FDA Division of Applied Regulatory Science

Bridging the gap between scientific innovation and drug regulation

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• Disclaimer: The opinions expressed in this presentation are mine and do not necessarily reflect the official views of the U.S. Food and Drug Administration (FDA)

• No conflicts of interest
Presentation goals

• Describe the FDA and its mission

• General interest of the FDA in bioengineering research

• The Center for Drug Evaluation and Research (CDER)

• The Division of Applied Regulatory Science

• Applications in Regulatory Science: liver and cardiac cellular systems

• Q&A
FDA Mission

• Protect the public health by ensuring the safety, efficacy, and security of:
  – Human and veterinary drugs
  – Biological products
  – Medical devices

• Ensure the safety of the U.S.:
  – Food supply
  – Cosmetics
  – Products that emit radiation
FDA Organization

- **Office of the Commissioner**
  - FDA Commissioner
  - Immediate Office of the Commissioner
  - National Center for Toxicological Research

- **Office of Foods and Veterinary Medicine**
  - Center for Food Safety and Applied Nutrition
  - Center for Veterinary Medicine

- **Office of Global Regulatory Operations and Policy**
  - Office of International Programs
  - Office of Regulatory Affairs

- **Office of Medical Products and Tobacco**
  - Center for Biologics Evaluation and Research
  - Center for Devices and Radiological Health
  - Center for Drug Evaluation and Research
  - Center for Tobacco Products
  - Office of Special Medical Programs
  - Oncology Center of Excellence

- **Office of Operations**
  - Office of Equal Employment Opportunity
  - Office of Finance, Budget and Acquisitions
  - Office of Information Management and Technology
FDA Interest in Tissue Engineering, Microfabrication and Biomechanics

• The regulatory use of novel technologies

• Regulation of medical products involving biomanufacturing and tissue regeneration:
  – Center for Biologics Evaluation and Research (CBER)
  – Center for Devices and Radiological Health (CDRH)

• Tools for drug development or predicting human/clinical effects of products:
  – Center for Drug Evaluation and Research (CDER)
  – National Center for Toxicological Research (NCTR)
  – Center for Biologics Evaluation and Research (CBER)
  – Center for Devices and Radiological Health (CDRH)
  – Center for Food Safety and Applied Nutrition (CFSAN)
What is Regulatory Science?

- Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.
Published Reports on Regulatory Science

Focus on the Center for Drug Evaluation and Research (CDER)

- Critical Path Opportunity List - 2006
- FDA’s Regulatory Science Strategic Plan - 2011
- 2011 CDER’s Science Needs Report
- Food and Drug Administration Safety Innovation Act (FDASIA) of 2012
- 2015 CDER’s Safety Research Priorities
- 2018 FDA Division of Applied Regulatory Science Annual Report

“In all cases, we look to FDA reviewers and scientists to identify the most pressing problems and scientific issues, so that we can recruit partners to help us address them.”

Janet Woodcock, 2007

http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm076689.htm
http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm
http://www.fda.gov/drugs/scienceresearch/ucm264327.htm
http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentsstotheFDCA/ucm356316.htm

Slide modified from Ruth Barratt and Alexandre Ribeiro, FDA/CDER
FDA Regulatory Science Priorities

1. Modernize Toxicology to Enhance Product Safety: Strategic Plan for Regulatory Science
2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes: Strategic Plan for Regulatory Science
4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies
5. Harness Diverse Data through Information Sciences to Improve Health Outcomes: Strategic Plan for Regulatory Science
6. Implement a New Prevention-Focused Food Safety System to Protect Public Health: Strategic Plan for Regulatory Science
7. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security
CDER: 7 Safety-Related Research Topics

1. Improve Access to Post-market Data Sources and Explore Feasibility of Their Use in Safety Signal Analyses
2. Improve Risk Assessment and Management Strategies to Reinforce the Safe Use of Drugs
3. Evaluate and Improve Risk Communication
4. Focus on Product Quality Attributes, Manufacturing Processes, and Product Performance relating to Safety
5. Develop and Improve Predictive Models of Safety in Humans, including Non-Clinical Biomarkers
6. Improve Clinical Trial Statistical Analyses for Safety and Benefit Risk
7. Investigate Clinical Biomarkers of Safety, Including Standards for Qualification

http://www.fda.gov/drugs/scienceresearch/ucm264327.htm

Slide modified from Ruth Barratt, FDA/CDER
What We Do in OTS and OCP

• **Office of Translational Sciences**
  – Promote innovation in drug regulatory review
  – Assure the validity of clinical trial design and analysis
  – Develop and apply quantitative approaches
  – Promote scientific collaboration
  – Ensure alignment of CDER research with CDER goals

