Juvenile Animal Studies and Pediatric Drug Development

Retrospective Review: use in regulatory decisions and labeling

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Juvenile Animal Studies and Pediatric Drug Development

- 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

Today's presentation

- 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

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

Species	Total	In label
Rat	14	12
Dog	4	3
Monkey	4	2
Mouse	1	0
Guinea pig	1	1
Rat & dog	10	8*
Rat & monkey	1	0
Rat & mouse	1	1

*only 1 species included

Distribution by year

Year	1 species	2 species	Other*
Pre-1998	5	3	2
1999-2002	6	5	
2003-2007 (Sept)	9	3	1
2007-2010	4	1	
	24	*12*	*3*

* 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

Yr. issued	1 species	2 species
Pre-2003	3*	2
2003-2009	7	2**

*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

Species	Total	Pre-2003	2003-2009
Rat only	5	1	4
Dog only	1	1*	-
'Non-rodent' only	1	1	
Not specified only	3		3
Rat and dog	2	2	
Rat and monkey	1		1**
Rat and non-rodent	1		1

*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 (1/10th 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?

*http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077469.htm

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