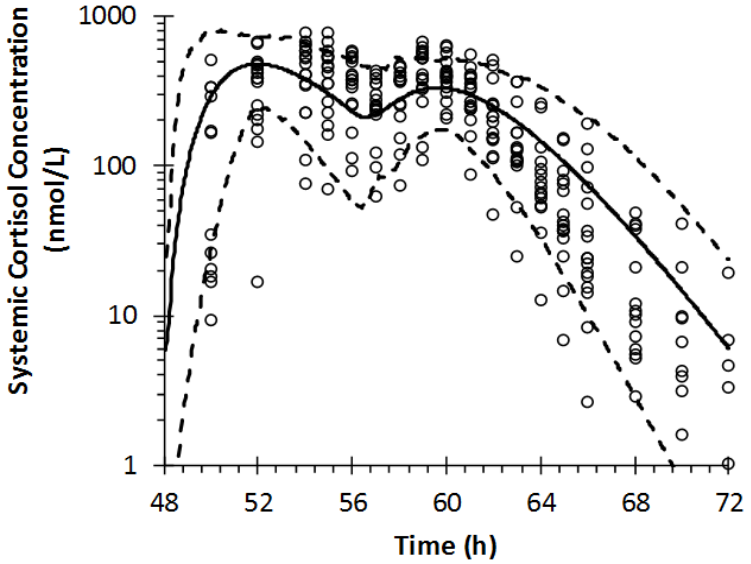
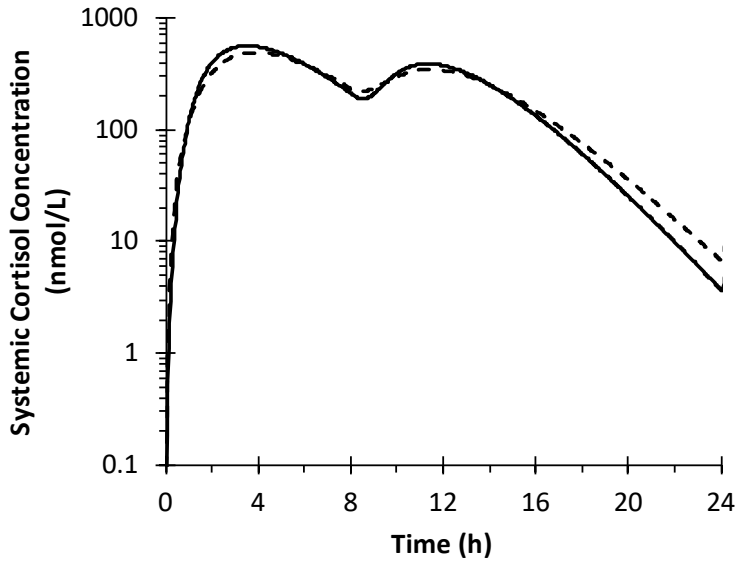
Chronocort PK in adults, dose projections in adolescents

Modelled as EC formulation with trigger pH = 7.2



20mg evening, 10mg morning in adults



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

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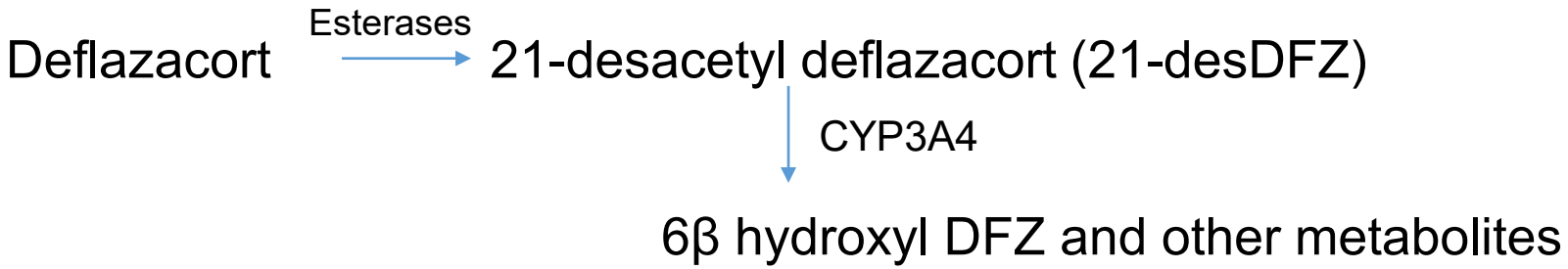
Case study 2: Deflazacort (Emflaza) example



- 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)

