U.S. FOOD & DRUG ADMINISTRATION

Public Stakeholder Meeting on Prescription Drug User Fee Act (PDUFA) Reauthorization

October 30, 2020

Dr. Theresa Mullin
Associate Director for Strategic Initiatives
Center for Drug Evaluation and Research
Food and Drug Administration

Outline for this meeting

- Welcome and Roll Call
- Presentation Topics:
  - Patient Focused Drug Development
  - Model-Informed Drug Development
  - Complex Innovative Designs for Clinical Trials
  - Other Areas of Regulatory Science: Advancing Translational Models & Tools
- Topics for upcoming meetings

U.S. FOOD & DRUG ADMINISTRATION

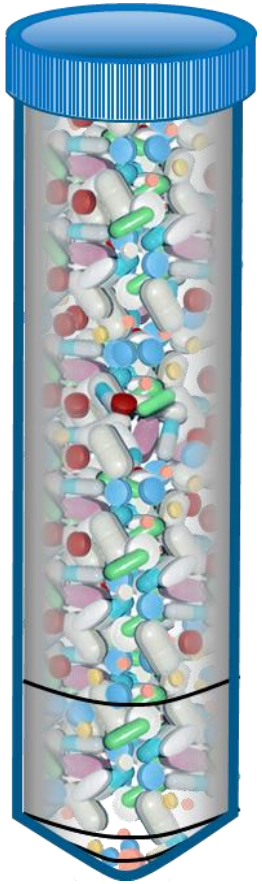
Other Areas of Regulatory Science: Advancing Translational Models & Tools (ATMT)

October 30, 2020

Dr. David Strauss
Center for Drug Evaluation and Research
Food and Drug Administration

Translational Models and Tools to Advance Drug Development

Drug Development



← >10,000 Compounds

← Optimize Compounds

← Preclinical Safety

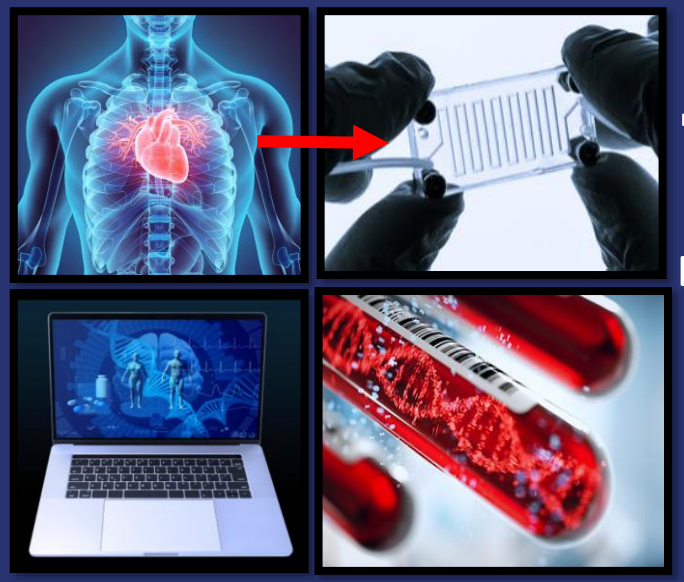
← Clinical Studies

← FDA Review

← 1 Approved Drug

Translational Models and Tools

New science (models and tools) can be used to overcome challenges and hurdles in drug development



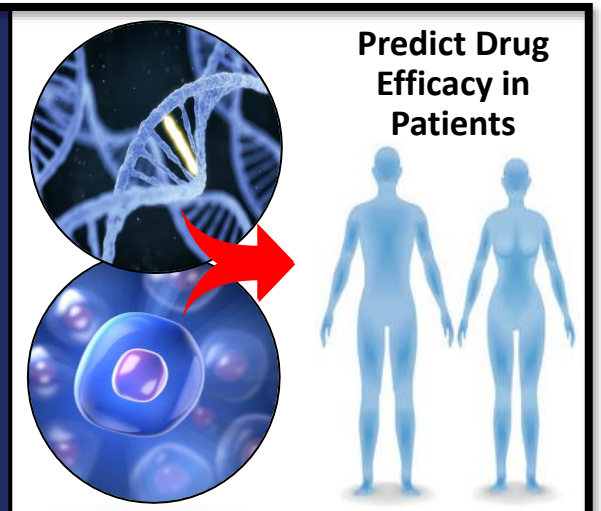
Safety & Efficacy in Patients

Successful implementation can lead to:

