Fetal Imaging in Regulatory Developmental Toxicity Studies

20 – 21 April 2015
Arlington, VA

Organized by the
ILSI Health and Environmental Sciences Institute
Developmental and Reproductive Toxicology Technical Committee

Abstract: Developing and using specific imaging technologies (e.g., micro-CT, MRI) allow for alternative methods for evaluating structural birth defects in animal models. As the technology develops increased capabilities and speed, this technique could eventually become a high-throughput method and allow for sharing of images between laboratories and regulatory agencies. In practice, it will eliminate the use of large quantities of processing chemicals and wet-specimen archives. At this time, the technical methods, the alterations observed, and their interpretation have not yet gained general regulatory acceptance. In order to facilitate acceptance, a set of criteria will be developed that would help organizations validate their individual imaging systems and provide the basis for acceptance of these technologies by the regulatory community.

This workshop aims to:

1) Introduce and discuss image capture technology relative to existing fetal evaluation methodology;
2) Understand the regulatory community's perspective and path for acceptance of results using imaging technology;
3) Discuss minimal acceptable criteria for imaging to comply with Good Laboratory Practices and Computer Validation requirements; and
4) Develop criteria to demonstrate concordance between new and existing examination methods and between testing results.

Charge Questions and Topics:

- What are the strengths and limitations of current staining methods for fetal skeleton evaluations in laboratory animal models?
- What is the state of the art of imaging equipment and methodologies? What are the strengths and limitation of imaging systems?
- Using micro-CT as a case study, what criteria will be used to ensure quality images that are comparable to existing staining methods?
- Are there general calibration criteria that can provide consistency among various imaging systems and laboratories?
- How is such a system and/or process developed so that it may be implemented in a GLP environment?
- How can imaging systems gain (international) regulatory acceptance?

DAY 1 (APRIL 20) – SCIENTIFIC PERFORMANCE TESTING

9:00am – 10:00am Registration/Breakfast

❖ **Session 1: Background and Introduction**

10:00am – 10:30am Introduction to workshop & current paradigm for fetal evaluations in regulatory developmental toxicology studies
Howie Solomon (GlaxoSmithKline)

10:30am – 11:00am Introduction to imaging technology
Chris Winkelmann (Merck)

❖ **Session 2: Using micro-CT for Fetal Skeletal Evaluations**

11:00am – 11:20am Micro-CT methodology
Hasan Alsaid (GlaxoSmithKline)

11:20am – 11:50am Using micro-CT for fetal evaluations – an alternative to alizarin red staining when evaluating fetal skeletons
Sandi Wood (Merck)

11:50am – 11:55am Introduction to break-out discussion groups
Susan Makris (US EPA)

11:55am – 12:15pm Break for working lunch

12:15pm – 1:15pm Working Lunch/ **Breakout #1: Methodology & Quality control**

1:15pm – 2:00pm Report-back from Breakout #1

❖ **Session 3: "Concordance" Criteria – How Do We Define Scientific Agreement?**

2:00pm – 3:15pm Concordance strategies for micro-CT and past efforts

Part I – Panel Presentations: Perspectives on concordance between the micro-CT as an alternative to traditional staining methods.
Julian French (Morphology Consulting, Inc.)
Sandi Wood (Merck)
Xiaoyou Ying (Sanofi)
Susan Makris (US EPA)

Part II: Moderated Discussion
Moderator: Daniel Minck (US FDA)

3:15pm – 3:30pm Coffee Break

3:30pm – 4:30pm **Breakout #2: Developing "concordance" criteria**

4:30pm – 5:15pm Report back from Breakout #2 & Close of Day 1

5:30pm – 6:30pm Light reception

DAY 2 (APRIL 21) – VALIDATION & GLP TESTING

8:00am – 9:00am Breakfast

9:00am – 9:10am Recap of Day 1 Conclusions & Charge for Day 2

❖ **Session 4: General Principles of Validation**

9:10am – 9:40am Regulatory perspectives – GLP (21 CFR Part 58) acceptance criteria
Zhou Chen (US FDA)

Regulatory perspectives – 21 CFR Part 11 Compliance
Jonathan Helfgott (Stage 2 Innovations)

9:40am – 10:15am GLP validation of technologies, software, and procedures
Lelia Scott (Charles River Laboratories, Regulatory Affairs Compliance)

10:15am – 10:30am Coffee Break

10:30am – 11:30am **Breakout #3: Considerations for GLP criteria & Part 11**

11:30pm – 12:15pm Report-back from break-out #3 & Discussion

12:15pm – 1:00pm Lunch

❖ **Session 5: Summary & Discussion of Future Issues**

1:00pm – 1:05pm Introduction to Session 5

1:05pm – 1:20pm Longitudinal study to follow-up a developmental abnormality
Luc De Schaepdrijver (Janssen R&D)

1:20pm – 1:35pm Automated Skeletal Analysis of Rabbit Fetus Micro-CT images in DART studies
Belma Dogdas (Merck)

1:35pm – 1:50pm 3D Imaging and Automated Analysis of Mouse Embryo Phenotypes
Mark Henkelman (The Hospital for Sick Children and University of Toronto)

1:50pm – 2:05pm High throughput imaging modalities for phenotyping structural birth defects in mice.
Cecilia Lo (University of Pittsburgh)

2:05pm – 2:15pm Workshop wrap-up