Advancing Translational Models & Tools into the Drug Review Process: Opportunities for MPS

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This presentation reflects the views of the author and should not be construed to represent FDA’s view or policies
Translational Models and Tools to Advance Drug Development

Drug Development

- >10,000 Compounds
- Optimize Compounds
- Preclinical Safety
- Clinical Studies
- FDA Review
- 1 Approved Drug

Translational Models and Tools

New science can be used to overcome challenges and hurdles in drug development

Including MPS

Safety, Pharmacology & Efficacy in Patients

DARS was created to move new science into the drug review process and close the gap between scientific innovation and drug review.
Learning from Our Recent Updates to the ICH Regulatory Guidelines for Cardiac Safety of New Drugs

ICH S7B Nonclinical
ICH E14 Clinical

Nonclinical Models Inform Approval Decisions & Labeling
Possible Risk? Low Risk

Guidance Document
E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential--Questions and Answers
Draft Guidance for Industry
September 2020

International Council for Harmonisation (ICH) Regulatory Guidelines implemented in 2005 have limitations
Example of Recent ICH Updates for Cardiac Safety: Collaborative Process to Increase the Role of Nonclinical Assays

ICH S7B Updates: Assay Standards and Best Practices

- Quality control criteria to document cell health
- Positive/negative controls
- Principles for proarrhythmia models (including qualification)
- How to report data to regulators to demonstrate quality
ICH E14/S7B Updates as a Potential Model for Other Safety Areas

**Clinical Pharmacology & Therapeutics**

**FDA Perspective**

Translational Models and Tools to Reduce Clinical Trials and Improve Regulatory Decision-Making for QTc and Proarrhythmia Risk (ICH E14/S7B Updates)

David G. Strauss, Wendy W. Wu, Zhihua Li, John Koerner, Christine Garnett

First published: 17 December 2020 | [https://doi.org/10.1002/cpt.2137](https://doi.org/10.1002/cpt.2137)

**Clinical Pharmacology & Therapeutics**

**Industry Perspective**

Time for a Fully Integrated Nonclinical–Clinical Risk Assessment to Streamline QT Prolongation Liability Determinations: A Pharma Industry Perspective

Hugo M. Vargas, Michael G. Rolf, Todd A. Wisialowski, William Achanzar, Anthony Bahinski, Alan Bass, Charles T Benson, Khuram W. Chaudhary, Nicolas Couvreur, Corina Dota... See all authors

First published: 31 August 2020 | [https://doi.org/10.1002/cpt.2029](https://doi.org/10.1002/cpt.2029)

“...The integrated nonclinical-clinical assessment here can also serve as a model for other safety areas in drug development and regulatory evaluation.”
Opportunities for MPS to Impact the Regulatory Evaluation of Drugs

1. Predict Safety in Patients
2. Reduce Clinical Drug Interaction Studies
3. Predict Efficacy in Patients
**Advance Drugs in Development with Potentially False-Positive Safety Signals**

**Safety need:** IQ industry-wide survey for attrition of small molecules due to unacceptable toxicity in animal studies

- **Late discovery phase terminations:**
  - Cardiovascular (18%)
  - Liver (16%)
  - Gastrointestinal (GI) (12%)
  - Central nervous system (CNS) (13%)

- **IND-enabling phase terminations:**
  - Cardiovascular (27%)
  - Testis (11%)
  - CNS (11%)
  - Kidney (9%)
  - Liver (5%)

**Example of Complex In Vitro Model (CIVM) Data Submitted to FDA**

- Other drugs in class discontinued from clinical development due to liver toxicity
- Some liver enzyme elevations in rat studies
- **Complex in vitro models with 3D spheroids combined with in silico modeling**
  - Reproduced observed liver toxicity of other drugs
  - Suggested new drug has significantly reduced risk of liver toxicity

**Regulatory Impact:** Data contributed to liver toxicity assessment as described in supervisory pharmacology-toxicology review for NDA

Introduction to a manuscript series on the characterization and use of microphysiological systems (MPS) in pharmaceutical safety and ADME applications.

*Lab Chip.* 2020 Mar 17;20(6):1049-1057

**Nonclinical NDA Review**
Reduce Clinical Drug Interaction Studies

- **Problem:** Impractical to evaluate every drug combination in clinical trials
- FDA Guidance documents describe how *in vitro* studies (in combination with PBPK modeling) inform the need for conducting clinical DDI studies
- However, there are limitations → opportunity for MPS

**Limitations of Conventional *In Vitro* Models + PBPK**

*Physiologically Based Pharmacokinetic Modeling in Regulatory Science: An Update from the U.S. Food and Drug Administration’s Office of Clinical Pharmacology*


- **Underpredict Clinical CYP3A Induction**
  - Drug may induce multiple enzymes (not accounted for)
  - Dual enzyme time-dependent inhibitor and inducer
  - Effect of inhibitors for phase II enzymes

- **Difficulty with Transporter-Mediated DDI**
  - Incongruence between in vitro and in vivo transporter behavior
  - Lack of correlation between transporters’ abundance and activity
  - Lack of knowledge about drug exposure at the site of action

**Opportunities For MPS to Impact Clinical Studies**

- Reduce the need for clinical DDI studies
- Impact the timing of clinical DDI studies

PBPK = physiologically-based pharmacokinetic modeling

DDI = drug-drug interaction
**In Vitro Models to Expand Drug Approvals for Rare Diseases**

**Rare Disease Drug Development Challenges**
- Small number of patients
- Thousands of genetic variants

**Innovative Approach**
Test drug efficacy in cell models with each genetic variant

**Cystic Fibrosis**
- Drug previously approved for 10 genetic variants
- Expanded approval to 24 more based on cellular models