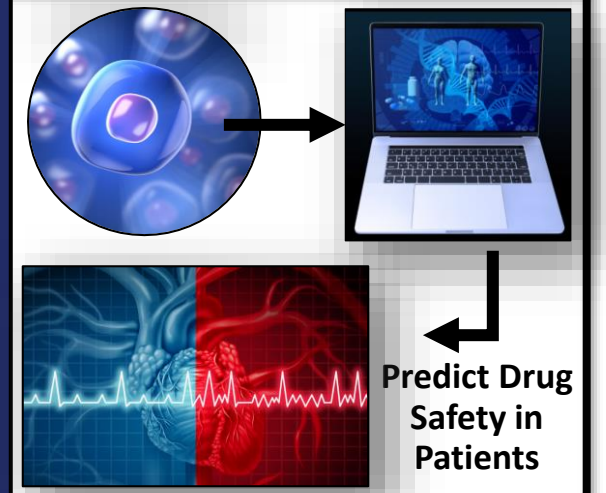
- ✓ Streamlined development
- ✓ Broader patient populations
- ✓ More drugs approved
- ✓ Reduced cost

Translating New Science Into the Drug Review Process: FDA's Division of Applied Regulatory Science

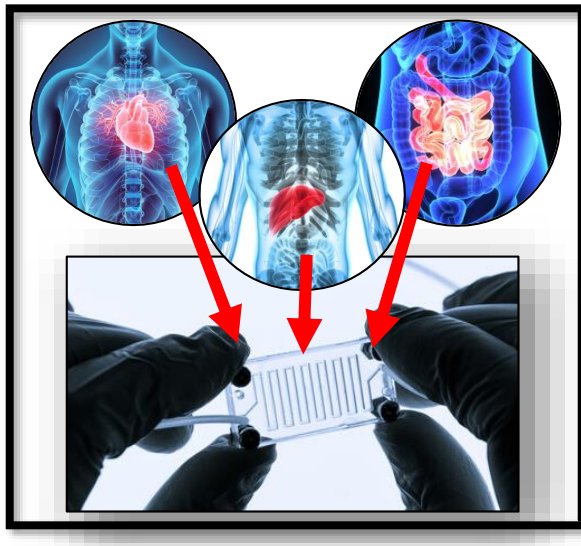
Laboratory Cellular Models to Expand FDA Approvals for Rare Diseases



Combined Cellular and Computer Models to Predict Drug Safety



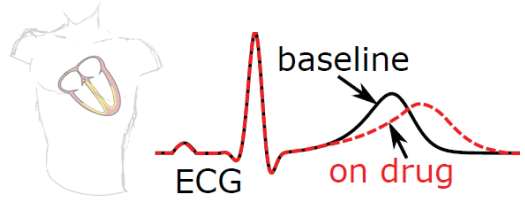
The Division of Applied Regulatory Science was created to move new science into the drug review process and close the gap between scientific innovation and drug review



Human "Organ-on-a-Chip" to Assess Drug Safety, Efficacy or Drug Interactions

Blood Biomarkers

Physiological Measurement Biomarkers



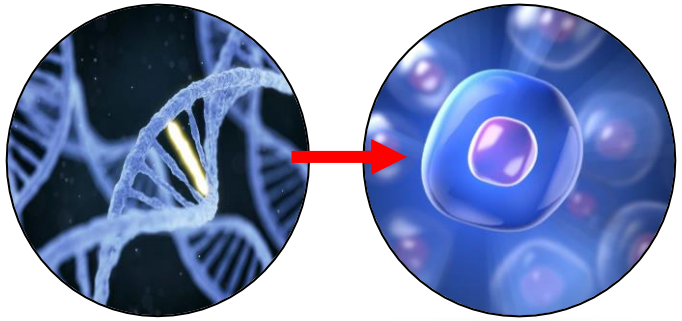
Novel Human Biomarkers for Use in Phase 1 Clinical Trials

Cell 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 FDA laboratory experience with specific models was critical to assess quality and reproduce results. Expanding FDA cellular model experience and expertise can further:

EXPAND APPROVAL AND REACH MORE PATIENTS

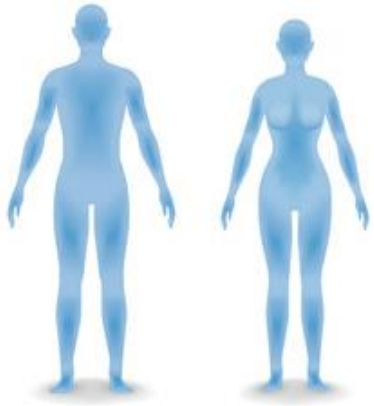
REDUCE NUMBER OF CLINICAL TRIALS

Large infeasible studies

Feasible study

Need to Study New Technologies for Model Development

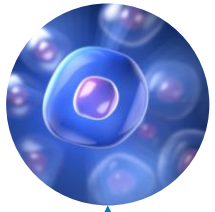
Specific patients



Cells from skin or blood

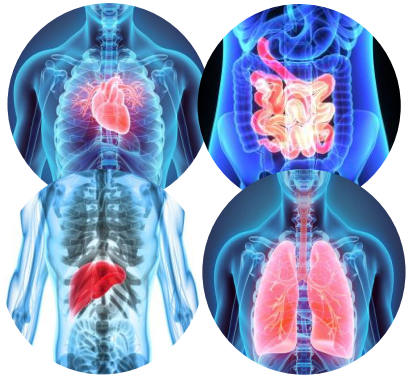
reprogram

Induced pluripotent stem cells (iPSCs)



differentiate

Patient-specific cells (e.g. heart, liver, intestine, lung)



Assess drug efficacy

CRISPR gene editing to create models with additional variants

2020 Nobel Prize in Chemistry – CRISPR

"For the development of a method for genome editing"

Examples of iPSC Models in Development

Links:

- Amyotrophic lateral sclerosis
- Alzheimer's disease
- Pediatric neurological diseases
- Cystic fibrosis
- Duchenne and Becker muscular dystrophies
- Hutchinson-Gilford progeria syndrome

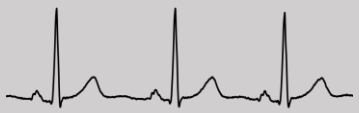
Need additional research to inform:

- **Standards**
- **Quality control criteria**
- **Best practices**

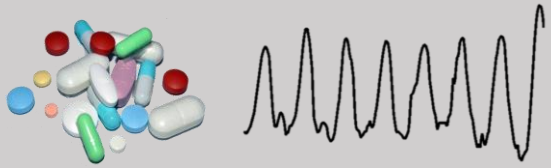
For laboratory models with these new technologies

New Approach for Assessing Heart Safety of All New Drugs

Normal Heart Rhythm



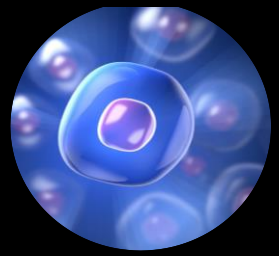
Drug-Induced ABNORMAL Heart Rhythm!



- Regulatory Guidelines require lab test and special clinical study for all new drugs
- These identify drugs that **may** cause abnormal heart rhythms
- However, there are **many false positives**
  - Drugs get "flagged" as having a problem, even though they are safe
- **Result**: Many expensive clinical trials and drugs dropped from development, sometimes unnecessarily

