Experience in FDA Submissions with Matching Pediatric Drug Exposure to Adult Drug Exposure

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# Extrapolation of Efficacy in Pediatric Drug Development

<table>
<thead>
<tr>
<th>Level of extrapolation</th>
<th>Products studied in response to BPCA *</th>
<th>Products studied under FDAAA/FDASIA +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full/Complete</td>
<td>14.5%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Partial (PK/PD, ER, uncontrolled efficacy, single efficacy study)</td>
<td>68%</td>
<td>72.6%</td>
</tr>
<tr>
<td>No Extrapolation</td>
<td>17.5%</td>
<td>16.1%</td>
</tr>
</tbody>
</table>


+ : FDA Office of Pediatric Therapeutics Descriptor of Pediatric Studies under FDAAA and FDASIA; Excludes CBER products including vaccines
Extrapolation of Efficacy: Exposure Matching

Extrapolation

Partial

- PK/PD, exposure/response, uncontrolled efficacy study

Full

- PK/safety study

Single efficacy study

Extrapolation of Efficacy: Exposure Matching

Partial Extrapolation
- Antivirals (HIV, HCV)
- Anti-infectives (CSSSIs, CAP, cUTIs, etc..)
- Sedation
- Pain
- GERD

Full Extrapolation
- Rhinitis
- JIA (NSAIDs)
- Antivirals (VZV)*

* The FDA no longer accepts extrapolation of efficacy for VZV

Key Question: What constitutes exposure matching (achieving similar exposure as adults)?
Exposure matching: Review of FDA Submissions

- Retrospective review of pediatric trials submitted under PREA or BPCA 1998-2012
- Included trials with full or partial extrapolation relying on exposure matching
- Data retrieved from FDA clinical pharmacology reviews*
- Excluded locally acting products; focus on systemic drugs
- Data on trial design, key exposure metric, justification for target exposure, acceptance criteria
- Excluded trials without mean pediatric and adult PK values + variability reported in FDA review

*Source: http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm
Characteristics of studies

A total of 31 products (86 trials) included from February 1998 to August 2012 with full or partial extrapolation relying on exposure matching:

- 12 (38.7%): Full extrapolation
- 19 (61.3%): Partial extrapolation
The majority of the products were antivirals and antihistamines. The majority (78.1%) were studied in more than one pediatric age group.

*Other drug classes include: analgesics, sedatives, proton pump inhibitors, and drugs in other drug classes.
Trial Design

- 7/86 trials (8.1%) had a pre-defined target exposure or an acceptance boundary to match adult exposures (e.g. 80-125%)
- Majority (80.3%) used intensive sampling (NCA)
  - 8 (9.3%) sparse sampling (Pop PK)
  - 9 (10.4%) both NCA and Pop PK
- Dosing: BW based (44.8%), BSA (24.1%), fixed dose (31.1%)
- Sample size varied across trials and between age groups
- Multiple trials evaluated more than 1 dose level in the target pediatric age group
Assessment of Similarity

- Assessment of pediatric and adult systemic exposures based on cross-study comparison; Adult data either healthy volunteers or patients with condition
- Key exposure metric consistently defined post-hoc for antivirals and anti-infectives
- Assessment of similarity was primarily based on comparison of mean exposure values
- Acceptable boundaries for exposure similarity not explicitly stated post-hoc
Assessment of Similarity

- **48 (55.8%)** approved at the studied dose
  - Mean Cmax (Ped/adult) ratio: 0.63-4.19
  - Mean AUC (Ped/adult) ratio: 0.36-3.60

- **18 (20.9%)** approved at a modified dose
  - To “match” adult exposures
  - Few to provide fixed dose recommendations for specific weight bands

- **20 (23.3%)** did not result in an indication in all or part of the studied population
  - 13 had insufficient evaluation of efficacy or qualitative evaluation of efficacy not supportive
  - 7 trials, dosing could not be established or sample size was too small
Case Example 1: Tipranavir

- Multiple dose, open-label, randomized study safety and PK study
- Age stratification: 2 to <6 yrs (n=24), 6 to <12 yrs (n=16) and 12 to 18 years (n=12)
- 2 dose levels evaluated 290mg/m^2 and 375mg/m^2
- Target concentration or exposure metric not predefined
- Sparse PK sampling performed at wk. 2

