Pharma Perspective on the Development of Context of Use (CoU) for Liver Complex In vitro Models (CIVM)

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3Rs of Animals Research

- **Replace**: Evade animal research when possible
- **Reduce**: Less studies with less animals
- **Refine**: Minimize animal impact

Survey from 15 pharmaceutical companies forecast that CIVM (MPS) could save companies 10–26% in R&D costs

Russell WMS, Burch RL-1959; Franzen N et al., DDT-2019

Visual created with BioRender.com
"Crucial to establish 'fit-for-purpose' qualification parameters to recapitulate aspects of human physiology and pathology to provide insights into mechanisms of drug responses, disease development, and progression"
Hurdles Associated with CIVM/MPS Implementation

CIVM/MPS components:
- Scaffolds
- Platform
  - Integration
  - Fabrication
- Cell sourcing
- Ease of use

Applications:
- Organ systems
- Safety testing
- Disease modeling
- ADME
- Internal decision-making
- Regulatory submissions

CoU is defined by the FDA-NIH BEST (Biomarkers, Endpoints, and other Tools):
“A statement that fully and clearly describes how the medical product development tool is to be used and the medical product development-related purpose of the use”
Translational Axis to Address Complex Problems

- Supporting regulatory submission
- Historical data
- Novel algorithms
- Testing strategies
- Address regulatory queries
- Top-down
- Bottom-up
- AI-ML tools
- Biomarkers
- CIVM CoU
- Proof-of-concept
- Small/large molecule
- Traditional markers
Technology-Driven Integration Strategies to Understand Translational Safety

- Multiparameter endpoints
- Data-driven decisions
- High-quality targets
  - Strong biological evidence

Data Integration

Preclinical

CIVM

AI/ML

Historical
Overview of the Strengths and Limitations of Liver CIVMs

<table>
<thead>
<tr>
<th>Context of use</th>
<th>Micropatterned hepatocytes</th>
<th>3D primary hepatocyte spheroids</th>
<th>Stem cell-derived organoids</th>
<th>3D bioprinted liver</th>
<th>Liver-on-a-chip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessing toxicity endpoints</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Advanced architectural integration of nonparenchymal cells</td>
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<tr>
<td>High throughput formats</td>
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<tr>
<td>Donor-matched cells to study immune-mediated DILI, specific patient populations, or disease with long term consistent supply</td>
<td>✓</td>
<td></td>
<td>✓</td>
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<td>Bile acid homeostasis</td>
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<td>✓</td>
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<tr>
<td>Studying transporter mechanisms and biliary clearance of drugs</td>
<td>✓</td>
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<tr>
<td>Histopathology with microscopic processing/tissue staining</td>
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<td></td>
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<td>✓</td>
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<tr>
<td>Regulated fluidic flow for sampling of media flow-through for metabolites and biomarkers</td>
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<tr>
<td>Oxygen gradients and metabolic zonation for studying zone specific toxicities</td>
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<td>✓</td>
</tr>
</tbody>
</table>

“High-throughput, reproducibility, and cost are critical criteria for consideration”
**Tool Compound Recommendations for Liver CIVMs**

"Focusing on drugs that include the DILI mechanisms challenging to de-risk with currently available in vitro models"
Benefits and Risks of CIVM Adoption

+ Strategic implementation allows the selection of the best candidates
+ Early assessment of safety liabilities and predictability
+ Enhanced in vivo study designs and distilled dose selection during preclinical testing
+ Delineate the molecular basis of diseases/treatment & strengthening the scientific outcome
+ Promote robust human risk assessment and drug discovery

– FDA and other regulation requirements
– Structure of organoids, fabrication, and culture conditions, bioengineering tools, and preclinical assays
– Unable to recapitulate the full extent of pathophysiology
– Robust disease-relevant preclinical models and to predict clinical outcomes
– Costs and throughput considerations
Drug Safety Research & Development (DSRD)

Summary

The liver is complex: “one solution does not fit all”

The intricacy of DILI needs a multiparametric approach

Data-driven strategies allow for understanding specific business challenges & support effective solutions

Academic Partners

Pharmaceutical Industry

Model Developers

Regulatory Agencies
Discussion

Thank You