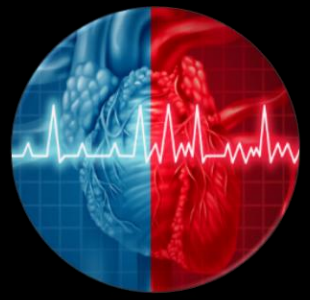
New Approach

1. Laboratory Cell-Based Models



2. Integrate in Computer Model

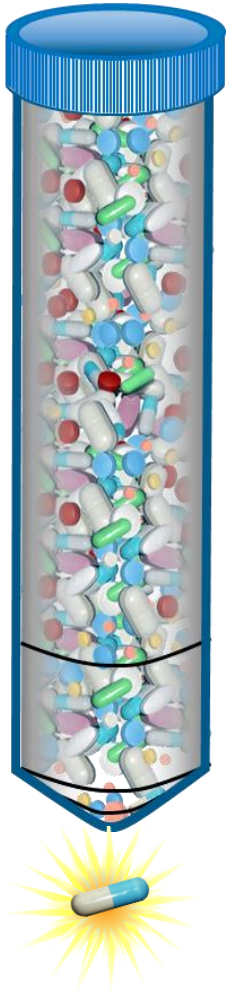
3. Predict Heart Safety in Patients



Choose compounds to advance so we don't lose promising new drugs

Replace imperfect clinical trials

Inform regulatory decision making



FDA Research Led to Update to International Regulatory Guidelines

Systematic Process

Prior FDA Research

- Nonclinical models
- Clinical biomarkers

FDA-Led International Regulatory Draft Guideline Released Sept 2020

FDA

ICH harmonisation for better health

International Council for Harmonisation

Nonclinical Models Reduce Number of Clinical Studies

Studies

Studies

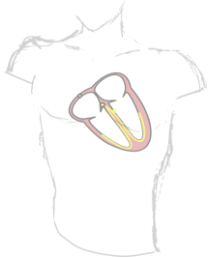
Nonclinical Models Inform Approval Decisions & Labeling

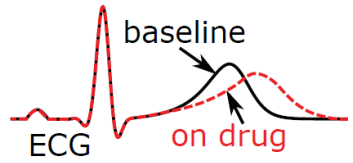
Possible Risk? → **Low Risk**

However, Current Updates Focus on Limited Clinical Scenarios

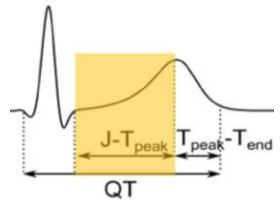
We Need to Study More Drugs and Toxicity Mechanisms in Nonclinical Models

Further Validate Novel Clinical Biomarkers to be Used in Phase 1 Clinical Trials with Some Drugs