• **Office of Clinical Pharmacology**
  – Evaluate pharmacokinetics and pharmacodynamics
  – Understand inter-patient variabilities
  – Optimize dose and dose regimen to balance benefit and risk
  – Conduct research to advance clinical pharmacology and better evaluate benefit and risk
Division of Applied Regulatory Science (DARS)

Vision
- To move new science into the CDER review process and close the gap between scientific innovation and product review

What does DARS do?
- Performs mission-critical applied research to develop and evaluate tools, standards and approaches to assess the safety, efficacy, quality and performance of drugs
- Performs expert regulatory review consultations for mechanistic safety evaluation for immediate regulatory needs combining
  - Critical review of existing knowledge
  - Computational analyses with informatics tools and disease-pharmacology models
  - In vitro and in vivo laboratory studies
  - Translational analysis of preclinical studies, clinical trials and post-market data
Division of Applied Regulatory Science Priority Areas

- Translational research

- Collaboration and interdisciplinary team approaches

- Implementation of new regulatory review methods and programs

Collaboration: OSE, OND, OGD, OTS, CDRH, CBER, NCTR, NIH, industry, universities

- Kevin Healy: UC Berkeley
- Ed Hsiao: UCSF
General Research Areas

1) Mechanistic safety assessment with humanized assays, genomics and biomarkers (nonclinical and clinical)
   - Model-informed, mechanistic-based cardiac safety
   - Genomic (microRNA) biomarkers for tissue injury
   - Humanized mouse models (immune and liver)

2) Bioanalytical, pharmacokinetics and drug-drug interactions (DDI)
   - In vivo biodistribution studies
   - Bioequivalence of topical ophthalmic products
   - In vitro + in vivo assessment of combination therapy to prevent antibacterial resistance

3) Chemical and Biomedical Informatics tools for research and regulatory review
   - Chemical informatics
   - Biomedical informatics
   - Mechanistic safety and pharmacology consults
Current Research projects

1. Modeling & Simulation
2. In Vitro Models
3. In Vivo Models
4. Biomarkers
5. Innovative Clinical Trial Designs
6. Advanced Manufacturing
7. Real World Data
8. Complex Generics & Biosimilars
Cellular systems are *in vitro* platforms to assay organ-specific function

- Combining cells in an engineered microenvironment originates in vitro settings with higher physiological relevance
- How important is physiological relevance for regulatory contexts of use?
We evaluate the regulatory use of *cellular systems* in drug development

**building confidence**

**analytical validation**

**Key Enablers**

- replicate biology
- demonstrate pharmacology and toxicology
- test for analytical reproducibility
- comparative studies
- evolution of use
- learn to make decisions
- clinical outcomes
- tincture of time/experience

**translational qualification**

**Our Lab**

- investigates critical technology for drug development
- complements work done by other researchers
- collaborates with different stakeholders

*Provided by Brian Berridge (National Toxicology Program - NIH)*
Emerging technologies evaluated in our laboratory

induced pluripotent stem cells (iPSCs)

from consenting adult

somatic cells:
- blood cells
- skin cells
- fat cells

reprogramming factors

induced pluripotent stem cells

microphysiological systems (MPS)
Heart and Liver toxicity is the main cause for drug attrition

<table>
<thead>
<tr>
<th>Phase</th>
<th>Preclinical</th>
<th>Phase I-III</th>
<th>Post-Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size:</td>
<td>156 CDs stopped</td>
<td>63 CDs stopped</td>
<td>47 drugs</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>24%</td>
<td>35%</td>
<td>45%</td>
</tr>
<tr>
<td>Liver</td>
<td>15%</td>
<td>29%</td>
<td>32%</td>
</tr>
<tr>
<td>Hematology</td>
<td>3%</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Neuro</td>
<td>12%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Immuno</td>
<td>7%</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>GI</td>
<td>5%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Reproductive</td>
<td>9%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Musculo-Skeletal</td>
<td>8%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Renal</td>
<td>6%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Genetic tox</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Carcinogenicity</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Adapted from Redfern et al (2010) and provided by Tim Hammond (AstraZeneca) and Kristina Howard (FDA-CDER)

