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
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

The Indian Journal of Pediatrics (December 2019) 86(12):1149 722
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.
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
A
Changes in Metabolic Capacity

Percentage of Adult Activity

- CYP3A4
- CYP1A2
- CYP2D6
- CYP2C9
- UGT2B7

Age

<24 hr 1–7 days 8–28 days 1–3 mo 3–12 mo 1–10 yr

B
Developmental Changes in Distribution Sites

Percentage of Total Body Weight

- Total body water
- Extracellular water
- Body fat

Age

Birth 3 mo 6 mo 9 mo 1 yr 5 yr 10 yr 20 yr 40 yr

C
Changes in Gastrointestinal Function

Percentage of Adult Activity

- Hydrochloric acid production
- Bile acid secretion
- Intestinal and body length
- Intestinal glutathione conjugation
- Intestinal CYP4A1

Age

Birth 1 wk 2 wk 3 wk 1 mo 3 mo 1–3 yr 4–6 yr 5–10 yr Adult

E
Integumentary Development

Thickness
Perfusion
Hydration
Body-surface area: weight

Pre-term neonate Full-term neonate Infant Child Adolescent Adult

D
Acquisition of Renal Function

GFR (ml/min/1.73 m²)

P-aminobenzoic acid clearance (ml/min/1.73 m²)

Age

1–2 yr 2–4 yr 4–6 yr 6–12 yr 12 yr

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?
Dosing in Renal Dysfunction

Drug Monographs in Lexicomp (n=1,121)

Drug Monographs with Pediatric Renal Recommendations in Lexicomp (n=126)

FDA Labeling Review (n=126)

Published Reference Review (n=126)

Pediatric renal recommendations (n=19)

No pediatric renal recommendations (n=107)

Comparison with FDA labels (n=126)

Recommendations equivalent in adult and pediatric label sections (n=16)

Different recommendations (n=48)

Lexicomp provided additional recommendations (n=32)

Same recommendations (n=46)

Pediatric renal impairment clinical trial or case study found (n=42)

Case study only (n=11)
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%
Dealing with Dosage Drifts as Clinician - Ask Why and Do a Study

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

Jill A. Morgan, PharmD, BCPS, BCPPS, FNAP
Professor and Chair
CERSI Pediatric Dose Selection Meeting
October 2020
Review of the Adult Dose Selection EMA Workshop & application to paediatrics

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.
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

Information from preclinical and phase I studies
- FIM based methods
- PK/PD Modelling and Simulations
- Adaptive methods

Phase 2 study design optimization
- Regression models
- PK/PD Modelling and Simulations
- Quantitative systems pharmacology
- MCP-mod/model averaging

Characterisation of DER

Dose selection for Phase 3 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

\[ \Rightarrow \text{Bridging to the DER information in adults} \]
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**

**FT Musuamba et al, CPT 2017**

**EMA M&S Q&As**

**EMA Scientific advice and protocol assistance**

**Qualification of novel methodologies for medicine development**
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)
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.

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

- Initial dose selection
- Strategy used in pediatric study defining final dose
- Modeling and simulation

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

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)
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

Pharmacokinetics
Pharmacodynamics
Clinical response
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: 42, 39%
- Exposure Matching: 19, 17%
- PK-PD: 29, 27%
- PD-Response: 7, 6%
- Titration to Target Concentration: 7, 6%
- Titration to Target Response: 1, 1%
- MTD: 1, 1%
Dosing Strategy by Therapeutic Area

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

Number of Products

Aggregate Dosing Strategy

- Cardio/Nephro
- DM/Lipids/Obesity/Endo
- Hematology
- Derm/Dent
- GI
- Hep/Nut
- Pulm/Allergy/Crit Care
- Rheum/Transplant
- Urology/OBGYN
- Anti-infectives
- Antivirals
- Anesthesia/Addict/Pain
- Neuro
- Psych
- OTC
- Oncology
- Radiology
- Ophthal
- Biologic
- Other
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