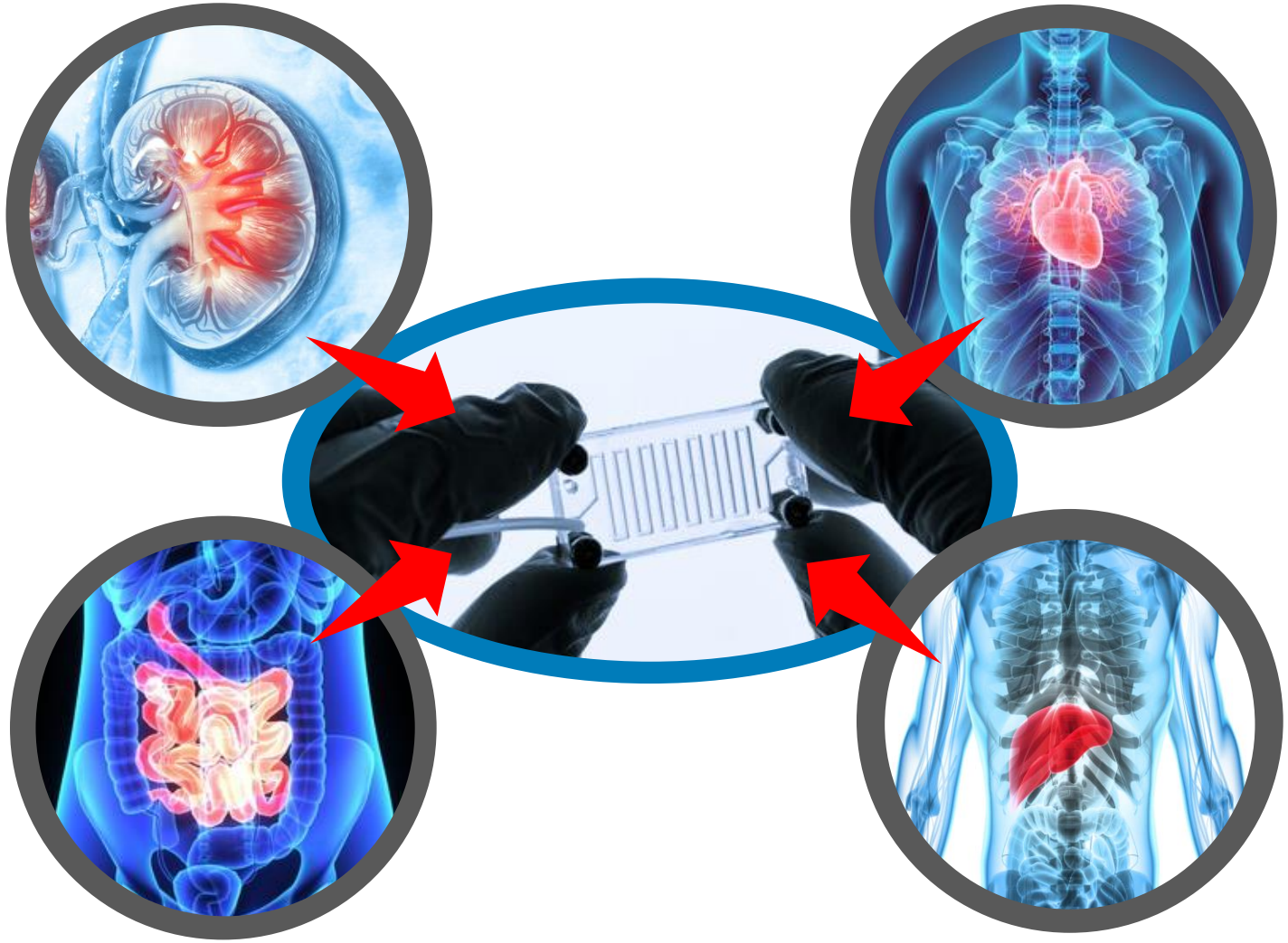


Novel Biomarkers



Requires more dedicated research to develop guidance on integrating nonclinical models with clinical phase 1 biomarkers

Microphysiological Systems (Organs-on-a-Chip)



What Are Organs-on-a-Chip?

- 3D cell models with multiple cell types
- Fluid flow through organs
  - ➢ Which can connect organs together
- Special organ features
  - Such as mechanical forces with heart

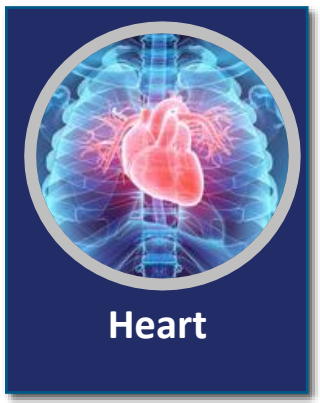
Applications in Drug Development

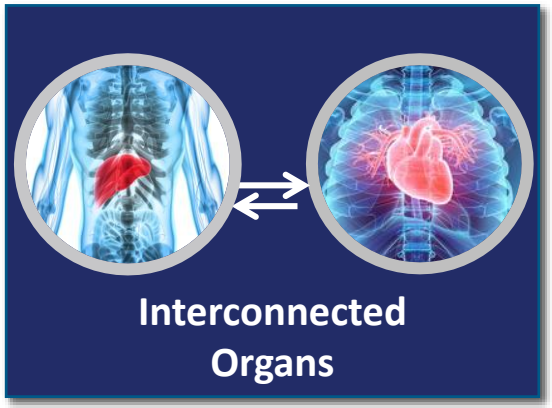
- Reduce/replace animal or clinical studies
- Assess safety and efficacy
- Assess drug-drug interactions

Translating Organs-On-A-Chip Into the Drug Review Process at FDA

FDA is performing preliminary studies on:


Liver


Heart


Interconnected Organs


Kidney (coming soon)

Recent FDA Publications:

- Liver systems
- Human iPSC-heart and liver cells
- Heart contractility

Example disease modeling areas:

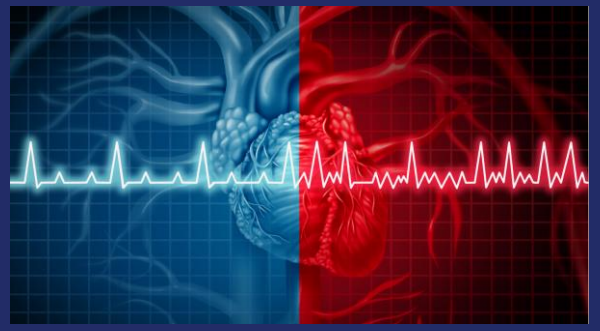
- Alzheimer's
- Cancer
- Diabetes
- Inflammatory bowel diseases
- **Rare diseases:**
  - Amyotrophic lateral sclerosis
  - Cystic fibrosis
  - Duchenne muscular dystrophy

