Juvenile Animal Studies and Pediatric Drug Development

Retrospective Review: use in regulatory decisions and labeling

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Objectives
Sources of data
Some metrics
Case examples
  - Informing and in the label
  - Informing but not in the label
  - Requested for a specific concern
  - Screening
What have we learned so far?
Retrospective Review

- **Objective**
  - To better understand the value that the juvenile animal study contributes to regulatory decision making for pediatric drug development
    - When have studies been included
    - What, if any, impact did they have on decisions made
    - Was the data incorporated into the label
  
  - To evaluate key parameters and/or study designs that should be considered when a juvenile animal study is conducted
    - Refine recommendations for testing strategies

Today’s presentation
Retrospective Review: What did we look at?

- Sources
  - Approvals and Supplements (NDA and BLA) 1998 - 2009
  - Written Requests 1998 - 2010
  - Labeled products (PREA and BPCA) 1998 - 2010
  - Selected Division files
  - PharmaPendium™ listings of juvenile animal studies 1976 – 2009

- Most current label for each product was reviewed for juvenile animal data
- Identified products for which juvenile animal testing had been done but data had not been included in the label
- Identified Written Requests that had included juvenile animal studies
- Reviewed a subset of products to assess impact of the juvenile animal study on the regulatory decision.
Relevant Parameters

- Pediatric Regulations
  - 1998 Pediatric Rule
  - 2002/3 Best Pharmaceuticals for Children Act (BPCA) & Pediatric Research Equity Act (PREA)
  - 2007 FDAAA (renewed BPCA & PREA)
- 2006 FDA Guidance – Nonclinical Safety Evaluation of Pediatric Drug Products
- Labels - Where is the juvenile animal data found?
  - Older labels in section, Pediatric Use
  - PLR* formatted sections 8.4 and/or 13.2 and sometimes 5

*Physician Labeling Rule
Physician Labeling Rule: Contents and Full Prescribing Information

Boxed Warning
1 Indications & Usage
2 Dosage & Administration
3 Dosage Forms & Strengths
4 Contraindications
5 Warnings & Precautions
6 Adverse Reactions
7 Drug Interactions
8 Use in Specific Populations*
  8.1 Pregnancy
  8.4 Pediatric Use
9 Drug Abuse & Dependence*
10 Overdosage
11 Description
12 Clinical Pharmacology*
  12.4 Pharmacokinetics in Special Populations
13 Nonclinical Toxicology*
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
  13.2 Animal Toxicology and Pharmacology
14 Clinical Studies
15 References
16 How Supplied/Storage & Handling
17 Patient Counseling Information
  17.11 FDA-Approved Medication Guide

* Indicates sections with specified numbering of subsections
The Data: Review of Labels*

- 400 labels with pediatric information
  - 25 were labeled under PREA
  - 169 exclusivity granted under BPCA [Written Request]
  - 20 were BLAs
- ~10% had juvenile animal data in the label
  - Some data from chronic toxicology studies initiated with immature animals

* 1998- 2010
The Data: Juvenile Animal Studies

- Queried data files for drugs with juvenile animal studies
- 39 drugs were selected for further review
  - 35 NDAs / 4 BLAs
  - Represented multiple disease areas
  - 29/39 had juvenile animal data in the label

Value
- Increased sensitivity
  - Some helped to set age limits for use
- Unique toxicity
- Replicated toxicities already characterized
  - Least likely to show up in the label
## Species Use

<table>
<thead>
<tr>
<th>Species</th>
<th>Total</th>
<th>In label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Dog</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Monkey</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Mouse</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rat &amp; dog</td>
<td>10</td>
<td>8*</td>
</tr>
<tr>
<td>Rat &amp; monkey</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Rat &amp; mouse</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*only 1 species included
## Distribution by year

<table>
<thead>
<tr>
<th>Year</th>
<th>1 species</th>
<th>2 species</th>
<th>Other*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-1998</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>1999-2002</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2003-2007 (Sept)</td>
<td>9</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2007-2010</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>24</strong></td>
<td><strong>12</strong></td>
<td><strong>3</strong></td>
</tr>
</tbody>
</table>

* Data from immature animals vs a juvenile study
The Written Request

- Written Request (WR) – formal agreement for pediatric studies under BPCA
- FDAAA 2007 allows for juvenile animal studies as needed to support pediatric clinical trials
- Reviewed 14 WR with juvenile animal study requests
### The Written Request – a closer look

<table>
<thead>
<tr>
<th>Yr. issued</th>
<th>1 species</th>
<th>2 species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-2003</td>
<td>3*</td>
<td>2</td>
</tr>
<tr>
<td>2003-2009</td>
<td>7</td>
<td>2**</td>
</tr>
</tbody>
</table>

*Single species requested but sponsor performed studies in 2 species

** sponsor initiated studies in one case

Rationale for requests

- 8 - ask for additional safety for labeling *
- 4 - are for specific concerns (toxicities)
- 2 - are for a safety assessment in the pediatric population
- 1 - to support pediatric clinical trials
- 1 - no reason given

