DART Technical Committee
The Value of Juvenile Animal Studies

HESI Annual Meeting
Alexandria, VA

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ILSI Health and
Environmental Sciences
Institute

The Value of Juvenile Animal Studies: Introduction

- This project was a follow-up of activities initiated in 2001
- Juvenile Animal Studies in Assessments of Pediatric Safety
  - Initiated based on regulatory activities of the FDA and discussions in EU

Juvenile Animal Studies in Assessments of Pediatric Safety (2001)

1a. Ten reviews of comparative organ system development published in Birth Defects Research Part B, 2003-2006

Bone growth and development	Heart development
Renal development	Immune system development
Lung development	CNS: Functional measures
Male reproductive system	CNS: Anatomic
Female reproductive system	Gastrointestinal system development

1b. Review of preclinical and clinical experience.
Brent RL. Birth Defects Research Part B 2004.

Juvenile Animal Studies in Assessments of Pediatric Safety (2003)

2. Conduct a workshop to define decision process to determine when juvenile animal studies are needed and propose effective study designs and testing strategies
   - Over 125 global participants from industry, academia and regulatory agencies.
   - Workshop summary published in Birth Defects Research Part B, 2004

Conclusions of Workshop

1. Studies need to be considered on a case-by-case basis
   - Indication, patient population, known adult target organ toxicity, MOA, class effects
2. Single species sufficient
   - Rat preferred
   - Consider other species when rat clearly not appropriate
3. Studies should include TK/PK assessment
4. Endpoints and duration of study based on individual case

- **Workshop Summary published in BDR (Part B) 71: 281-288 (2004)**

Juvenile Animal Studies in Assessments of Pediatric Safety

- Impact:
  - Reviews provide an essential reference for industry, academic, and government toxicologists.
    - Among the top 25 cited papers for BDR-B during the period 2004-2006.
    - Many cited in FDA final Guidance document (2006)
  - Information incorporated in final US and EU regulatory guidance documents.

Drivers For New Project

- Discussions about these studies with a variety of company representatives demonstrated the similarities in design of study requested by regulatory agencies despite the available data, the MOA and indication.

- Perception that the studies were not generating anything new and the findings that were observed were predictable from the known toxicology, pharmacology or the stages of development.

The Value of Juvenile Animal Studies

Goal: To host a workshop to examine the issues on the value of juvenile animal studies so that they're appropriately performed when truly necessary**.**

Steering Team:

Karen Davis Bruno	U.S. FDA
Luc De Schaepdrijver	Johnson & Johnson
Kok Wah Hew	Takeda
Mark Hurtt	Pfizer
Jim Kim	HESI
Isabelle Leconte	sanofi-aventis
Beatriz Lima	Instituto Nacional da Farmacia e do Medicamento
Ulla Wändel Liminga	Sweden Medical Products Agency
Jeffrey Moffit	Boehringer Ingelheim
Georg Schmitt	Roche
Melissa Tassinari	U.S. FDA
Kary Thompson	BMS

The Value of Juvenile Animal Studies

- Survey of HESI DART TC members and broader scientific community (e.g., ETS, Teratology Society) for experiences with juvenile animal studies
- Workshop held in Washington, DC on May 5-6, 2010
  - Approximately 130 attendees including government, academic and industry scientists from North America, Europe, and Japan
  - Special issue of Birth Defects Research Part B forthcoming that has the presentations, summaries of the case study breakout sessions and discussions, conclusions and completed juvenile animal studies (August 2011)

Workshop Objectives

- Discuss the impact of juvenile animal studies conducted so far
  - Understand how the study data is being used and its impact in labeling and risk assessment
- Key Learnings – what do we need to improve?
- Where do go from here?
  - Next steps

The Value of Juvenile Animal Studies

- Workshop Presentations
  - Pediatric Clinical Perspective, Klaus Rose
  - European Regulatory Perspective, Jacqueline Carleer
  - Japan Regulatory and Industry Perspective, Kazuhiro Shimomura
  - U.S. Regulatory Perspective, Melissa Tassinari
  - Industry Perspective, Shaun Maguire
  - Survey “What have we learned from juvenile animal studies,” Graham Bailey and Luc DeSchaepdrijver
- Breakout Sessions
  - Case Studies

The Search for Information

- Problem, as with all new experimental developments, the majority of labs had insufficient studies for a valid assessment on a company specific basis. A cross-company collaboration was required.

- Challenge was the collection of sufficient information from each of the studies to make a meaningful assessment.

The Search for Information

- Questions to address: the intended use of the drug, the studies performed, the experimental findings and the relevance of findings in the juvenile to the adult.
- A simple spread sheet with ‘yes/no or +/-’ answers was developed for ease of entry.
- A specific assessment of each general toxicology endpoint wasn’t required, just a general assessment of sensitivity of the juvenile animal (exposure NOAEL / LOAEL vs Adult).

The Search for Information

Subjective assessment:

1. Any novel toxicity?
2. Results predictable from the pharmacology?
3. Results predictable from the adult?
4. Any added value for the pediatric trials?
5. Any change to the product label?

- Additional data collection table regarding the number of studies performed and whether these were requested or volunteered.

The Results - Rats

- The contributions from the 23 companies equalled 191 studies. Of these, 79 were DRF studies and 112 were main studies.
  - **The compound category with the most studies was CNS with 27 DRF's and 43 main studies.**
  - **Anti-infectives / anti-microbials had 25 studies of which 17 were main studies.**
  - **Cardio vascular compounds had 27 studies 10 of which were main studies.**

Rat Main Study Results - CNS

Age at commencement

Start dosing	Number of studies	Duration	Intended earliest clinical age		
			neonates	2 – 4 yrs	5 yrs +
07	15	4 = 1-2 wks 1 = 4 wks 10 = 7-8 wks	4	3	4 (11+)
10 / 12	6	4 = 40 days 1 = 11 wks	1	0	5
14	9	1 = 1 day 3 = 28 days 5 = 56 days	0	0	3 (3x 13 to17)
21	9	4 = 6 - 8 days 5 = 10 wks	0	0	9 (5-8 to Adult)
22+	3	4, 7, 10 &13 wks	0	0	3 (5-7 to Adult)

Rat Main Study Results - CNS

- Commencement and duration of dosing:
  - Start of dosing in many cases did not match the intended age of clinical dosing commencement.
  - Dosing commencing on Day 7 is approximately equivalent to a pre-term child, therefore when the clinical indication is for 5 years+ then this may be unnecessary

  - (*Romijn et al., 1991. Early Human Development 26, 61-67*):

    PND 10 rat = human birth

    PND 21 rat = 2 years old

Overall Sensitivity: Rats

Sensitivity	Number of studies	%
Much less sensitive than adult	0	0
Less sensitive than adult	6	6.2
Comparable to adult	62	64.6
More sensitive than adult	26	27.2
Much more sensitive than adult	2	2.0

Overall Survey Results

- 232 studies submitted from 24 companies
- In only 12 of reported programs was the existing adult pre-clinical data or clinical studies considered sufficient for inclusion of children in clinical trials (10% of reported programs)
- 79% of studies the species of choice was the rat with 12% in the dog
- Results not considered predictable from pharmacology or adult toxicity in 25% of the rat studies and 14% of the dog studies.

Overall Workshop Conclusions

- The workshop supported clear value for juvenile animal studies
  - Clinical trial design
  - Label
- Reinforced that a juvenile animal study is not always warranted
- Dialogue is an essential component to understand need for, design and role of these studies going forward
- Identified areas for continued effort
  - Global solution
  - Targeted study vs. General Tox study