Evaluation of Drug-Drug Interactions and Their Influence on Drug Dosing in the Pediatric Population

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• I receive funding for neonatal and pediatric clinical pharmacology research from the Eunice Kennedy Shriver National Institute for Child Health and Human Development (R01HD096435 and HHSN275201000003I)

• I will present examples that evaluate off label dosing of approved medications
Objectives

• To describe the prevalence of potential drug-drug interactions (DDIs) in the pediatric population

• To summarize barriers to evaluating pediatric DDI potential and discuss potential differences in DDI potential between adults and pediatric patients

• To present examples that use pharmacometric approaches or real-word data to evaluate DDI potential in pediatric patients
Potential DDIs are Common in Hospitalized Pediatric Patients

- Retrospective cohort study using the Pediatric Health Information System database

- For infants <1 year of age, 21.8% exposed to a potential DDI on Day 1, increasing to 32% by Day 30

- For those ≥1 year of age, 34.7% and 66.3% were exposed to a potential DDI on Day 1 and Day 30, respectively

Proportion of Pediatric Patients Exposed to a Potential Drug-Drug Interaction (PDDI)

DDI Potential in Adults and Pediatric Patients Can Differ

• A systematic literature review was performed to compare the magnitude of reported DDIs in children and adults

• The magnitude of DDIs for 24 drug pairs from 31 studies could be assessed and compared with adults

• The fold interaction was compared using area under the concentration vs. time curve, clearance, or steady-state concentrations

Challenges to Evaluating DDIs in the Pediatric Population

- No “healthy child volunteer”
- Ethical concerns
- Limited blood volume and timed sampling
- DDI potential may need to be assessed across pediatric age groups
- Low rates of parental informed consent
- Drug may be used in a critically ill population → increases variability
Proposed Workflow to Apply PBPK Modeling for Pediatric DDI Evaluation

**Develop Adult Model**
- drug properties
- system properties
- study protocol and formulation properties

**Adult DDI Evaluation**
- Incorporate relevant experimental interaction data
  - induction data
- Predict, learn, confirm

**Pediatric Modeling and DDI Prediction**
- Scale PBPK model to children, including ontogeny functions
- Evaluate pediatric PBPK model and scaling using pediatric clinical data
- Predict DDI and provide therapeutic modifications across pediatric ages

**Evaluate PBPK Model Predictions**
- Approach 1: Collect opportunistic data in children receiving the drug combination per standard of care
- Approach 2: Prospectively evaluate revised dosing recommendations using an adaptive trial design

PBPK Model Developed to Characterize Imatinib’s PK in Children and Adolescents

- The objective was to apply a PBPK modeling approach to investigate optimal dosing and potential DDIs for imatinib in the pediatric population.

- An adult imatinib PBPK model was developed and evaluated, and then scaled to children and adolescents (2-18 years of age).

- PBPK models of CYP3A modulators were verified using published pediatric data.
PBPK Model Predicts Potential Imatinib DDIs in Children and Adolescents

PopPK Modeling Characterizes Fluconazole’s Effect on Sildenafil Clearance

- 34 preterm infants; 109 plasma PK samples

- A two-compartment model for sildenafil and a one-compartment model for N-desmethyl sildenafil (DMS) characterized the data well

- Pre-systemic conversion of sildenafil to DMS was incorporated into the model

- After accounting for body weight, fluconazole co-administration was found to decrease sildenafil clearance by 59%
PopPK Model Simulations of the Sildenafil-Fluconazole DDI in Infants

*Pink and teal shaded regions represent the 95% prediction intervals for virtual infants with and without fluconazole, respectively.

PBPK Modeling Workflow to Characterize the Sildenafil-Fluconazole DDI in Infants

1. Develop Adult Sildenafil PBPK Model
2. Determine Fluconazole CYP3A Inhibition
3. Model Sildenafil + CYP3A Inhibitors in Adults
4. Evaluate Sildenafil + Fluconazole PBPK Model in Infants
5. Optimize Dosing for Sildenafil + Fluconazole in Infants