* most consistently requested endpoints were for growth, neurologic/neurobehavioral and reproductive.
The Written Request – a closer look

<table>
<thead>
<tr>
<th>Species</th>
<th>Total</th>
<th>Pre-2003</th>
<th>2003-2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat only</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Dog only</td>
<td>1</td>
<td>1*</td>
<td>-</td>
</tr>
<tr>
<td>‘Non-rodent’ only</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Not specified only</td>
<td>3</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Rat and dog</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Rat and monkey</td>
<td>1</td>
<td></td>
<td>1**</td>
</tr>
<tr>
<td>Rat and non-rodent</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

*Single species requested but sponsor performed studies in 2 species
** sponsor initiated studies
CASE STUDIES

How were the data from the juvenile animal studies applied?
Case study – in the label

Darunivir (treatment of HIV infection)

- Species – rat
- Single and multiple dose studies at different ages
  - Convulsions and mortality when given to pups <23 days old
  - Exposure in plasma, liver and brain >> adult rats
  - Toxicity profile of animals > 23 days similar to adult rats.
  - Attributed to ontogeny of CYP450 system and immaturity of the blood brain barrier
- Section 8.4 – do not administer to patients <3 yrs because of toxicity and mortality in juvenile rats
- Section 13.2 – description of study findings

Value – increased sensitivity, set age limitation for dosing
Case study – in the label

Vigabatrin (Adjunctive therapy for refractory complex partial seizures in adults and infantile spasms in pediatric patients)

- Species - rat
- Multiple dose studies starting on PND 4
  - Standard toxicological endpoints with added assessments for neurotoxicity and retinal toxicity based on previous adult findings
  - Mortality and neurobehavioral deficits, convulsions, brain lesion that was unique, retinal and brain lesions at exposures less than those used in adult rats and less than projected clinical doses
- Pediatric Section
  - Notes abnormal MRI signal changes in infants treated for infantile spasms
  - Description of juvenile rat studies

Value - increased sensitivity, possible clinical correlate
Case study – Informing regulatory decisions during development

Drug A (NMDA receptor antagonist)

- Species – rat
- Neuronal lesions in adult animals drove the design of the juvenile studies
- Dosing PND 14 – 67; recovery to PND 91
- Similar sensitivity and toxicities to adult rats (vacuolation and necrosis of brain)
- Drove the setting of the clinical dose in pediatric trials (1/10\textsuperscript{th} the juvenile rat plasma concentration at the NOAEL)
- Findings described in consent form

*Value – clinically relevant toxicity*
Case study – Informing regulatory decisions during development

Drug B (treatment of 1° and 2° hyperparathyroidism)

- Species – rat and dog
- Rat: age at dosing PND 21 – 49; recovery to PND 67
  - No unexpected toxicity; adverse effects attributed to pharmacology
- Dog: age at dosing PND 70 – 98 recovery to PND 126
  - Cardiac toxicity
  - Findings drove request for an additional dog study for safety
  - Pediatric studies on hold until completed
- Dog: 6 month study; age at dosing PND 70 with 3 month recovery
  higher doses used
  - No cardiac toxicity; other findings consistent with excess pharmacology
  - Pediatric studies now underway

Value – unexpected finding in a study with a ‘general toxicity’ design had potential clinical consequence; further, more directed study supported resumption of pediatric program
Case study – Informing regulatory decisions but not in label

Drug C – (IL-1β blocker)

- Species – mouse using antibody homolog
- Dosing weekly SC PND 7-70; Assessed for growth, reflex development, immune function, learning and memory, reproductive competency
- No differences noted from vehicle treated mice.
- Plasma exposure at the NOAEL supported weight-based dosing information in children ≥ 4 yrs

Value – use of surrogate in animal model to support pediatric studies
Case study – No added information

Drug D – (treatment of thrombocytopenia)

- Species - rat
- Dosing PND 4- 31; standard 28 day general toxicity study design, no juvenile specific parameters
- Findings showed no unique toxicities or sensitivity

*Value- no impact on label information*
What Have We Learned

- More studies performed than are reflected in the labels
- Most studies requested are for cause
  - Some requests for screening studies – hard to distinguish from unsolicited studies
- Post-FDAAA if a study is done relevant data will be placed in the label
  - WR template* now asks for review of nonclinical toxicology to assess need
- Further analysis of the programs will give insight on when and where these studies have been impactful and when and where these studies should be considered
  - When does asking for 2 species make sense?
  - Does any one age group trigger studies?

Conclusion

- What is the ‘value’ of the juvenile animal study?
  - Safety assessment
  - To aid in characterizing the risks
  - Detect unique toxicity, increased sensitivity

- The advice in the guidance is sound

- Expect to see more studies as PIP requirements are completed
  - Important to inform Division of nonclinical as well as clinical pediatric plans
Next steps

- To evaluate key parameters and/or study designs that should be considered when a juvenile animal study is conducted
  - Refine recommendations for testing strategies