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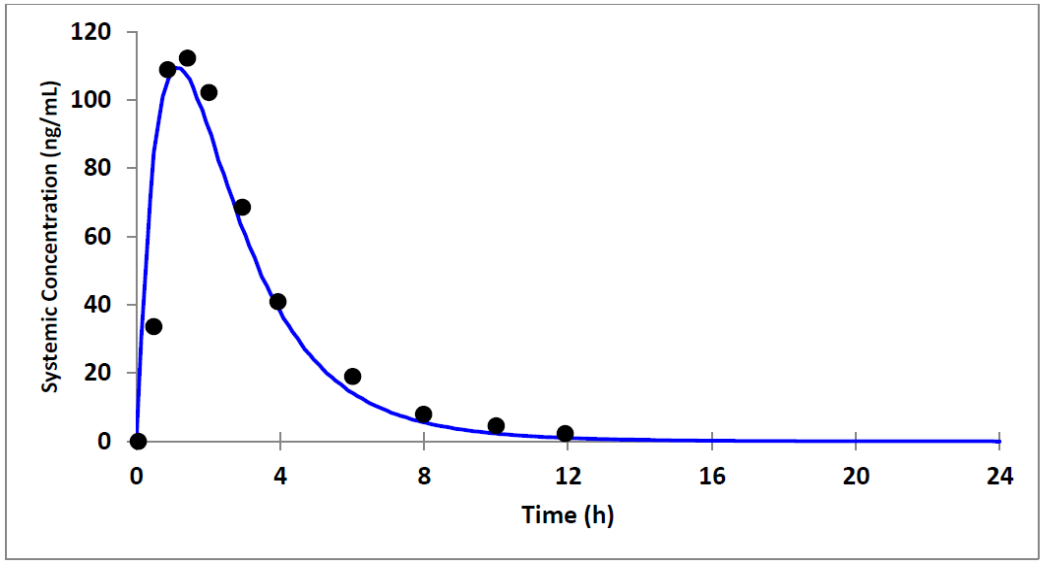
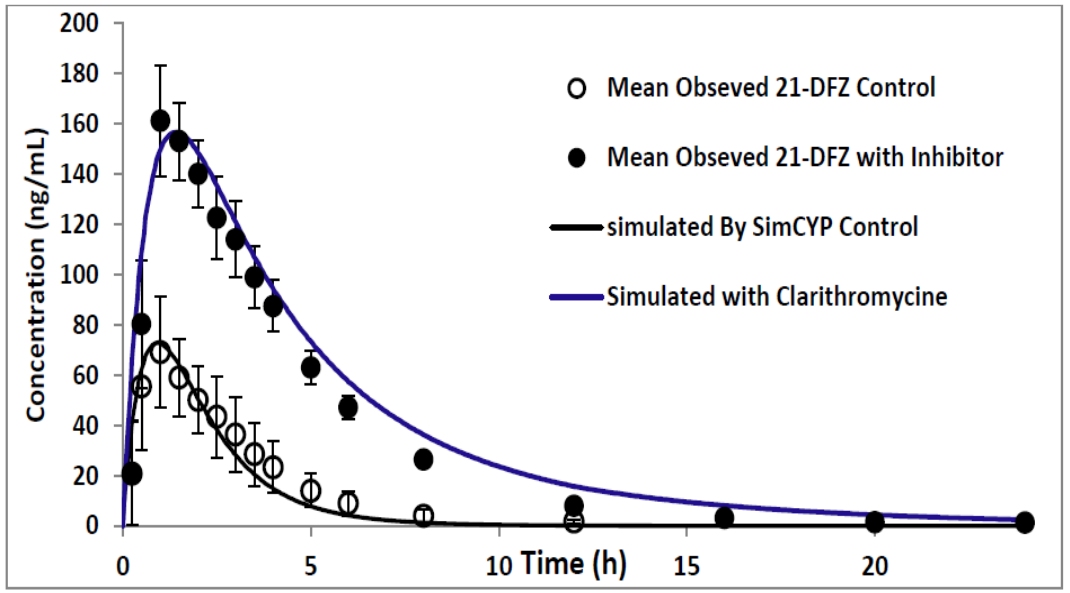
Model Verification in Adults