**Fabry’s Disease**
- Affects Many Organ Systems
- Clinical trial included 63 patients with 40 genetic variants
- Drug approved for 348 genetic variants based on cell model

**Extensive laboratory experience from FDA/CDER DARS staff with specific assays was critical to assess quality, reproduce results and gain confidence for in vitro data to serve as primary efficacy data for expanding indications**

**Summary publication is forthcoming**
1. Liver MPS Using Primary Cells

- Assayed Output

- Liver
- Heart

- Connected system designed to use iPSC-derived cells

- Assayed Output

2. Engineered Heart Tissue (EHT)

- Assayed Output

- Contractility
- Calcium cycling
- Length of contractions

- iPSC-cardiomyocytes

3. Heart-Liver System

- Connected system designed to use iPSC-derived cells

- Assayed Output

- Cell death
- Metabolism
- Biomarkers
- Gene expression
- Drug distribution
Liver Microphysiological Systems for Predicting and Evaluating Drug Effects

Alexandre J. S. Ribeiro, Xinning Yang, Vikram Patel, Rajnikanth Madabushi, David G. Strauss

Clinical Pharmacology & Therapeutics 2019;106:139-47.

2-D cultures → 3-D organoids → microphysiological systems (MPS) → model multi-organ physiology

- interconnected systems
- physiological modeling of experiments and data
- steady-state operation
- organoid technology
- microfabrication of dedicated compartments
- microfluidic circulation of media

MPS Questions

- What is the performance of MPS compared to 2D cultures and 3D organoids?
- For MPS to be used for regulatory applications in drug development, can criteria to ensure reproducibility of results be developed?
MPS Cultures Hepatic Cells in 3D with Fluid Flow

12-Well Plate

Flow

Cells cultured within scaffold exposed to flow

Enhances the Physiology of Cell Culture

Physiologic Liver Lobule

Kupffer cells = liver macrophages (immune cells) critical for liver function

Rubiano et al. Clinical and Translational Science 2020;
Ribeiro et al. Clinical Pharmacology and Therapeutics 2019
Hepatocytes in MPS were more functionally stable than those in other culture platforms
- CYP3A4 activity (above) and albumin secretion remained prominent for >18 days
- Functional decline occurred earlier in spheroids (12 days) and sandwich cultures (7 days)

Proof of Principle: MPS Quality Control Based on Assaying Culture Media

Hepatic cells

Culture medium supernatant sample

Quality?

Lactate Dehydrogenase (LDH) Production

Quality Control: Before experiments exclude LDH statistical outliers

Liver MPS Reproduced Hepatotoxicity of Drug Withdrawn from Market Due to Causing Idiosyncratic Acute Liver Failure and Death

Co-dosing with lipopolysaccharides (LPS) to induce inflammatory signaling

Kupffer Cells
- Activates
- Cytokines

Hepatocytes
- Diminished Hepatic Function
  - Cytotoxicity
  - LDH ↑
  - CYP3A4 ↓

Trovafoxacin + Levofloxacin
- Trovafoxacin
- Levofloxacin
- No Effect

Liver MPS detects inflammatory-induced drug toxicity

Liver Toxicity Reproducibility

- Similar Results Between Two Sites
- Similar Results Within a Site When Using Different Batches of Kupffer Cells
- Identified Quality Control Criteria for Kupffer Cells

Examples:

1. Establish quality control criteria that ensure proper assembly and preparation of functional systems
2. Test cellular properties to enable the intended system use
IQ-MPS has published dedicated papers on ADME, liver, kidney, GI, lung, skin & biologics (CNS/BBB & cardiovascular in development)

www.iqmps.org/publications

Example: Liver MPS Development Guidelines for Safety Risk Assessment

“... guidance on best approaches to benchmark liver MPS based on 3 stages of characterization ...”

Liver microphysiological systems development guidelines for safety risk assessment in the pharmaceutical industry
Additional FDA/CDER Research: Differences in Drug Response between 2D and 3D Approaches to Culturing iPSC-Cardiomyocytes

- **Evaluating contractility endpoints:**
  - Reproducibility of distinct lines of iPSC-cardiomyocytes
  - Response to inotrophic agents
  - Cardiotoxicity of oncology drugs

- **Evaluating calcium cycling endpoints:**
  - Concordance with contractility endpoints
  - How to dissect drug mechanism
Additional FDA/CDER Research: Characterization of Combined Heart-Liver System

- Characterize function reproducibility of additional liver and heart MPS that utilizes iPSC-differentiated cells:

- Test interconnecting heart-liver systems:
  - Effects of liver metabolism/drug interactions on cardiotoxicity
  - Dual liver-heart drug toxicity

Lee-Montiel et al. BioRXiv 2020 doi.org/10.1101/2020.05.24.112771
Images: courtesy Dr. Kevin Healy (UC Berkeley)
Translating MPS Into the Drug Review Process at FDA

FDA/CDER Research Discussed:

- Liver
- Heart
- Interconnected Organs

SUMMARY:

- MPSs can yield reproducible results if system preparation, drug administration and measurement schedules are carefully planned
  - Assess drug adsorption and stability of metabolites and specific endpoints
- Quality control criteria for cells and functional MPSs can be assessed prior to drug experiments to increase reproducibility
  - Similar principles have been implemented in ICH S7B Guideline updates
- Full characterization and qualification for use in drug development depends on the specific context of use

Planned FDA/CDER Research:

- Small Intestines
- Kidney
- Lungs
Thank You!

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