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Label dose</th>
<th>Derived dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Infective</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>Yes (Peds)</td>
</tr>
<tr>
<td>Antiviral</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>Yes (Peds)</td>
</tr>
<tr>
<td>Transplant</td>
<td>2</td>
<td>1</td>
<td>1 (therapeutic window)</td>
<td>Yes (Peds)</td>
</tr>
<tr>
<td>CardioRenal</td>
<td>3</td>
<td>1-2</td>
<td>&gt;=1 (titration)</td>
<td>Yes</td>
</tr>
<tr>
<td>Neurology</td>
<td>3</td>
<td>2</td>
<td>&gt;=1 (titration)</td>
<td>Yes (Peds)</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>3</td>
<td>2</td>
<td>&gt;=2 (titration)</td>
<td>Yes</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>3</td>
<td>&gt;1</td>
<td>&gt;1 (titration)</td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>3</td>
<td>&gt;1</td>
<td>1 (titration)</td>
<td>Yes</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3</td>
<td>2</td>
<td>1 (&gt;1 initial dose)</td>
<td>Yes (Peds)</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>3</td>
<td>1-2</td>
<td>1 (rare ↑dose)</td>
<td>Yes (Peds)</td>
</tr>
<tr>
<td>Dermatology</td>
<td>2</td>
<td>1-2</td>
<td>1-2</td>
<td>Yes (Peds)</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>3</td>
<td>1-2</td>
<td>1-2</td>
<td>Yes (Peds)</td>
</tr>
<tr>
<td>Bone</td>
<td>2</td>
<td>1</td>
<td>1 (&gt;1 regimen)</td>
<td></td>
</tr>
<tr>
<td>Reproductive</td>
<td>3</td>
<td>1-2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Urology</td>
<td>2</td>
<td>1-2</td>
<td>1 (titration)</td>
<td></td>
</tr>
<tr>
<td>Oncology</td>
<td>&lt;=2</td>
<td>1</td>
<td>1 (&gt;1 regimen)</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td>3</td>
<td>1-2</td>
<td>&gt;1 (titration)</td>
<td>Yes (Peds)</td>
</tr>
</tbody>
</table>
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

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

# PMC/PMR Studies for Lower Dose

<table>
<thead>
<tr>
<th>Year approved</th>
<th>Drug name (brand name)</th>
<th>Indications</th>
<th>Approved highest maintenance dose in adults</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Gabapentin enacarbil (Horizant)</td>
<td>Restless legs syndrome (RLS)</td>
<td>600 mg</td>
<td>PMC: 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</td>
</tr>
<tr>
<td>2011</td>
<td>Vilazodone (Viibryd)</td>
<td>Major depressive disorder (MDD)</td>
<td>40 mg</td>
<td>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</td>
</tr>
<tr>
<td>2010</td>
<td>Dalfampridine (Ampyra)</td>
<td>Multiple sclerosis (MS)</td>
<td>10 mg twice daily</td>
<td>PMC: to evaluate the efficacy of 5-mg twice-daily dose in MS</td>
</tr>
<tr>
<td>2010</td>
<td>Cabazitaxel (Jevtana)</td>
<td>Hormone-refractory metastatic prostate cancer (mHRPC)</td>
<td>25 mg/m(^2) every 3 weeks</td>
<td>PMC: to compare a lower dose (20 mg/m(^2)) with 25 mg/m(^2) in mHRPC</td>
</tr>
<tr>
<td>2010</td>
<td>Fingolimod (Gilenya)</td>
<td>Multiple sclerosis</td>
<td>0.5 mg daily</td>
<td>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</td>
</tr>
<tr>
<td>2010</td>
<td>Lurasidone (Latuda)</td>
<td>Schizophrenia</td>
<td>160 mg</td>
<td>PMC: to identify the lowest effective dose; to evaluate with a dose lower than 40 mg (e.g., 20 mg daily)</td>
</tr>
<tr>
<td>2009</td>
<td>Asenapine (Saphris)</td>
<td>Schizophrenia and bipolar mania</td>
<td>10 mg twice daily</td>
<td>PMC: to identify the lowest effective dose; to study a dose &lt;10 mg twice daily (e.g., 5 mg twice daily) in bipolar mania and to study a dose &lt;5 mg twice daily (e.g., 2.5 mg twice daily) in schizophrenia</td>
</tr>
<tr>
<td>2008</td>
<td>Rilonacept (Arcalyst)</td>
<td>Cryopyrin-associated periodic syndrome</td>
<td>160 mg weekly</td>
<td>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</td>
</tr>
<tr>
<td>2008</td>
<td>Desvenlafaxine (Pristiq)</td>
<td>MDD</td>
<td>50 mg</td>
<td>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</td>
</tr>
<tr>
<td>2006</td>
<td>Paliperidone (Invega)</td>
<td>Schizophrenia</td>
<td>12 mg</td>
<td>PMC: to conduct a study to explore for a minimal effective dose</td>
</tr>
</tbody>
</table>