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



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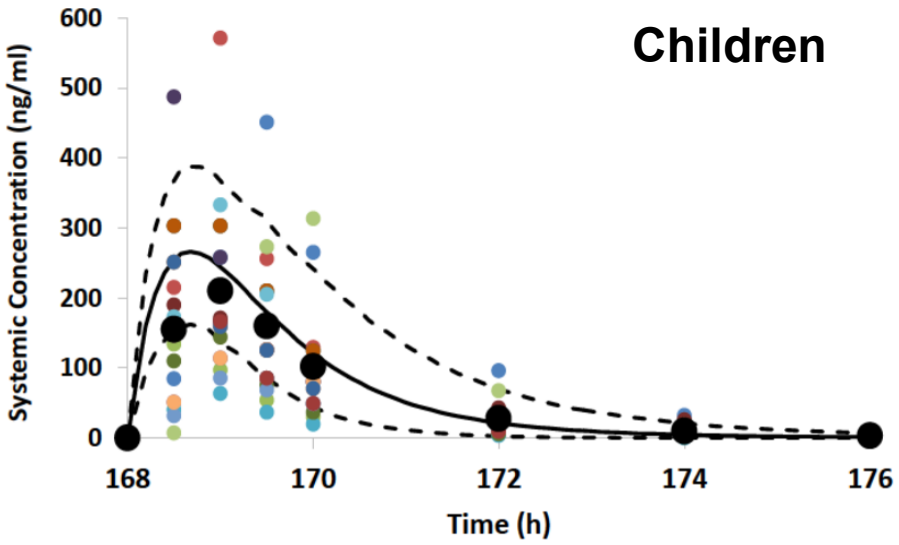
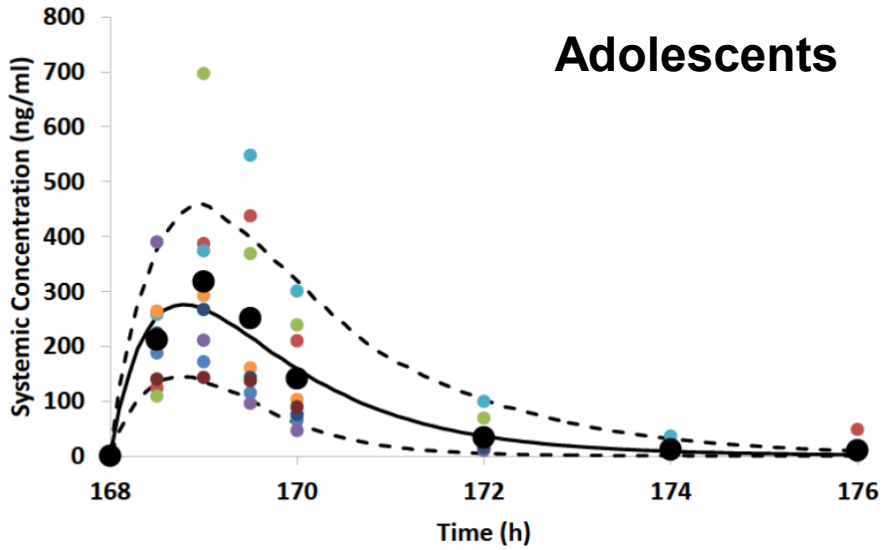
Model Verification in Paediatrics

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





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Model Application: DDI liability prediction

	Children		Adolescents	
Predicted	Cmax Ratio	AUC Ratio	Cmax 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

	Children		Adolescents	
Predicted	Cmax Ratio	AUC Ratio	Cmax 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_{max} Ratio	AUC Ratio
Observed	2.25	3.37
Predicted	2.1	4.2

	Adult	
Rifampicin (600 mg)	C_{max} Ratio	AUC Ratio
Observed	0.06	0.08
Predicted	0.22	0.15

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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)
- Fu 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%).

16

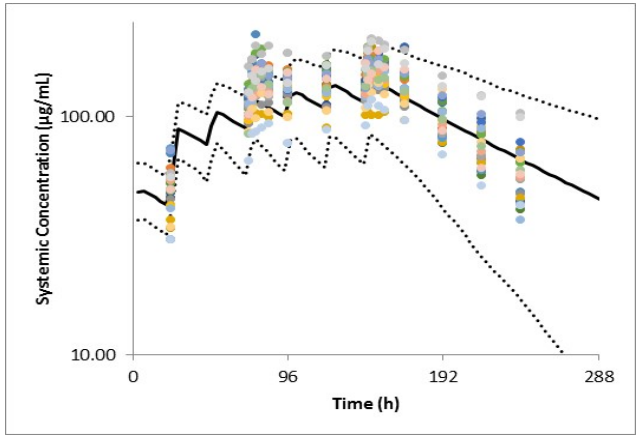
PBPK modelling strategy: from adult to paediatric

