Lessons Learned about Pediatric Drug Development from BPCA and PREA Studies under FDAAA

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The opinions expressed in this talk are those of the author, and should not be interpreted as the position of the U.S. FDA
Types of Pediatric Studies Conducted Under BPCA and PREA


<table>
<thead>
<tr>
<th>Type of Study</th>
<th>BPCA</th>
<th>BPCA + PREA</th>
<th>PREA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy/Safety</td>
<td>42</td>
<td>31</td>
<td>199</td>
<td>272</td>
</tr>
<tr>
<td>PK/Safety</td>
<td>9</td>
<td>36</td>
<td>19</td>
<td>64</td>
</tr>
<tr>
<td>PK/PD</td>
<td>14</td>
<td>8</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>Safety</td>
<td>5</td>
<td>4</td>
<td>24</td>
<td>33</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>70</strong></td>
<td><strong>82</strong></td>
<td><strong>253</strong></td>
<td><strong>405</strong></td>
</tr>
</tbody>
</table>

Total number of patients in completed FDAAA studies: 174,273
22,885 in BPCA studies; 36,657 in CDER PREA studies;
114,731 in CBER PREA studies (Vaccines and Blood Products)
FDAAA studies conducted under BPCA and PREA

<table>
<thead>
<tr>
<th>PEDIATRIC LABELING</th>
<th>PREA PMR No. Number (%)</th>
<th>No PREA PMR Number (%)</th>
<th>TOTAL of 158 Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labeled for pediatric use in some age group</td>
<td>51 (37%)</td>
<td>52 (38%)</td>
<td>119 (74.8%)</td>
</tr>
<tr>
<td>Not labeled for pediatric use</td>
<td>6 (4%)</td>
<td>20 (15%)</td>
<td>29 (18.2%)</td>
</tr>
<tr>
<td>Not labeled for pediatric use for the studied indication (other pediatric labeling)</td>
<td>2 (2%)</td>
<td>6 (4%)</td>
<td>10 (6.3%)</td>
</tr>
</tbody>
</table>

As of 8/17/202
Completed pediatric studies (no PREA PMR)

• Labeled for pediatric use  \( n=52 \ (67\%) \)

• Not labeled for pediatric use for the studied indication
  – Not labeled for pediatric use  \( n=20 \)
  – Labeled, but not for this indication  \( n=6 \)
  – TOTAL this category  \( n=26 \ (33\%) \)
Reasons for Trials Not Resulting in a Pediatric Indication

• Efficacy not demonstrated; different pediatric indication than in adults (17 products)
  – Dose, endpoints, disease
• No dose range investigated (8 products)
• Exposure was limited to the adult drug exposure (n=5)
  – Would a higher dose/exposure be effective?
• Trial design failure for 4 products
  – Met the study endpoint, but was not given the pediatric indication (3 products)
• Insufficient sample size (n=4); poor data quality (n=3); efficacy not established for indication approved in adults (n=3);
Planning is the key - regulatory

- FDA Guidance recommends early meetings for discussion of the pediatric assessment and plan
  - PREA Guidance: “For these (i.e. life-threatening illness) products, FDA encourages applicants to discuss the pediatric plan at pre-investigational new drug (pre-IND) meetings and end-of-phase 1 meetings.”
  - “For products that are not intended for treatment of life-threatening or severely debilitating illnesses, applicants are encouraged to submit and discuss the pediatric plan no later than the end-of-phase 2 meeting.”

- FDA Safety and Innovation Act of 2012 (Title V, Section 506)
  - “TIMING.—An applicant shall submit the initial pediatric plan…… No later than 60 days after the date of the end-of-phase 2 meeting”
Planning is the key - industry

PhRMA Statement Before the Institute of Medicine Committee on Pediatric Studies Conducted Under BPCA and PREA

• “PhRMA strongly believes that the necessity of every study under BPCA or PREA should be carefully evaluated before allowing such study to be conducted.

• FDA should endeavor to make the best use of existing data (published or otherwise) as well as information the Agency may garner from other regulatory authorities.”

http://www.phrma.org/phrma-statement-institute-medicine-committee-pediatric-studies-conducted-under-bpca-prea
Focus was on pediatric drug development, and the problems that have been encountered over the past 10 years.

1. Should modeling and simulation methods be considered in all pediatric drug development programs?

(VOTE) YES: 13    NO: 0    ABSTAIN: 0
Therapeutic Drug Monitoring

• Measuring plasma/blood concentrations to adjust dosage
  – Everolimus was labeled for the treatment of pediatric patients with SEGA associated with tuberous sclerosis in Summer of 2012
  – Dose titrated to trough blood level of 5 – 15 ng/ml

• Using a PD marker to adjust dosage
  – A point-of-care test has been developed for the thienopyridine platelet-inhibiting agents (VerifyNow P2Y12, Accumetrics)
  – If available previously, it may have prevented over 900 infants from being treated with an ineffective dose of clopidogrel
Clinical Pharmacology Planning

• Background information
  – Early discussion and planning is essential;
  – Modeling and simulation should be used in pediatric study design for all development programs;
  – Getting to the right dose is still problematic; TDM could represent one answer;
  – Pharmacogenetics should be incorporated, when appropriate, in pediatric clinical pharmacology studies;
  – Sample size for pediatric PK studies should be designed to provide precise estimates;
  – Pediatric formulations are a critical part of the development plan; and
  – Avoiding unnecessary studies is a scientific and ethical issue.
Summary

• Experience with pediatric studies under FDAAA (BPCA/PREA) has demonstrated that planning for dose finding, sample size identification and trial design is critical.

• Early planning on the part of the sponsor and the FDA review divisions is essential for the success of pediatric trials.

• New clinical pharmacology tools should help us to optimize the use of pediatric study data, and increase the success rate for labeled pediatric indications.