TO ACHIEVE SUCCESS, WE NEED APPLIED RESEARCH TO DEFINE:

- **Quality and performance standards for organs-on-a-chip:**
  - Cells, extracellular components, media (fluid)
  - Assessing baseline organ function
  - Experimental protocols, data analysis, scaling to humans
- **Principles for validation criteria for specific applications**
  - Safety, efficacy, drug interactions

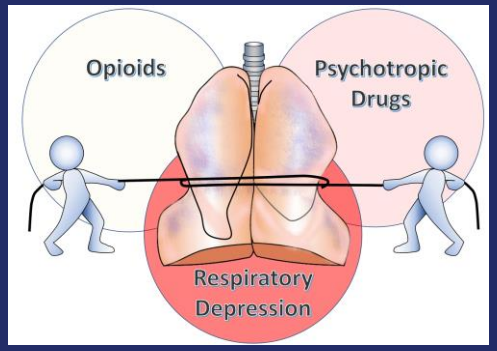
Leading Efforts to Identify and Validate Novel Biomarkers

Clinical Safety Biomarkers



Biomarkers to better understand heart risk

(3 FDA clinical trials completed)



Biomarkers to study interaction between opioids and other drugs on breathing

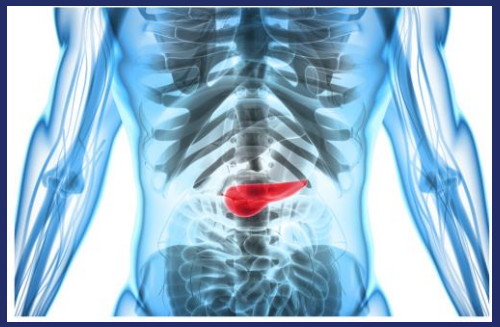
(1 ongoing FDA clinical trial)

Blood-Based Biomarkers

Prior Work With Nonclinical Biomarkers; Need to Translate to Clinical Use

Kidney-Injury Biomarkers

Vascular-Injury Biomarkers

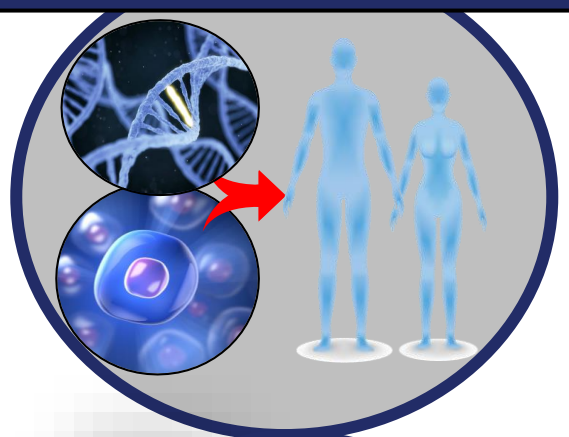


Pancreatic-Injury Biomarkers

- **Clinical biomarker development is historically a slow process**
- **Collaborative approaches could speed development and qualification**

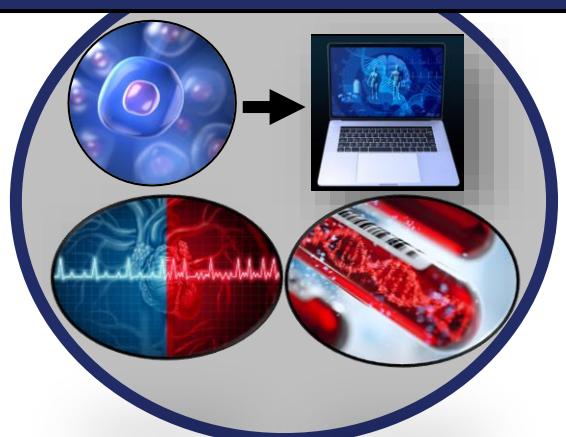
Translational Models and Tools to Overcome Hurdles in Drug Development