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

Learn, Confirm, Modify

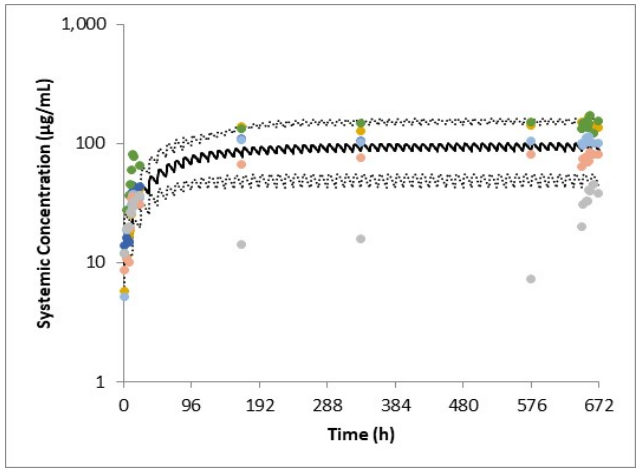
Integrate physiological changes related to SCD
DISEASE EFFECTS



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

Learn, Confirm, Modify

Integrate age-related changes
AGE EFFECTS



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

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

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

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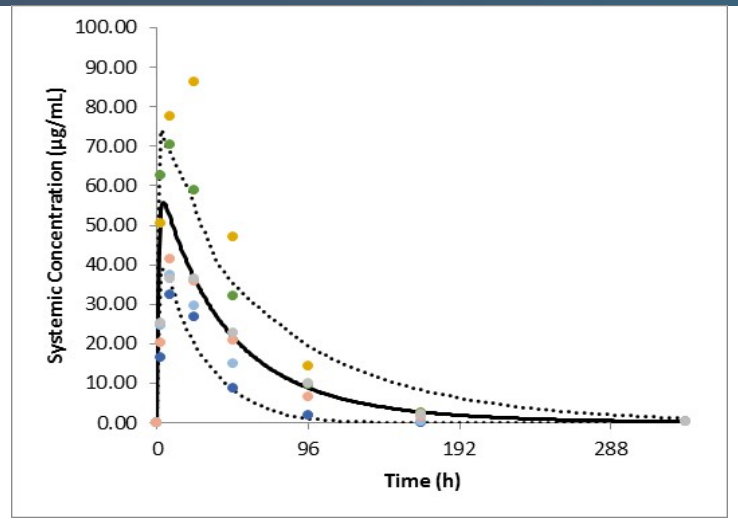
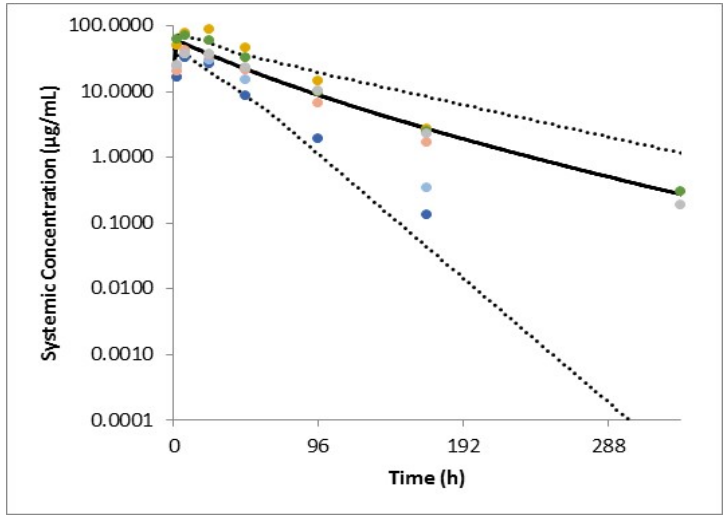
GBT440: simulated blood exposures in children (6 to < 12 years) with SCD





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 5th and 95th percentiles of the simulated population. Circles are observed data.

