Industry Potential Interest Conflicts

- **Employer:** Employed by and have equity in ICPD, a company that provides pharmacometric services to industry
- **Financial Interests or Benefits:** Achaogen, Actelion, AiCuris, Arsanis, Basilea, Cellceutix, Cempra, Cidara, Contrafect, Debiopharm, Genentech, Geom, GSK, Insmed, Kalyra, Medicines Company, Meiji Seika Pharma, Melinta, Merck, Nabriva, Nexcida, Northern Antibiotics, Novartis, Paratek, Raptor, Roche, Spero, Takeda, Theravance, Tetraphase, VenatoRx, Wockhardt, Zavante, Zogenix
- **Speaker’s Bureau:** None

Christopher M. Rubino, Pharm.D.
Using Pharmacometrics to Facilitate the Design and Analysis of Anti-Infective Drug Studies in Neonates

15 September 2016

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Overview of Pharmacometrics

- Role of pharmacometrics in adult and pediatric drug development
- Examples of pediatric applications

Study Design Issues

- Model-based approaches
- Thoughts for discussion
Background

Setting the Stage
Pharmacometrics in Adults

Pre-Clinical

In Vitro & Animal Models

Phase 1 Studies

Phase 2 Studies

Phase 3 Studies

Clinical Development

Charles Bonapace, FDA, 16 April 2004
Setting the Stage
Pharmacometrics in Adults

- Right Dose
- Pharmacodynamics
- Clinical Data
- Pharmacokinetics
- Microbiology
- Modeling & Simulation
Potential Approaches

**Top Down**

- Dose
- CLd/F
- Ka, (1-Fp)
- Ka, Fp
- CL1/F
- Km, Cl/O
- VcM/F/Fm
- CLdM/F/Fm
- VpM/F/Fm
- CLtM/F/Fm

**Bottom Up**

- Blood
- Spleen
- Liver
  - Vmax, Km
- Gut Tissue
- Enterocyte
- Gut Lumen
- Kidney
  - CLj
- Brain
- Muscle
- Remainder
Pediatric Pharmacometrics Example
Top Down Approach

Peripheral CMT
($A_p$, $V_p$)

CLd

$k_0$

Plasma
($A_c$, $V_c$)

AUC$_{0-24}$
(mg/hr/L)

Cutoff = 50 kg Cutoff = 60 kg

Cutoff = 70 kg Cutoff = 80 kg

Age Group

Time Since Start of Infusion (h)

Cefazolin Concentration (mg/L)

Time Since Last Dose (h)

Prediction-Corrected Cefazolin Concentration (mg/L)

### Pediatric Pharmacometrics Example

**Bottom Up Approach**

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL-based Sims</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBPK (Literature)</td>
<td>PBPK Refined</td>
<td></td>
</tr>
<tr>
<td>Adult, Phase 1 DDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3 PK Run-in</td>
<td>Phase 3 #3 (Combination Therapy)</td>
<td></td>
</tr>
<tr>
<td>Phase 3 #1 (monotherapy)</td>
<td></td>
<td>PBPK Finalized</td>
</tr>
</tbody>
</table>

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The diagram illustrates the flow of pediatric pharmacometrics from CL-based simulations to PBPK models, including phases for adult DDI, phase 3 PK run-in, and combination therapy with monotherapy.
Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies

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

Keywords: pediatric drug development; pharmacokinetics; regulatory requirement; precision

Journal of Clinical Pharmacology, 2012;52:1601-1606
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“The Signal and The Noise”

The Signal is There…

… But Kids Can Be Noisy

Pharmacometrics Can Help
Top Down Approach

What About Bottom Up? Qualifying PBPK Models

X.X mg/kg Monotherapy in Adults

Plasma Concentration (ng/mL) vs. Time (hr)
Hybrid Approach

Reality Sometimes Gets in the Way

(A) Cumulative numbers of patients contributing PK information and (B) median numbers of PK samples per patient in 25 programmes conducting at least one PK trial, stratifying randomization into PK studies by age and stipulating intended sampling schedules. Numbers in each age group are based on programmes developing in that age group. Three (of 25) programmes obtain (some) PK samples from urine or saliva.

(A) Cumulative PK patient numbers. , total (red); , 0–27 days (light green); , 1–23 months (green); , 2–11 years (blue); , 12–17 years (purple) and (B) median numbers of PK samples per patient. , non-orphan (green, dashed); , orphan (red, solid)

“It may be appropriate to accept a greater degree of uncertainty regarding the benefit:risk balance when developing new antibacterial agents that can be used to treat patients with limited treatment options, e.g. it may be acceptable to conduct trials in smaller numbers of patients than would usually be required”
Il meglio è nemico del bene
(The better is enemy of the good)
Thank you for your attention.