Hypothesis that motivates this focus:
- Physiological and human-specific cellular systems can better predict clinical drug effects and reduce drug attrition in clinical trials
Human-specific cellular systems have higher potential to predict clinical drug effects

- Tissues/biopsies isolated from humans/patients

- Induced pluripotent stem cells (iPSCs)
  - reprogramming factors
  - induced pluripotent stem cells (iPSCs)
  - Potential to differentiate into any human cell type

  - somatic cells:
    - blood cells
    - skin cells
    - fat cells

- primary hepatocytes
- primary Kupffer cells

- iPSC-derived cardiomyocytes

www.fda.gov
Use of human cellular system depends on readiness of cellular materials.

- Ready
- Almost ready
- Need improvement
- Under development

Donor cells:
- Liver
- GI
- Kidney
- Neurons
- Immune

iPSC derived cells:
- Heart
- Neurons
- Liver
- GI
- Kidney
- Immune
In vitro systems are used early in drug development

- Biochemical and molecular assays
- High throughput and low sensitivity assays
- Cell types for different contexts of use
- Mechanistic assays
Throughput, sensitivity, mechanistic relevance and cost dictate the use of cellular systems

large screens in early testing:
- high throughput
- cheap
- low sensitivity
- phenomenological
- cover broad mechanisms

liver as an example

HepG2 cells
HepaRG cells
iPSC-hepatocytes

endpoints: metabolism, transport, cell death mechanisms

primary hepatocytes
microphysiological systems

HL-1 cells
isogenic
isolated
gineered cardiac
microsystems with iPSC-cardiomyocytes
time of in vitro testing in drug development

H9C2 cells
iPSC-cardiomyocytes
isolated tissue/cardio(myocytes

engineered cardiac microsystems with iPSC-cardiomyocytes

AC16 cells
HEK cells

endpoints: electrophysiology, calcium, contractility, mitochondria, energetics, biomarkers, cell death mechanisms

for cardiac

www.fda.gov
Cellular systems should be designed for a context of use of drug evaluation

- **Organ-specific properties?** cell types, co-cultures, expression of specific receptors

- **Human-specific properties?** human mechanisms that differ from animals or data showing human-animal differences

- **Physiological experimental settings/microenvironment?** nutrients, hormones, other organ systems, mechano-electrical factors

- **The example of iPSC-cardiomyocytes?** human-specific cells that can be engineered to predict different contexts of drug toxicity

- **When to use them in the drug development route?** early, late, reliability and robustness matter
• Evaluation of microphysiological systems: LiverChip

• Contractility of iPSC-cardiomyocytes

• Future: multi-organ systems and compare with \textit{in vivo} data
In addition to toxicity, the liver is a key organ to model metabolism and pharmacokinetics

Liver:

- generation of toxic drug metabolites
- drug metabolism
- drug clearance
- drug-drug interactions
- data needed for physiologically-based pharmacokinetic and pharmacodynamic models

Bauman JL European Heart Journal Supplements 2001
LiverChip cultures hepatic cells in 3D and exposed to flow

- Perfusate: media in contact with cells
- Cells: tissue within the scaffold
Criteria for evaluating LiverChip system

• Site-to-site variability: the developers repeat experiments

• Chip-to-chip variability: how different chip batches (device + cells) affect results

• Focus on PTMS protocols: Preparation, Treatment and Measurement Schedules
Project evaluation goals

1. assemble, operate and **assay** the LiverChip
   a) variability: chip-to-chip and well-to-well.
   b) endpoints: cell viability, cytochrome P4503A (CYP3A4) activity, gene expression and structural organization.
   c) contexts of evaluation: use of known toxicants.

2. different drug contexts of use for measuring hepatic properties
   a) detect **phase II metabolism** by analyzing drug bioprocessing
   b) test predictability of **differential toxicity** of drugs.

