Application of PBPK Modeling and Simulations in Pediatric Drug Development

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Disclosures and Acknowledgements

• Disclosures
  – The views expressed in this presentation are that of the speaker and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.

• Contributors to the ideas presented today
  – Division of Pharmacometrics/Office of Clinical Pharmacology
Outline

- Pediatric PK/PD – Dosing in Children
- Update of FDA Public Workshop (March 10, 2014)
- Predicting drug concentrations in children: Current experience and thinking
Drug Development (1 of 2)

- Drug developers are encouraged by regulatory agencies to carry out studies in children and use models for PK and PD relevant to children.
- From a PK perspective—in children, infants—especially neonates—size, maturation processes and organ function are important.

\[ CL_{PREDICTED} = CL_{STD} \cdot \left( \frac{WT}{WT_{STD}} \right)^{3/4} \]

- The missing piece is the link between drug concentrations and clinical outcomes.

Drug Development (2 of 2)

- The ability to study each age group (e.g., neonates, infants, young children, and older children) is small and we are interested in the most scientific and practical drug development programs for each group.
- We can combine data across all pediatric populations to develop an integrated view of human pharmacology.
- If PK is “known”, doses can be calculated rationally by understanding the concentration-response relationship:

\[
\text{Dose Regimen} = \text{Target Concentration} \times \text{CL (age group)}
\]

- Therefore, any “system/approach” should be geared to understanding dosing in children and whether pharmacodynamics behavior in pediatrics differs from that in adults.

**Pediatric Study Decision Tree**

Reasonable to assume (pediatrics vs adults)
✓ similar disease progression?
✓ similar response to intervention?

**NO**

- Conduct PK studies
- Conduct safety/efficacy trials*

**NO**

- Is there a PD measurement** that can be used to predict efficacy?

**YES**

- Conduct PK/PD studies to get C-R for PD measurement
- Conduct PK studies to achieve target concentrations based on C-R

**YES TO BOTH**

- Reasonable to assume similar concentration-response (C-R) in pediatrics and adults?

**NO**

- Conduct PK studies to achieve levels similar to adults
- Conduct safety trials

**YES**

- Conduct safety trials
Application of PBPK in Regulatory Decision Making

A. Patient Factors

Intrinsic factors

Extrinsic factors

B. PBPK Model components

System component (drug-independent)

Drug-dependent component

Physiology
Anatomy
Biology

Drug disposition
Drug action

PBPK Model

Predict, Learn, Confirm

Apply

Adapted from Zhao P, et al Clin Pharmacol Ther 2011
1. Applications of PBPK: Discussed potential applications of PBPK in drug evaluation, and to determine which areas relevant to drug development and review are currently amenable to the use of PBPK.

2. PBPK Model Verification and Reporting in Regulatory Submissions: Discussed assessment of model fidelity and best practices in reporting.
PBPK regulatory review experience

A. No model details (meeting requests, planning/strategizing)
B. Full study report/model details submitted, may need re-analyses
C. FDA de novo modeling and analyses
By Sponsors, How is PBPK Being Utilized?

- Increased use of PBPK by drug developers
- Majority of the cases were related to drug-drug interactions (~60%); pediatrics ranks the second

Huang et al, J Pharm Sci, 2013

Pan, ASCPT Annual Meeting, 2014, Atlanta, GA
## PBPK applications: Current status

<table>
<thead>
<tr>
<th>Applications</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug as enzyme substrate</strong></td>
<td>• Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling</td>
</tr>
<tr>
<td><strong>Drug as enzyme perpetrator</strong></td>
<td>• Use to confirm the lack of enzyme inhibition</td>
</tr>
<tr>
<td><strong>Transporter-based</strong></td>
<td>• In vitro-in vivo extrapolation not mature due to lack of information,</td>
</tr>
<tr>
<td></td>
<td>• Complicated by transporter-enzyme interplay</td>
</tr>
<tr>
<td><strong>Organ impairments (hepatic and renal)</strong></td>
<td>• Predictive performance yet to be improved</td>
</tr>
<tr>
<td></td>
<td>• System component needs more information</td>
</tr>
<tr>
<td><strong>Pediatrics</strong></td>
<td>• Allometry is reasonable for PK down to 2 years old</td>
</tr>
<tr>
<td></td>
<td>• Less than 2 years old ontogeny and maturation need to be considered</td>
</tr>
<tr>
<td><strong>Additional specific populations and situations</strong></td>
<td>• Yet to be determined</td>
</tr>
</tbody>
</table>
PBPK and Pediatrics
## Pediatric submissions containing PBPK