Cellular Models to Approve Drugs for More Patients



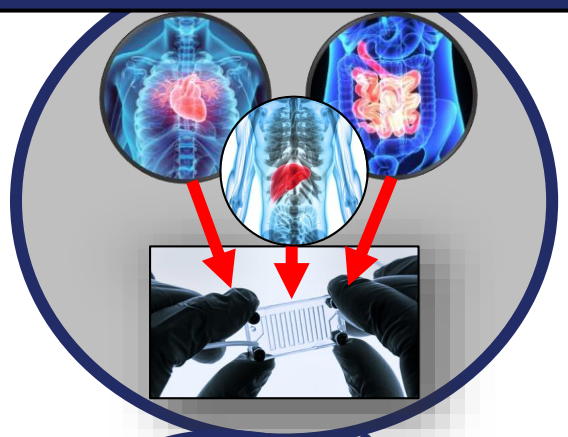
Impractical to Perform Rare Disease Clinical Trials for Efficacy

Cellular + Computer Models and Biomarkers to Predict Patient Safety



False-Positive Safety Signals Lead to Drugs Dropped From Development Unnecessarily

Human "Organs-on-a-Chip" to Replace/Reduce Clinical Trials



Expensive Clinical Trials with Limited Prediction of Effects in Patients

More Drugs Approved for Broader Patient Populations at Less Cost

Links for Additional Information

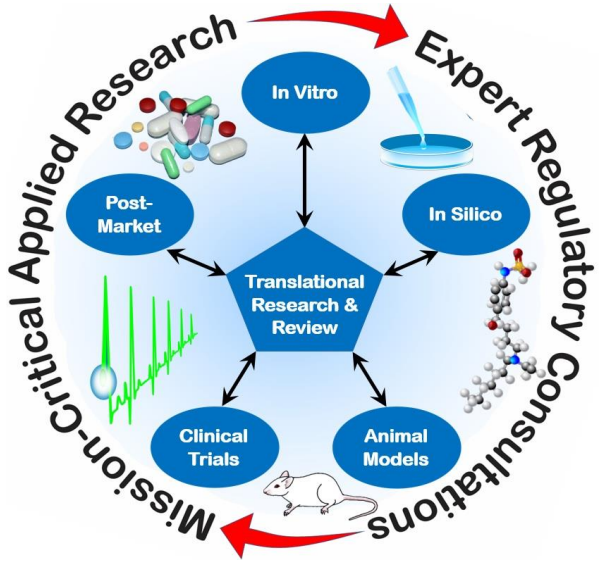
Division of Applied Regulatory Science (DARS)

Regulatory Science: Review DIA

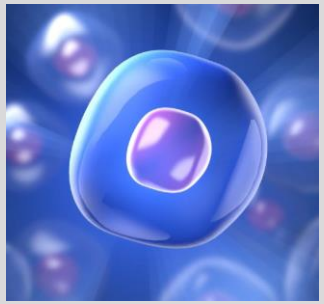
Translating New Science Into the Drug Review Process: The US FDA's Division of Applied Regulatory Science

Rodney Rouse, DVM, MBA, PhD[1], Naomi Kruhlak, PhD[1], James Weaver, PhD[1], Keith Burkhart, MD[1], Vikram Patel, PhD[1], and David G. Strauss, MD, PhD[1]

Therapeutic Innovation & Regulatory Science 2018.



Laboratory Cellular Models



- Organs-on-a-chip (workshop)
- Clinical pharmacology
- Cellular efficacy data (cystic fibrosis)

Publications link

Biomarkers

- Organ injury biomarkers
- Human immune system
- Respiratory depression

Publications Link

- Heart Safety Biomarkers
- Opioids Effects on Breathing Biomarkers
- Biologics and biosimilars

Publications link

Computer Models

- Systems pharmacology & heart safety
- Chemical & biomedical informatics

Publications link

Other Clinical Studies

- Sunscreen absorption studies (*2 JAMA publications*)
- Most read JAMA article of 2019
- Ranitidine metabolites (NDMA) *(1 ongoing study)*

DARS: Mission/Vision Research Overview Video Annual Report Clinical Trials DIA Podcast JAMA News Article