• 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)
2009 DART TC Membership

Amgen, Inc.  Merck & Co., Inc.
AstraZeneca AB  Novartis Pharmaceuticals Corporation
Bayer AG  Pfizer Inc.
Boehringer Ingelheim Pharmaceuticals, Inc.  sanofi-aventis
Bristol-Myers Squibb Company  Takeda Pharmaceutical Company Ltd.
E.I. DuPont de Nemours and Company  The Dow Chemical Company
Hoffmann-La Roche Inc.  The Procter & Gamble Company
Johnson & Johnson Pharmaceuticals  sanofi-aventis
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.


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<tr>
<th>Bone growth and development</th>
<th>Heart development</th>
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<td>Renal development</td>
<td>Immune system development</td>
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<td>Lung development</td>
<td>CNS: Functional measures</td>
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<tr>
<td>Male reproductive system</td>
<td>CNS: Anatomic</td>
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<tr>
<td>Female reproductive system</td>
<td>Gastrointestinal system development</td>
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1b. Review of preclinical and clinical experience.

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
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.
Workshop on the Value of Juvenile Animal Studies

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

   Dr. Shaun Maguire
<table>
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<tr>
<th>Time</th>
<th>Event</th>
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<tr>
<td>12:15 – 1:15</td>
<td>Lunch</td>
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</table>
| 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                                                            |
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
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