Fluconazole CYP3A4/CYP3A5/CYP3A7 Inhibition

Lineweaver Burk plots for CYP3A4, CYP3A5, and CYP3A7 fluconazole inhibition

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Inhibition type</th>
<th>Kᵢ (µM) global</th>
<th>Alpha</th>
<th>Kᵢ (µM) competitive</th>
<th>Kᵢ (µM) uncompetitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>Mixed</td>
<td>29.4 (20.3-43.8)</td>
<td>16.6 (6.1-178)</td>
<td>20.9 (16.8-25.9)</td>
<td>83.1 (67.4-102.9)</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>Mixed</td>
<td>182.5 (86.7-556.4)</td>
<td>2.6 (0.5-13.9)</td>
<td>70.8 (48.5-104.3)</td>
<td>238.7 (183.2-318.9)</td>
</tr>
<tr>
<td>CYP3A7</td>
<td>Mixed</td>
<td>84.8 (30.5-296.8)</td>
<td>13.5 (1.8-∞)</td>
<td>45.9 (21.7-88.9)</td>
<td>389.0 (266.7-610.3)</td>
</tr>
</tbody>
</table>

*Value and the 90% confidence interval based on triplicate samples using recombinant enzyme expressing either CYP3A4, CYP3A5, or CYP3A7.
Sensitivity Analysis Comparing CYP3A Influence on Sildenafil AUC

PBPK Model Dosing Simulations

- **Sildenafil co-administration with treatment doses of fluconazole (12 mg/kg i.v. daily)**
  - Reducing the sildenafil dose by 64% resulted in a geometric mean ratio of 1.01 for simulated AUC at steady-state, but simulated Cmax values were slightly lower
  - Reducing the sildenafil dose by 48% resulted in a geometric mean ratio for simulated Cmax of 0.99, but overestimated simulated AUC at steady-state

Use of Real-World Data to Evaluate AKI Risk in Infants

• The objective was to determine the incidence of acute kidney injury (AKI) in infants exposed to nephrotoxic drug combinations

• Data from 268 neonatal intensive care units managed by the Pediatrix Medical Group

• We included infants born at 22-36 weeks gestational age, ≤120 days postnatal age, exposed to nephrotoxic drug combinations, with serum creatinine measurements available, and discharged between 2007 and 2016
  • Among 8286 included infants, 1384 (17%) experienced AKI

• We used the serum creatinine definition of AKI based on the Kidney Disease: Improving Global Outcomes criteria
## Use of Real-World Data to Evaluate AKI Risk in Infants

<table>
<thead>
<tr>
<th>Category</th>
<th>AKI Odds Ratio (95% Confidence Interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age (weeks)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24</td>
<td>0.92 (0.58-1.46)</td>
<td>0.72</td>
</tr>
<tr>
<td>24 to 26</td>
<td>0.85 (0.58-1.26)</td>
<td>0.42</td>
</tr>
<tr>
<td>27 to 29</td>
<td>0.86 (0.60-1.21)</td>
<td>0.38</td>
</tr>
<tr>
<td>30 to 32</td>
<td>0.86 (0.65-1.15)</td>
<td>0.31</td>
</tr>
<tr>
<td>33 to 36</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td><strong>Post-natal age (weeks)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>1.33 (0.98-1.80)</td>
<td>0.07</td>
</tr>
<tr>
<td>2 to 3</td>
<td>0.98 (0.73-1.33)</td>
<td>0.91</td>
</tr>
<tr>
<td>4 to 5</td>
<td>0.81 (0.58-1.12)</td>
<td>0.20</td>
</tr>
<tr>
<td>6 to 7</td>
<td>1.05 (0.72-1.51)</td>
<td>0.81</td>
</tr>
<tr>
<td>8 to 16</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.03 (0.91-1.17)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.92 (0.78-1.10)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.11 (0.94-1.31)</td>
<td>0.23</td>
</tr>
<tr>
<td>Other</td>
<td>0.82 (0.60-1.12)</td>
<td>0.22</td>
</tr>
<tr>
<td>White</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td><strong>Sepsis</strong></td>
<td>1.25 (1.09-1.44)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Respiratory distress syndrome</strong></td>
<td>0.96 (0.82-1.12)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

*Results of a random effects logistic model of AKI among infants born at 22-36 weeks gestation between 2007 and 2016.

Conclusions

• Potential DDIs are common in hospitalized pediatric patients, but DDI studies are rarely performed in the pediatric population for ethical and practical reasons.

• PBPK and population PK modeling can be used to characterize PK-mediated DDIs and evaluate dosing in infants, children, and adolescents.

• Using PBPK modeling, adult DDI data can be leveraged, and opportunistic clinical data collected from pediatric patients receiving the drug combinations per standard of care can be used for model evaluation.