<table>
<thead>
<tr>
<th>Drug-specific data in adult PBPK model</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Drug C</th>
<th>Drug D</th>
<th>Drug E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Integrate Physico-chemical data</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Integrate ADME data</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

### Pediatric PBPK model development

<table>
<thead>
<tr>
<th>Verify adult model using i.v. and p.o. data</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Drug C</th>
<th>Drug D</th>
<th>Drug E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demonstrate adequacy of adult model</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Justify age-dependent ADME processes</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

### Application of the pediatric PBPK model

<table>
<thead>
<tr>
<th>Plan dedicated “first in pediatric” PK study</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Drug C</th>
<th>Drug D</th>
<th>Drug E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimize study design</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Verify model of certain age groups</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommend starting dose by targeting</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>appropriate steady-state exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inform enzyme ontogeny using bench-mark drug</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facilitate covariate analysis</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
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Updated from Leong et al, Clin Pharmacol Ther, 2012
Predicting PK in Children

Allometry

PBPK

2-Fold over/under prediction
Acetaminophen (APAP) PBPK Model
Development and Validation Work Flow

Development of adult PBPK Model
- *In vitro* enzyme kinetic studies
- Human pharmacogenetics studies (UGT1A1, 1A6 and 2B15)
- Intravenous (I.V.) PK data in healthy adults
- Oral PK data in healthy adults (solutions, tablets and syrups/elixirs)

Validation of PBPK model with independent adult PK data
- I.V. PK data in healthy adults (bolus and infusion)
- Oral PK data in healthy adults (solutions, tablets and syrups/elixirs)
- Oral PK data in cirrhosis patients (tablets)

Pediatric simulation with developed PBPK Model
- I.V. PK data (infusion)
- Oral PK data (solutions and syrups/elixirs)
APAP: Prediction of PK AND Metabolism

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Urinary APAP-Glucuronide/APAP-Sulfate Ratio (Steady State)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(12.5 and 15 mg/kg)</td>
</tr>
<tr>
<td>Neonates (0 – 0.08 year)</td>
<td>0.603 (N = 2)</td>
</tr>
<tr>
<td>Infants (0.08 – 2 years)</td>
<td>0.970 (N = 13)</td>
</tr>
<tr>
<td>Children (2 – 12 years)</td>
<td>1.38 (N = 15)</td>
</tr>
<tr>
<td>Adolescents (12 – 16 years)</td>
<td>1.24 (N = 13)</td>
</tr>
</tbody>
</table>
Verify Adult PBPK Before Applying in Children

PBPK model in adults

Drug-dependent Parameters + System-dependent Parameters (Adults)

Develop, verify, and refine adult PBPK model

PBPK model in children

Drug-dependent Parameters + System-dependent Parameters (Pediatrics)

Develop, use, and refine PBPK model in pediatrics
- Simulate pediatric PK in all age groups
- Optimize design of “first in pediatric” PK study (dosage, formulation, sampling time)

Verify PBPK model with available pediatric data
- Data from conventional studies
- Data from small trial with intense PK sampling

Submitting PBPK Information to FDA

- Summary of model input parameters and software version
- Logical description of model building and verification processes
- The details of all simulation conditions
- Model files in a executable format

Early communication with the Agency regarding including PBPK into your development plan is strongly encouraged

Modified from Zhao et al, Clin Pharmacol Ther 2012
Summary

- Increased PBPK submissions to the FDA. Experience and confidence differ among different applications.

- For pediatrics PK prediction, use PBPK where the question justifies its use and consider integration of predicted concentrations with exposure-response analysis.

- PBPK may complement allometry for predicting PK in younger age groups (e.g. < 2 years old).

- Model should be verified in healthy adult subjects before it can be used to predict pediatric PK.

- Predictive performance needs to be improved and focus should be on updating the system component.
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