IVIVE for High-Throughput Prioritization and Decision Making

Day 1 Wrap-Up

Barbara A. Wetmore, Ph.D.
ScitoVation

February 17, 2016
**In Vitro-to-In Vivo Extrapolation for High-Throughput Prioritization and Decision-Making**

- **Webinars:** First Wednesdays, 11:00AM E.D.T.
  - October 7 – Barbara Wetmore: Setting the Stage
  - November 4 – John Wambaugh: Model Development
  - December 2 – Lisa Sweeney: Model Evaluation
  - January 6, 2016 – Corey Ellison: Internal TTC

- **In-person Meeting:** February 17-18, 2016
  - US EPA, Research Triangle Park, NC
**In Vitro - In Vivo Extrapolation**

**Definition:** Utilization of *in vitro* experimental data to predict phenomena *in vivo*

- **IVIVE-PK/TK (Pharmacokinetics/Toxicokinetics):**
  Fate of molecules/chemicals in body
  - Considers ADME; uses PK / PBPK modeling

- **IVIVE-PD/TD (Pharmacodynamics/Toxicodynamics):**
  Effect of molecules/chemicals at biological target *in vivo*
  - Assay design/selection important; perturbation as adverse/therapeutic effect, reversible/irreversible

- **Both contribute to predict *in vivo* effects**
Population-based *In Vitro-In Vivo* Extrapolation

- Primary Hepatocytes
  - Hepatic Clearance
    - $Cl_{in\ vitro}$
  - CYP1A2
  - CYP2D6
  - CYP2C8
  - CYP2E1
  - UGT1A4
  - CYP3A5
  - CYP3A4
  - CYP2C19
  - UGT1A1
  - CYP2C9
  - CYP2B6

- Intrinsic Clearance Rates
  - $r_{CYP1A2}$
  - $r_{CYP3A4}$
  - $r_{UGT...}$

- Plasma $C_{ss}$ for:
  - General Population
  - Neonates
  - Asians
  - Northern Europeans
  - Children
  - And so on...
In Vitro Assays - Considerations Relevant for IVIVE to Predict Chemical PD/TD

- Span from cell-free to immortalized lines to physiologically relevant systems
- Consideration of relevant mass balance / uptake issues
- Coverage of biological space?
  - Suite of relevant assays
  - Genomics/transcriptomics
  - Sufficient coverage across potential adverse outcomes?
- Ability to discriminate reversible perturbation from irreversible effect, potential adverse outcome
- Temporality – relating in vitro to in vivo
Day 1 Take-Home

- Terminology
- Fit for (what) purpose?
- Domain of applicability
- Multidisciplinary efforts and collaboration key
- Education and Re-education
- Tackling Variability...
- Solely in vitro? We are not there yet...
- Value in parallelogram; tiered approaches; frameworks
- Although many gaps and considerations exist in applying IVIVE to inform TK and TD issues in prioritization and decision-making, many of these can – and are – being addressed.
Day 2: Breakout Sessions

- **90 minutes** each, a projector and note taker will be available in each room.
- Participants will be allowed to choose which session they want to attend and may change rooms.
- Breakout group leaders will be asked to summarize the breakout group discussion in preparing a section for the workshop report.

**Guiding questions:**

- Moderators are asked to focus conversations around the questions below.
- During the discussion, participants are asked to keep in mind:
- What are the effects/implications when considering human vs rat values, non-animal vs in silico.
- How are we defining the purpose in fit for purpose and what are the implications for using the approach or assumption in each application (prioritization/screening/risk assessment).
## -- Day 2 Breakout Sessions --

<table>
<thead>
<tr>
<th>Session</th>
<th>A: TK model considerations</th>
<th>B: In silico and non-animal methods for obtaining TK parameters</th>
<th>C: Application to prioritization/screening/risk assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM1</td>
<td>Annie Jarabek, EPA</td>
<td>John Wambaugh, EPA</td>
<td>Scott Lynn, EPA</td>
</tr>
<tr>
<td></td>
<td>Alicia Paini, EURL ECVAM</td>
<td>Nisha Sipes, NIEHS</td>
<td>Nicole Kleinstreuer, NICEATM</td>
</tr>
<tr>
<td>AM1</td>
<td>1  What needs to be done to determine the state of the science (including current toolbox)? How well are these tools working for understood chemicals / kinetic processes?</td>
<td>What experiments/methods are needed for determining oral bioavailability? What about methods for other routes of exposure?</td>
<td>Who are the stakeholders? What are their needs? How do their needs vary?</td>
</tr>
<tr>
<td>AM1</td>
<td>2  What are the pros and cons of a simple (1 compartment) model? How do we assess when models are good enough?</td>
<td>What is best practice for rapidly parameterizing a model? How should confidence in these parameters be evaluated and reported?</td>
<td>How do we increase buy-in and what are the training needs? On regulatory and industry side? How do we build capacity and what resources are needed?</td>
</tr>
<tr>
<td>Break</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM2</td>
<td>3  How can the in vitro output be related to the in vivo toxicity/adverse outcome?</td>
<td>How do we define the domain of applicability for the in silico models? How should this be evaluated and reported?</td>
<td>Can IVIVE refine how default uncertainty factors are applied? Can it be used to develop data-driven uncertainty factors (interspecies and inter-individual)?</td>
</tr>
<tr>
<td>AM2</td>
<td>4  How do we validate methods and approaches (context, limitations, scope)?</td>
<td>How do we store/share models and information/data? What reporting requirements are needed? Do existing reporting formats currently exist, or can existing formats be changed to meet our needs?</td>
<td>What are the requirements or implications for use in prioritization/regulation? What areas are ready to incorporate IVIVE in the short-term? Long-term?</td>
</tr>
</tbody>
</table>