• Real-world data available through electronic health record databases can be used to evaluate drug safety in infants receiving drugs that may interact with each other.
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Renal Impairment in Pediatric Patients: Current Approaches to Drug Dosing

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Office of New Drugs, CDER
Disclosure Statement

• I have no financial relationships to disclose relating to this presentation

• The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA
Goals of Drug* Dosing in Renal Impairment

Reduce risk of exposure-related toxicity
Maintain exposures in an effective range

Provide Data-Driven Information about Need for Pediatric Dosing Adjustments in Labeling

* Refers to both small molecules and therapeutic biologics regulated by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research
Overview

• Drug Characteristics and Intended Use
• Definition of Renal Impairment
• At Risk Pediatric Population
• Serum Creatinine-Based Prediction Equations
• Approaches to Assess Impact of Renal Impairment on Pharmacokinetics (PK)
• Ongoing Challenges
Drug Characteristics:
Impact of Renal Impairment

Not Likely to Alter PK
- Single-dose use
- Locally-acting drugs
- Predominantly eliminated by lungs

Likely to Alter PK
- Multiple-dose
- Systemically-acting drugs
- Substantially eliminated by kidneys

Sept 2020 Guidance for Industry PK in Patients with Impaired Renal Function:
https://www.fda.gov/media/78573/download
Drug Characteristics

• “Substantially eliminated” by kidneys
  – Fraction of systemically available drug or active metabolite excreted unchanged in urine is > 30%
  – Contributed by glomerular filtration, tubular secretion, and/or tubular reabsorption

Sept 2020 Guidance for Industry PK in Patients with Impaired Renal Function: https://www.fda.gov/media/78573/download
Impact of Renal Impairment on PK

- Decrease in renal excretion of drug or active metabolites
- Changes in absorption, plasma protein binding, and/or tissue distribution
- Alter some drug metabolism and transport pathways in liver and gastrointestinal tract
Normal Renal Maturation

Nephrogenesis completed by 36 weeks gestational age
Glomerular function reaches adult values by 2 years of age
Tubular function matures between 7-12 months of age

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean GFR (mL/minute/1.73m²)</th>
<th>Standard Deviation (mL/minute/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>41</td>
<td>15</td>
</tr>
<tr>
<td>2-8 weeks</td>
<td>66</td>
<td>25</td>
</tr>
<tr>
<td>&gt; 8 weeks</td>
<td>96</td>
<td>22</td>
</tr>
<tr>
<td>2-12 years</td>
<td>133</td>
<td>27</td>
</tr>
<tr>
<td>13-21 years (males)</td>
<td>140</td>
<td>30</td>
</tr>
<tr>
<td>13-21 years (females)</td>
<td>126</td>
<td>22</td>
</tr>
</tbody>
</table>

Definition of Renal Impairment

- Reversible reduction in glomerular filtration rate (GFR) as seen with acute kidney injury (AKI)
- Irreversible reduction in GFR as seen with chronic kidney disease (CKD)
Pediatric Populations with Renal Impairment

**AKI**
- Reduced kidney perfusion
- Intrinsic glomerular disease and/or tubular toxicity
- Urinary tract obstruction

**CKD**

<table>
<thead>
<tr>
<th>Age</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 4 years</td>
<td>Congenital anomalies of kidneys and urinary tract</td>
</tr>
<tr>
<td></td>
<td>Hereditary diseases</td>
</tr>
<tr>
<td>5 to 14 years</td>
<td>Hereditary diseases</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td>Systemic diseases</td>
</tr>
<tr>
<td>15 to 19 years</td>
<td>Glomerular diseases</td>
</tr>
<tr>
<td></td>
<td>Hereditary diseases</td>
</tr>
</tbody>
</table>

## Acute Kidney Injury (AKI)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine (SCr)</th>
<th>Urine Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5-1.9 times baseline OR $\geq 0.3$ mg/dL increase</td>
<td>$&lt; 0.5$ mL/kg/hr for 6-12 hrs</td>
</tr>
<tr>
<td>2</td>
<td>2.0-2.9 times baseline</td>
<td>$&lt; 0.5$ mL/kg/hr for $\geq 12$ hrs</td>
</tr>
<tr>
<td>3</td>
<td>3.0 time baseline; OR increase in SCr to $&gt; 4.0$ mg/dL; OR start dialysis; OR estimated GFR $&lt; 35$ mL/minute/1.73m$^2$ in age $&lt; 18$ years</td>
<td>$&lt; 0.3$ mg/kg/hr for $\geq 24$ hrs; OR anuria for $\geq 12$ hrs</td>
</tr>
</tbody>
</table>