[888x460 to 937x519]

[Image 138x10 to 778x480]

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

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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

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

Krekels 2019 CPT:PSP
PBPK- Integrating Systems & Drug Information

- **Systems Data**
  - Age
  - Weight
  - Tissue volumes
  - Tissue composition
  - Concentrations
  - Renal function
  - Plasma
  - Enzymes
  - Ontogeny

- **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**
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)

2) Chronocort EC granule formulation (Diurnal variation)
Hydrocortisone PBPK Modelling workflow

- Hydrocortisone model (IV and immediate-release oral tablet)
- Infacort® model
- Chronocort® model

Hydrocortisone physicochemical data

- Development and verification of adult hydrocortisone PBPK model in Simcyp® using data from published IV studies

- Further development and verification of adult hydrocortisone PBPK model in Simcyp® using data from published oral studies

- Model refinement: distribution/metabolism

- Model refinement: oral absorption

- Model verification using PK data after Infacort® administration in adults

- Model development: oral absorption of sustained release formulation

- Development of paediatric Infacort® PBPK model using demographic changes with age and enzyme ontogeny

- Paediatric model verification and application to neonates, infants, and children 0.044 – 4.7 years of age

- Model verification using PK data after Chronocort® administration in adults

- Model application to predict Chronocort PK in adolescents 12 – 18 years old

- Model refinement: distribution/metabolism

- Model refinement: oral absorption
Oral Infacort PK in adults and pediatrics

**Adults**

- **2 mg PO**
- **5 mg PO**
- **(D) 10 mg PO**

**Pediatrics**

- **0.16 mg/kg given to children 2 - 4.7 y (Cohort 1)**
- **0.22 mg/kg given to infants 0.3 – 1.8 y (Cohort 2)**
- **0.53 mg/kg given to neonates 0.044 – 0.071 y (Cohort 3)**
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/m² evening, 5.8 mg/m² 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

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.8 mg/kg</td>
<td>0.9 mg/kg</td>
</tr>
<tr>
<td></td>
<td>(C_{\text{max}})</td>
<td>(AUC_{(0,8)})</td>
</tr>
<tr>
<td>Simulated</td>
<td>261 (ng/mL)</td>
<td>499 (ng/mL*hr)</td>
</tr>
<tr>
<td>Observed</td>
<td>214 (ng/mL)</td>
<td>374 (ng/mL*hr)</td>
</tr>
</tbody>
</table>

### Graphs
- **Children**
  - Systemic Concentration (ng/mL) vs Time (h)
  - Time points: 168, 170, 172, 174, 176

- **Adolescents**
  - Systemic Concentration (ng/mL) vs Time (h)
  - Time points: 168, 170, 172, 174, 176
## Model Application: DDI liability prediction

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predicted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>C&lt;sub&gt;max&lt;/sub&gt; Ratio</td>
<td>AUC Ratio</td>
</tr>
<tr>
<td>(7.5 mg/kg)</td>
<td>1.97</td>
<td>3.85</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>1.96</td>
<td>3.61</td>
</tr>
<tr>
<td>(6 mg/kg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Adult

