Value of Pharmacokinetics in Pediatric Clinical Development

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Disclaimer:
1. I have no conflict of interest to report.
2. The views presented here are my personal.
Outline

• Introduction
  – Pharmacokinetics (PK)
  – Characterization of pediatric PK

• Value of PK in Pediatric Clinical Development
  – Overview
  – Research and policy development
  – Pediatric clinical development cases
    • Efficacy extrapolation
    • Pediatric dose selection/determination
    • Clinical trial design

• Take Home Message
Pharmacokinetics

- Pharmacokinetics (**PK**): refers to the movement of drug into, through, and out of the body – the time course of its _Absorption, Distribution, Metabolism, and Excretion_ (ADME).

The PK profile reflects:
- Patient characteristics
- Formulation features
- Chemical and physical properties of the drug

The PK links to clinical outcomes:
- Effectiveness
- Adverse events
Characterization of PK in Pediatrics

Approaches for charactering PK in pediatrics:
• A PK study with intensive sampling
• Sparse PK sampling in pediatric patients
• Modeling and simulation (e.g., Pop-PK)

Potential Changes in pediatric PK:
• Exposure
• Shape of PK profile change

• PK features
• Patient age difference
• Formulation
• Clinical relevant exposure/PK variables
• .......
Value of PK in Pediatric Clinical Development

**Drug Development**
- Efficacy Extrapolation based on PK-Matching
- Dose Optimization using PK Information.
- Clinical Trial Design based on PK in Pediatrics.

**Research and Policy Development**
- Efficacy Extrapolation
- Joint Efficacy and Safety Trial with adults
Policy Development

• Efficacy extrapolation:
  – Basis for extrapolation
    • Similar progression of disease
    • Similar response of disease to treatment
    • Similar exposure-response relationship
  – Role of PK
    • PK should be obtained from an adequately designed PK and tolerability study in which single and/or multiple doses of the investigational drug are administered in patients 4 to 16 years of age.
    • PK data should be sued to determine pediatric dosage and regimens based on PK-matching.
Extrapolation in Subgroups of ADHD Pediatric Patients

• Sponsors are highly encouraged to discuss their development strategy with the Agency during the Pre-IND stage. Some of the factors that should be considered to allow the extrapolation include:
  – The active ingredient of the 505(b)(2) product should only be methylphenidate or amphetamine.
  – The 505(b)(2) product should be given in the morning and target a duration of 12 hours or less.
  – Shape of the pharmacokinetic profile of the active moiety(ies) of the 505(b)(2) product must be similar across children, adolescents, and adults.
  – The approved patient population of the listed drug should include children, adolescents, and adults. The dose for each patient population should be clearly defined.
  – An adequate bridging must be established between the 505(b)(2) product and the listed drug, such that the dose of the 505(b)(2) product in each patient population can be reliably derived.
  – Patients ages 4 and 5 years should be included in clinical trials. Although it is reasonable to extrapolate efficacy from older children to 4- and 5-year-old children, clinical trial data is necessary to compare the safety profile in this population to what is known about the listed drug.

Efficacy can be extrapolated from children to adolescents and adults with ADHD.

### Efficacy Extrapolation in Pediatric Development

#### Partial Onset Seizure in Pediatric Patients > 4 Years

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Approaches to Support Pediatric Indication</th>
<th>Role of PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eslicarbazepine</td>
<td>Partial onset seizure in patients &gt; 4 years</td>
<td>Extrapolation</td>
<td>Bridging efficacy and deriving pediatric dosing</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Partial onset seizure in patients &gt; 4 years</td>
<td>Extrapolation</td>
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<tr>
<td>Pregabalin</td>
<td>Partial onset seizure in patients &gt; 4 years</td>
<td>Extrapolation</td>
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<tr>
<td>Brivaracetam</td>
<td>Partial onset seizure in patients &gt; 4 years</td>
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</tbody>
</table>
• Drug X (A recombinant human IgG1 monoclonal antibody that binds to human tumor necrosis factor-alpha (TNFα)) is indicated for the treatment of Hidradenitis suppurativa (HS).

• HS is a rare disease in pediatric patients, where the prevalence is 0.002%, 0.027%, and 0.114% in patients < 9 years, 10-14 years, and 15-17 years.

• FDA expanded the adalimumab dosing regimen to adolescent HS patients 12 years and older, weighing at least 30 kg without additional clinical data in adolescent HS patients without clinical trials.
Pediatric Dose Selection – Case Study (2)

- Dosing regimen in patients > 12 years was determined through M&S relying on **PK-matching** with other patient populations (e.g. adults).
  
  – Pop-PK model with > 500 pediatric patients (other diseases) + > 3000 adults. Simulation was conducted to test alternative dosing regimens.

<table>
<thead>
<tr>
<th>Body Weight of Adolescent HS Patients (12 years and older)</th>
<th>Recommended Dosing regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 kg (66 lbs) to &lt; 60 kg (132 lbs)</td>
<td>• 80 mg initially on Day 1</td>
</tr>
<tr>
<td></td>
<td>• 40 mg on Day 8 and subsequent doses: 40 mg every other week</td>
</tr>
<tr>
<td>≥ 60 kg (132 lbs)</td>
<td>• 160 mg initially on Day 1; and</td>
</tr>
<tr>
<td></td>
<td>• 80 mg on Day 15</td>
</tr>
<tr>
<td></td>
<td>• 40 mg on Day 29 and subsequent doses: 40 mg every week</td>
</tr>
</tbody>
</table>
# Dose Determination

## Examples from Application of Animal Rule

<table>
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<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Approval Basis for Pediatric Use</th>
<th>Role of PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raxibacumab</td>
<td>Treatment and prophylaxis of inhalational anthrax</td>
<td>Animal study + Extrapolation</td>
<td>M&amp;S to predict exposure in pediatric patients and to match exposure in adults receiving 40 mg/kg.</td>
</tr>
<tr>
<td>Tecovirimat</td>
<td>Treatment of human smallpox disease</td>
<td>Animal study + Extrapolation</td>
<td>M7S to predict exposure in pediatric patients and to match exposure in adults receiving 600 mg BID</td>
</tr>
</tbody>
</table>
Clinical Trial Design

Case study: Aripiprazole is an atypical antipsychotic.

**Role of PK**

PK in pediatric patients 10-17 years showed similar exposures of the major active moieties as compared to adults

Determine dose ranges for pediatric clinical trials

Schizophrenia: 6-week, placebo-controlled clinical trial in 202 pediatric patients 13-17 years

Bipolar I disorder: 4-week, placebo-controlled clinical trial in 197 pediatric patients 10-17 years

Irritability associated with autistic disorder: two 8-week, placebo-controlled clinical trials in 212 pediatric patients 6-17 years

Tourette’s disorder: One 8-week (7-17 years) and one 10-week (6-18 years).
Take Home Message

• PK in pediatric patients can be characterized in different ways
  – Intensive PK sampling in dedicated studies.
  – Sparse PK sampling
  – Modeling and simulation.

• PK information is critical to inform pediatric drug development:
  – To support policy development
  – To facilitate pediatric clinical development
    • Efficacy extrapolation
    • Dose selection/determination
    • Clinical trial design
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