**KDIGO 2012 Clinical Practice Guideline for Acute Kidney Injury**
Definition of Renal Impairment

- Reliance on absolute changes in SCr for drug dosing is problematic
- Reliance on serum creatinine (SCr) based prediction equation to estimate GFR most common
- Reliance on measured creatinine clearance (CrCl) less common
- CrCl \( \leq \) eGFR

Star RA. Perspectives in Renal Medicine 1998.
eGFR Prediction Equations in Pediatrics

• Schwartz equations
  – Original Schwartz formula: eGFR = k x height in cm/SCr
    • Jaffe method to assay SCr
    • k constant directly proportional to muscle mass which varies with age and sex
  – Bedside Schwartz formula: eGFR = 0.413 x height in cm/SCr
    • Enzymatic reaction by isotope dilution mass spectrometry to assay SCr
    – Validated across GFR range of 15-75 mL/min/1.73m²
• 2012 Multivariable Chronic Kidney Disease in Children (CKiD) equation: incorporates SCr and cystatin C
eGFR Prediction Equations in Pediatrics

• Inaccurate when SCr is rapidly changing
• Useful indicator of GFR over time when measured sequentially and when SCr has stabilized
• Can underestimate true GFR when Cr production is increased (e.g. creatine supplements)
• Can overestimate true GFR when Cr production is decreased (e.g. reduced muscle mass, malnutrition)
• Widely used to guide drug dosing decisions at bedside
Approaches:
Assess Impact of Renal Impairment on PK in Adults

• Dedicated renal impairment study
  – More common approach

• Population PK analysis
  – Leverage PK data across studies available for a specific program
  – Less common approach
  – Phase 3 trials often exclude enrollment of patients with comorbidities such as severe renal impairment
Dedicated Renal Impairment Study

- Single-dose: Dose-proportional and time-independent PK at anticipated concentrations
- Compares adults with a range of renal impairment to control group of adults with normal renal function
- Can include pharmacodynamic measure(s)
- Dose recommendations in renal impairment group based on exposure matching to control group

Sept 2020 Guidance for Industry PK in Patients with Impaired Renal Function: [https://www.fda.gov/media/78573/download](https://www.fda.gov/media/78573/download)
Dedicated Renal Impairment Study

Classification of Kidney Impairment

<table>
<thead>
<tr>
<th>Description</th>
<th>Range of Values for Renal Function (mL/minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (normal renal function)</td>
<td>≥ 90</td>
</tr>
<tr>
<td>Mild Impairment</td>
<td>60-89</td>
</tr>
<tr>
<td>Moderate Impairment</td>
<td>30-59</td>
</tr>
<tr>
<td>Severe Impairment</td>
<td>15-29</td>
</tr>
<tr>
<td>Kidney Failure</td>
<td>&lt; 15 mL/minute OR on dialysis</td>
</tr>
</tbody>
</table>

Values derived from SCr-based prediction equations validated for use in adults or CrCl using Cockcroft-Gault equation.
Dedicated Renal Impairment Study

Assumptions

• Dose adjustment to match exposures will result in similar risk-benefit profile as that observed in adult phase 3 population
  – Underlying renal disease and associated co-morbidities may alter exposure-response relationship and overall risk-benefit profile
Approaches:
Assess Impact of Renal Impairment on PK in Pediatrics

• Dedicated renal impairment study NOT common
  – Feasibility concerns due to relatively smaller CKD population
  – Ethical considerations with single-dose design offering benefit to pediatric population being studied

• Application of same adult renal dosing recommendations to pediatric patients based on adult renal impairment PK data more common
  – Assumes similar proportional effects of renal impairment on PK between adults and pediatric patients
  – Often without observed pediatric data to validate this assumption
Approaches:
Assess Impact of Renal Impairment on PK in Pediatrics

• Deriving pediatric renal dose adjustments from adult renal impairment data may be reasonable in patients > 2 years of age on case by case basis
• Open phase 3 trial enrollment to pediatric patients with CKD, AKI, or both for PK assessment
Ongoing Challenges

• Greater uncertainty with deriving dosing recommendations in pediatric patients with immature renal function

• Greatest need for reliable estimate of GFR to allow accurate and precise dose adjustments
  – AKI when eGFR values are likely to be least reflective of true GFR
  – Drugs with narrow safety margin
Thank You!
Predictive Performance of PBPK Dose Estimates for Pediatric Trials

Dr. Ibrahim Ince
Dr. André Dallmann

Bayer AG

2020-10-22

Online FDA/MCERSI
Pediatric Dose Selection Workshop
Conflicts of interest / disclaimer

All authors are full time employees of Bayer AG

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**Disclaimer:** The views expressed in this presentation do not reflect the official policies of the U.S. Food and Drug Administration or the U.S. Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.
PBPK modelling has been the scientific foundation for predictive exposure matching based on clinical studies for almost 2 decades

• Physiology based pharmacokinetic (PBPK) models have often supported the development and guidance of dosing strategies in children.