3. human-specific metabolism
   a) drugs with human-specific metabolism
This evaluation compares the LiverChip with other in vitro systems: *sandwich culture*

Limitations:

- Hepatic properties do not last beyond day 4
- Other hepatic cells are absent
- Absence of a physiological microenvironment: 3D + flow

The liver microenvironment is **3D**, under **fluid flow** and **multicellular**

LiverChip:
- long-lasting hepatic properties
- heterogeneity of cell types
- universally reliable and robust properties

![LiverChip diagram]

- hepatocytes
- Kupffer cells
- sinusoidal endothelial cells
- stellate cells
Albumin production is higher in cells cultured in the LiverChip than in other platforms.
Adding multiple cell types improves the ability to predict different mechanisms

Kaplowitz, N, Adv Clin Infect Dis, 2004
We tested the use of co-cultures to screen drug toxicity with known drugs

levofloxacín (FDA-approved)

trovafloxacín (restrictions for use due to hepatotoxicity)

We developed a protocol:

• Defined treatment schedules

• Co-dosing with (Lipopolysaccharides) LPS: induce inflammatory signaling

• Concentrations (0, 25, 100) µM
We observed toxicity induced by trovafloxacin and enabled by inflammation.
• Contractility of iPSC-cardiomyocytes

• Towards multi-organ systems
iPSC-cardiomyocytes: assay human heart function in a dish


Our goal is to evaluate drug toxicity assays
The use of iPSC-cardiomyocytes is limited by their fetal-like properties

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Immature CMs</th>
<th>Mature CMs</th>
<th>Methods / Metrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcomere Structure / Length / Stability</td>
<td>Disarrayed / 1.6 μm / fluid</td>
<td>Organized / 2.2 μm / fixed</td>
<td>FFT / measure length / dynamic of myofibrils</td>
</tr>
<tr>
<td>Mitochondria Distribution</td>
<td>Occupies a small fraction</td>
<td>≈ 40% of cell</td>
<td>Mitochondria Dies</td>
</tr>
<tr>
<td>Binucleation Number</td>
<td>Mononucleated</td>
<td>≈ 25% binucleated</td>
<td>Counting</td>
</tr>
<tr>
<td>Electrophysiology Upstroke velocity / Resting potential</td>
<td>≈ 50 V/s / -60mV</td>
<td>≈ 250 V/s / -90 mV</td>
<td>Patch clamp</td>
</tr>
<tr>
<td>Excitation-Contraction Coupling Pacing of Cells</td>
<td>Partially Developed - relate to calcium</td>
<td>Mature</td>
<td>Calcium imaging</td>
</tr>
<tr>
<td>Contractile Force Biomechanical Phenotypes</td>
<td>≈ nN range/cell</td>
<td>≈ μN range/cell</td>
<td>Traction Force Microscopy</td>
</tr>
</tbody>
</table>

Stem Cell – CM Fetal-like

Adult CM Mature

www.fda.gov

Yang, X et al., Circ Res. 2014
Cellular systems are also used to improve maturity of iPSC-cardiomyocytes

- Evaluate the effects of these approaches on drug response
- Focus on contractility endpoints: non-destructive and minimally invasive

1D: single cell
2D: cell monolayer
3D: engineered heart tissue

- co-culture with support cells
- electrical stimulation
- extracellular composition
- genetic engineering

Cell alignment
Extracellular rigidity
Stiff (GPa)
Soft (kPa)
iPSC-cardiomyocytes can be cultured in microfabricated platforms to measure contractility

- methods must be feasible, robust and reliable
- physiologic relevance must be ensured
Cardiac contractility results from actin-myosin interactions
Engineered heart tissues

Ronaldson-Bouchard et al. Nature 2018
Mannhardt et al. Stem Cell Rep 2016
Hinson, Chopra et al. Science 2015
Mathur et al. Sci Rep 2015
Ultimate Goal: Evaluate More Systems and Compare Different Platforms

Collaboration with the Healy Lab

Learn & compare

Injury

Drugs

Blood brain barrier on a chip

Liver on a chip

Heart on a chip

Kidney on a chip

Bone marrow

Thymus

Modulate immunity on a chip

Humanized mouse

Clinical data

Biomarkers of toxicity and efficacy

Modulate immunity
Key takeaways

• FDA CDER laboratories are heavily invested in evaluating novel technologies to better predict clinical drug effects

• Human cellular systems should answer focused mechanistic questions

• Design of systems should be focused on physiological relevance and validation of functional endpoints to measure

• Efforts must be developed to set contexts of use of different systems:
  – what types/ classes of drugs?
  – what mechanism(s) of drug effects?
  – how predictable functional endpoints are?
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CDER: 7 Safety-Related Research Topics

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http://www.fda.gov/drugs/scienceresearch/ucm264327.htm

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Thanks!