HESI

ILSI Health and Environmental Sciences Institute

Workshop on the Value of Juvenile Animal Studies

Westin City Center Hotel
Washington, DC
May 5-6, 2010

HESI

ILSI Health and Environmental Sciences Institute

- ILSI is a public, non-profit scientific foundation
  - ILSI HESI provides an international forum to advance the understanding and application of scientific issues related to human health, toxicology, risk assessment, and the environment with participation from **government, academia and industry scientists**.
    - Programs primarily supported by its industry membership
    - Additional support received from a variety of government agencies (both US and international)

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2009 DART TC Membership

Amgen, Inc.

AstraZeneca AB

Bayer AG

Boehringer Ingelheim Phamarceuticals, Inc.

Bristol-Myers Squibb Company

E.I. DuPont de Nemours and Company

Hoffmann-La Roche Inc.

Johnson & Johnson Pharmaceuticals

Merck & Co., Inc.

Novartis Pharmaceuticals Corporation

Pfizer Inc.

sanofi-aventis

Takeda Pharmaceutical Company Ltd.

The Dow Chemical Company

The Procter & Gamble Company

sanofi-aventis

DART Technical Committee Mission

The HESI Developmental and Reproductive Toxicology (DART) Technical Committee provides a forum where scientists from industry, government and academia can exchange information and initiate activities to advance science related to reproductive and developmental toxicology, and to develop consensus on the appropriate use of experimental toxicity data for human health risk assessment.

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)

Unresolved Design Issues

1. Use of MTD or toxic dose levels
2. Use of multiples of anticipated human exposure
3. Definition of triggers for immunotoxicity or neurotoxicity
4. Use of most sensitive species (most relevant)

Targeted versus General Design

Considerable discussion with no consensus on whether the study design should be targeted on known or anticipated effects from adults studies versus a general study design to evaluate all potential outcomes

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.**
  - **Information incorporated in final US and EU regulatory guidance documents.**

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Steering Committee Membership

- Graham Bailey
- Karen Davis Bruno
- Luc De Schaepdrijver
- Kok Wah Hew
- Mark E Hurtt
- James Kim
- Isabelle Leconte
- Beatriz Siva Lima
- Ulla Wandel Liminga
- Jeffrey Moffit
- Georg Schmitt
- Kary Thompson
- Melissa Tassinari

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Agenda Day One

9:00 – 9:15	Welcome and Workshop Objectives Dr. Mark Hurtt Dr. Luc de Schaepdrijver
9:15 – 9:45	A Pediatric Clinical Perspective Dr. Klaus Rose
9:45 – 10:15	European Union Regulatory Perspective Dr. Jacqueline Carleer
10:15 – 10:45	Japanese regulatory and industry perspective Dr. Kazuhiro Shimomura
10:45 – 11:00	*Break*
11:00 – 11:30	U.S. Food and Drug Administration Regulatory Perspective Dr. Melissa Tassinari
11:30 – 12:15	Industry Perspective – Preclinical Pediatric Drug Development in a Global Context Dr. Shaun Maguire

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Agenda Day One

12:15 – 1:15	*Lunch*
1:15 – 1:45	Juvenile animal studies – study design considerations and warm-up case study Dr. Graham Bailey
1:45 – 2:00	Introduction of Break-out Session 1 Dr. Luc de Schaepdrijver
2:00 – 3:30	Break-out Session 1 - Review 1st set of case studies
3:30 – 3:45	*Break*
3:45 – 6:00	Break-out Session 1 – Reports from Groups
6:30 – 8:00	*Reception*

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Agenda Day Two

7:00	*Continental Breakfast available*
8:00 – 9:30	Feedback of the ILSI-HESI Survey with audience discussion Dr. Graham Bailey
9:30 – 9:45	Introduction to Break-out Session 2 Dr. Luc de Schaepdrijver
9:45 – 12:00	Break-out Session 2 - Review 2nd set of case studies
10:45	*Break*

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Agenda Day Two

12:00 – 1:00	*Lunch*
1:00 – 2:45	Summaries from Break-out Groups (rapporteurs)
2:45 – 3:00	*Break*
3:00 – 5:00	Discussion / Consensus Building Dr. Mark Hurtt Dr. Melissa Tassinari
5:00pm	*Adjourn*

Workshop Objectives

- Discuss the impact of juvenile animal studies conducted so far (over 200 studies submitted for the survey)
  - 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