• These models incorporate age dependent changes of the relevant anthropometric and physiological parameters and apply ontogeny and variability of active processes involved in the elimination of pharmaceutical compounds.

• As most changes occur in the first 2 years of life, a good understanding of age-related changes in these processes is of upmost importance.

• Several studies have been performed for Bayer compounds, applying dosing schemes in children based on PBPK predictions.
PBPK modeling in adults and translation to children in Open Systems Pharmacology (PK-Sim / MoBi)

Building blocks of a PBPK model for adults

Drug properties
- Lipophilicity
- Molecular weight
- pKa/pKb

Organism properties
- Fraction unbound
- Partition coefficients
- Mass Balance
- Lipophilicity
- Molecular weight
- pKa/pKb

Study protocol and formulation properties
- Fractional CL contributions
- Permeability
- Active processes (K_{int}, V_{max})
- Organ volumes
- Surface areas
- Tissue composition
- Blood flow rates
- Expression levels

Drug-biology interaction
- Anatomy & physiology
- Administration protocol (dose and dosing regimen)
- Special events (food intake, exercise, EHC)

Building blocks of a PBPK model for children

Drug properties
- Lipophilicity
- Molecular weight
- pKa/pKb

Organism properties
- Fraction unbound
- Partition coefficients
- Mass Balance
- Fractional CL contributions
- Permeability
- Active processes (K_{int}, V_{max})
- Organ volumes
- Surface areas
- Tissue composition
- Blood flow rates
- Expression levels

Study protocol and formulation properties
- Modified formulations (e.g. minitablets, syrup)
- Adjusted administration protocol (e.g. mg/kg dosing)
- Different special events

Resulting age-dependent changes in drug-biology interaction

Physicochemical properties
- Modified formulations (e.g. minitablets, syrup)
- Adjusted administration protocol (e.g. mg/kg dosing)
- Different special events

Age-dependent changes in anatomy & physiology

Physicochemical properties
- Modified formulations (e.g. minitablets, syrup)
- Adjusted administration protocol (e.g. mg/kg dosing)
- Different special events

Anatomy & physiology
- Modified formulations (e.g. minitablets, syrup)
- Adjusted administration protocol (e.g. mg/kg dosing)
- Different special events

Formulation (empirical or mechanistic dissolution function)
Bridging from adults to children - Workflow

**Step 1:**
Development and verification of a PBPK model for adults

**Step 2:**
Translation of the adult PBPK model to children using prior physiological information about growth and maturation of relevant processes

**Step 3:**
Prediction of pharmacokinetics in children by means of simulations of virtual pediatric trials

**Step 4:**
Support of clinical decision process by evaluating adequate dosing, sampling or cohort size

Ince I. et al. J. Clin. Pharmacol. 59(S1), 2019
## Pediatric dosing schemes in children supported by PBPK predictions

Overview of Bayer small molecule compounds applied in children since 2005

<table>
<thead>
<tr>
<th>Market Name</th>
<th>Age range (years)</th>
<th>Involved processes in PBPK model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>0.01 – 16</td>
<td>GFR</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.2 – 6.6</td>
<td>CYP1A2, TS, GFR, Bil.CL</td>
</tr>
<tr>
<td>Copanlisib</td>
<td>13 – 17</td>
<td>CYP3A4, PgP, PIK3a</td>
</tr>
<tr>
<td>Gadovist</td>
<td>0.2 – 18</td>
<td>GFR</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>12 – 18</td>
<td>Hepatic CL</td>
</tr>
<tr>
<td>Magnevist</td>
<td>0.2 – 2</td>
<td>GFR</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0 – 18</td>
<td>UGT1A1, SULT2A1, Bil.CL, TS/GFR</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>2 – 17</td>
<td>CYP3A4, UGT1A9, Bil.CL</td>
</tr>
<tr>
<td>Riociguat</td>
<td>6 – 18</td>
<td>CYP1A1, CYP3A4, CYP3A5, CYP2C8, CYP2J2,UGT1A2, UGT1A9, Bil.CL (Pgp, BCRP), TS/GFR</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0 – 18</td>
<td>CYP3A4, Plasma Hydrolysis, GFR, TS, CYP2J2</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>1 – 19</td>
<td>CYP3A4, UGT1A9, Reduction, Unspecific CL</td>
</tr>
</tbody>
</table>