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt; Ratio</th>
<th>AUC Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>2.25</td>
<td>3.37</td>
</tr>
<tr>
<td>(500 mg)</td>
<td>Predicted</td>
<td>2.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt; Ratio</th>
<th>AUC Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>0.06</td>
<td>0.08</td>
</tr>
<tr>
<td>(600 mg)</td>
<td>Predicted</td>
<td>0.22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt; Ratio</th>
<th>AUC Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>0.43</td>
<td>0.29</td>
</tr>
</tbody>
</table>

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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)].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended dose of DFZ in the presence of a</th>
<th>Based on Cmax</th>
<th>Based on AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>0.4 to 0.5</td>
<td>0.2 to 0.3</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>0.4 to 0.5</td>
<td>0.2 to 0.3</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>3.6</td>
<td>&gt;5.4</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>2.0</td>
<td>3.0</td>
<td></td>
</tr>
</tbody>
</table>
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%).
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 5th and 95th percentiles of the simulated population. Circles are observed data.

<table>
<thead>
<tr>
<th>Trial (n=6)</th>
<th>C_{max} (µg/mL)</th>
<th>AUC (µg/mL.h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51.8</td>
<td>3344</td>
</tr>
<tr>
<td>2</td>
<td>55.9</td>
<td>2279</td>
</tr>
<tr>
<td>3</td>
<td>44.5</td>
<td>2560</td>
</tr>
<tr>
<td>4</td>
<td>61.0</td>
<td>3405</td>
</tr>
<tr>
<td>5</td>
<td>54.5</td>
<td>2693</td>
</tr>
<tr>
<td>6</td>
<td>51.6</td>
<td>3077</td>
</tr>
<tr>
<td>7</td>
<td>59.8</td>
<td>3666</td>
</tr>
<tr>
<td>8</td>
<td>61.9</td>
<td>2464</td>
</tr>
<tr>
<td>9</td>
<td>56.6</td>
<td>2185</td>
</tr>
<tr>
<td>10</td>
<td>59.0</td>
<td>2007</td>
</tr>
<tr>
<td>Population (n=60)</td>
<td>55.4</td>
<td>2716</td>
</tr>
<tr>
<td>Observed (n=6)</td>
<td>47.3</td>
<td>2785</td>
</tr>
<tr>
<td>S/O</td>
<td>1.17</td>
<td>0.98</td>
</tr>
</tbody>
</table>

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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.

<table>
<thead>
<tr>
<th>Populations (n=70)</th>
<th>Dose equivalent</th>
<th>$C_{\text{min}}$</th>
<th>$C_{\text{max}}$</th>
<th>$\text{AUC}(0,24)$</th>
<th>$C_{\text{min}}$</th>
<th>$C_{\text{max}}$</th>
<th>$\text{AUC}(0,24)$</th>
<th>Ratios (relative to adult)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 months to 2 years - Simcyp ontogeny</td>
<td>200</td>
<td>73.7</td>
<td>118</td>
<td>2330</td>
<td>1.25</td>
<td>1.34</td>
<td>1.31</td>
<td></td>
</tr>
<tr>
<td>9 months to 2 years - Upreti ontogeny</td>
<td>200</td>
<td>43.6</td>
<td>87.9</td>
<td>1590</td>
<td>0.74</td>
<td>1.00</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>2 to 5 years</td>
<td>300</td>
<td>67.7</td>
<td>112</td>
<td>2190</td>
<td>1.15</td>
<td>1.27</td>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td>6 to 11 years</td>
<td>400</td>
<td>55.0</td>
<td>89.5</td>
<td>1754</td>
<td>0.93</td>
<td>1.02</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>12 to 17 years</td>
<td>900</td>
<td>70.0</td>
<td>109</td>
<td>2180</td>
<td>1.19</td>
<td>1.24</td>
<td>1.22</td>
<td></td>
</tr>
<tr>
<td>adults</td>
<td>900</td>
<td>58.9</td>
<td>87.9</td>
<td>1780</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>
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
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  • Jennifer Bonner

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  • Richard Ross
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PBPK for Pediatrics: Really?

Joga Gobburu

Center for Translational Medicine
Department of Pharmacy Practice & Science
University of Maryland, Baltimore
The Premise

Pediatric Development Program vs. Academic Research