	C_{max}	AUC
Trial (n=6)	(µg/mL)	(µg/mL.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

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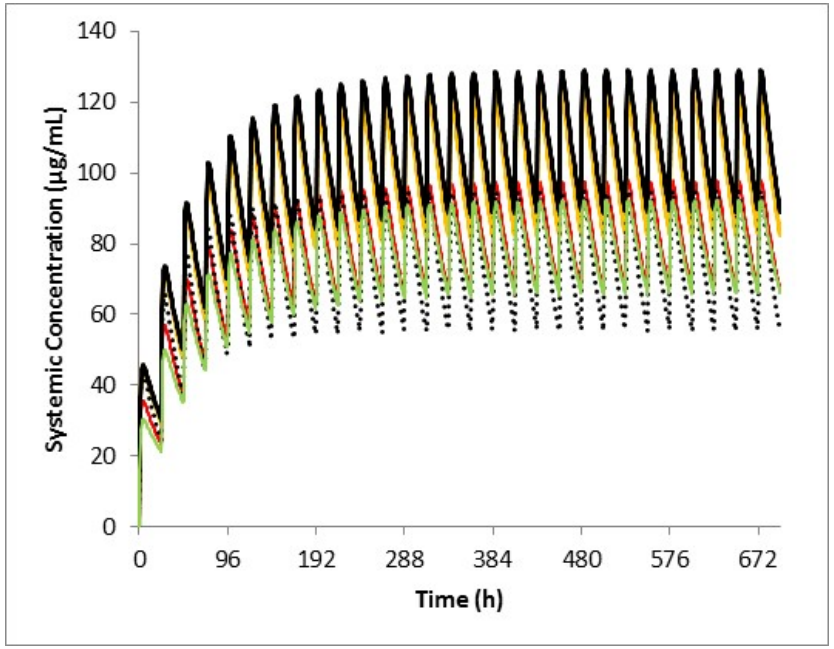
Dose projections in paediatrics with SCD



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_{min}	C_{max}	AUC(0,24)	C_{min}	C_{max}	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

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CENTER FOR TRANSLATIONAL MEDICINE

PBPK for Pediatrics: Really?

Joga Gobburu

Center for Translational Medicine

Department of Pharmacy Practice & Science

University of Maryland, Baltimore

Gobburu is co-founder of Pumas-AI which commercializes Pumas software

The Premise

Pediatric Development Program vs. Academic Research

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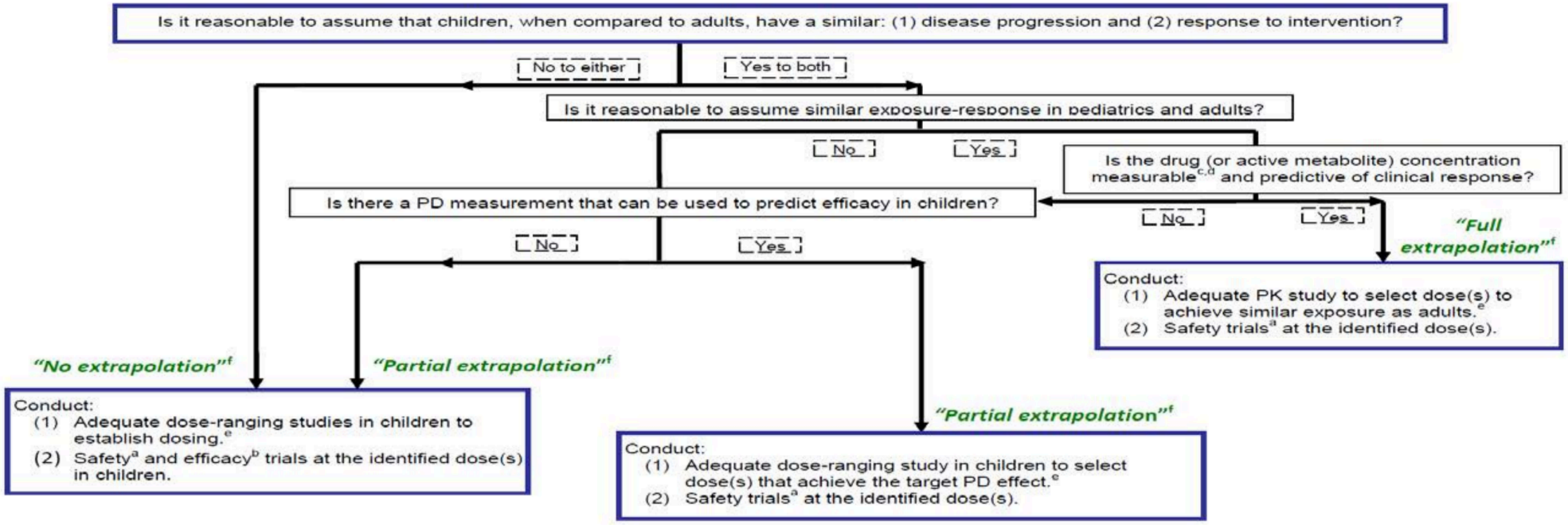
Pediatric Study Planning & Extrapolation Algorithm



Footnotes:

a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.