*TS: tubular secretion, Bil.CL: biliary clearance, PIK3a: phosphatidylinositol 3-kinase alpha*
Prospective evaluation of PBPK predictions with data observed during clinical studies in children are continuously performed

**Example: Moxifloxacin**

- black line: PBPK prediction for children (median)
- gray shaded area: PBPK prediction for children (90% interval)
- symbols: individual data derived from clinical observations using population PK modelling in pediatric phase 1 and 3 trials following single or multiple oral or intravenous doses


**Example: Rivaroxaban**

- dark gray area: PBPK prediction for children (90% interval)
- light gray area: extended PBPK prediction range (0.5 x 5th to 1.5 x 95th percentile)
- symbols: individual data derived from clinical observations following single administration of 10 mg-equivalent dose

Evaluation of 10 Bayer Compounds applied in Children

Evaluated pediatric PBPK models for 10 Bayer compounds
Via Ratio-calculation PBPK vs reported PK (popPK and NCA of clinical data)

<table>
<thead>
<tr>
<th>Evaluation of predictive performance</th>
<th>Ratio of Predicted PBPK vs PopPK and NCA of clinical data-based PK-Parameters</th>
</tr>
</thead>
</table>
|                                      | $AUC_{24,ss}$  
|                                      | $C_{trough}$  
|                                      | $C_{365days}$  
|                                      | Clearance  |
| Predefined age groups                | 0–<2 years  
|                                      | 2–<6 years  
|                                      | 6–<12 years  
|                                      | 12–<18 years  |

PBPK simulation software
Open Systems Pharmacology (OSP) Suite (PK-Sim / MoBi) *
(or formerly BTS Computational Systems Biology Suite)

Calculation & Illustration software
Rstudio Version 1.2.5033

Confirmation of predictive power of PBPK

Predicted versus observed

For all pediatric age groups
100% of observed data within 2-fold range of prediction
67% within BE interval
Discussion

Successful and adequate prediction of PBPK models for 10 compounds

Clear illustration of the predictive power of PBPK for guiding dosing schemes for compounds in the pediatric population.

Distribution and clearance in children are now relatively well understood, whereas dissolution and absorption often lack a more systematic and mechanistic understanding \(^1\)

The use of PBPK modeling for biopharmaceutics applications in adults and children is an area of ongoing research

Filling the gap: PBPK modeling for biopharmaceutics applications

Workflow for virtual bioequivalence testing

in vitro dissolution model

PBBM

Variability module

Cross-over population simulation with variability on model parameters

Note: Developed in collaboration with Andrea Edginton (University of Waterloo), Michael Neely (Children’s Hospital Los Angeles), and Eleftheria Tsakalozou (FDA); overall support for this work provided by a grant from the FDA (award number: U01FD006549).
Filling the gap: PBPK modeling for biopharmaceutics applications

- FDA encourages the use of PBPK modeling for biopharmaceutics applications under certain conditions \([1]\)

- Pediatric PBPK models for oral drug formulations have been successfully used to predict drug pharmacokinetics

- Recently, first efforts were made to use pediatric PBPK models for virtual bioequivalence assessment \([2,3]\)

- Biorelevant media are unlikely to be biopredictive for children; adaptations may be required

- Technical frameworks for virtual bioequivalence testing with OSP are being developed

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Thank you!

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Michael Block
Michaela Meyer
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Rolf Burghaus
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Pharmacogenetics and Drug Dose Selection
A Case Study of Thiopurines

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Oct 2020
Common Relationship between Drug Dose and Response

- **Sensitive (toxicity)**
- **Resistant (poor resp.)**

Response vs. Drug Dose:
- **Low**
- **High**

Efficacy vs. Toxicity:
- **Sensitivity**
- **Resistance**

Graph showing the common relationship between drug dose and response, indicating that as the drug dose increases, the response also increases, but toxicity increases at a faster rate, making it challenging to find an optimal dose.
Does the variation in our genetic make-up explain the variability in drug response?

Pharmacogenetics: Genetic Variation Linked to Drug Response

Pharmacogenetics

Evaluates how an individual’s genetic makeup corresponds to the response to a particular medication.

Pharmacogenetics

Goal

Tailor medical treatments to the individual, increasing their effectiveness while reducing side effects.