Case Example 1: Tipranavir

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Adult HIV+ Females</th>
<th>Adult HIV+ Males</th>
<th>All Pediatric Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 14)(^a)</td>
<td>(n = 106)(^a)</td>
<td>(n = 51)</td>
</tr>
<tr>
<td>(C_{p0,12h}) ((\mu M))</td>
<td>41.6 ± 24.3</td>
<td>35.6 ± 16.7</td>
<td>29.36 – 42.17(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>39.02 – 65.32(^c)</td>
</tr>
<tr>
<td>(C_{\text{max}}) ((\mu M))</td>
<td>94.8 ± 22.8</td>
<td>77.6 ± 16.6</td>
<td>77.51 – 120.73(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>125.58 – 147.39(^c)</td>
</tr>
</tbody>
</table>

adult patients receiving TPV/r 500/200 mg; \(^b\) 290/115m2 dose group; \(^c\) 375/150mg/m2 dose group

- Low dose (290mg/m2) “reasonably matched” adult exposures at approved 500mg dose.
- 14 mg/kg ultimately approved:
  - Dose predicted to provide similar exposures to the high dose (375 mg/m2 dose)
  - Supported by ER in adults and need to maximize benefit
  - Simulations used to predict distribution of min concs under various BW dosing regimens
Case Example 2: Nelfinavir; Unapproved in infants

- Studies evaluated BID and TID dosing of nelfinavir in pediatric patients birth-13 yrs
- Doses 10-35mg/kg TID and 14-75mg/kg BID evaluated
- Formulation: tablet, crushed tablet mixed with liquid, or oral powder mixed with liquids or food
- Predefined target exposure: $\text{AUC}_{24} = 43.6-52.8 \text{ mg*hr/mL}$
- Method for assessing/quantifying similarity in exposure not pre-specified

Case Example 2: Unapproved in infants

- None of the doses studied in infants < 2 yrs reliably achieved target nelfinavir exposure
- Additional studies not required by the FDA
- Resulted in lack of approval and dosing recommendation for nelfinavir in infants < 2yrs

<table>
<thead>
<tr>
<th>Age Category</th>
<th>AUC24 (Mean +/- SD)</th>
<th>Dosing (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (n=10)</td>
<td>52.8+/-15.7</td>
<td>1250mg BID</td>
</tr>
<tr>
<td>(n=11)</td>
<td>43.6+/-17.8</td>
<td>750mg TID</td>
</tr>
<tr>
<td>2-9 months (n=4)</td>
<td>33.8+/-8.9</td>
<td>39+/-4 TID</td>
</tr>
<tr>
<td>(n=12)</td>
<td>37.2+/-19.2</td>
<td>66+/-8 BID</td>
</tr>
<tr>
<td>0-6 weeks (n=10)</td>
<td>44.1+/-27.4</td>
<td>37+/-7 BID</td>
</tr>
<tr>
<td>(n=10)</td>
<td>45.8+/-32.1</td>
<td>29+/-12 BID</td>
</tr>
</tbody>
</table>

Summary

- Exposure matching is an important part of pediatric dose development when exposure is a surrogate for efficacy
- Variable methods for assessing similarity of systemic exposures in reviewed sample
- Target exposure range and acceptance criteria not consistently pre-defined
- No specific trend by therapeutic area or indication
Points for discussion

• Need for a consistent approach to assessing similarity of exposures in the context of the drug, indication, age group, and formulation?

• Need for a priori determination of similarity?
  – Target exposure range and acceptance criteria
  – Basis for target criteria based on therapeutic range of the drug and risk benefit of the product for a given indication
  – Simulations of doses when planning pediatric trials
  – Need for adaptive approach to achieve target exposure versus using modeling and simulation post-hoc for dose optimization?

• Need for statistical equivalence approach for assessing exposure similarity?
  – e.g. X% CI for ratio of mean exposure metric in pediatric vs adult within a predefined limit based on defined target criteria;
  – e.g. X% of population at different age/weight groups within a predefined exposure range
Acknowledgement

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- Skip Nelson
- Kevin Krudys
Questions?
Back-up slides