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
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
- More drugs approved
- Broader patient populations
- Reduced cost
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.
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

- Large infeasible studies
- Feasible study

REDUCE NUMBER OF CLINICAL TRIALS
Need to Study New Technologies for Model Development

Induced pluripotent stem cells (iPSCs)

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

Assess drug efficacy

Specific patients

Cells from skin or blood

reprogram

differentiate

CRISPR gene editing to create models with additional variants

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

2020 Nobel Prize in Chemistry – CRISPR
"For the development of a method for genome editing"

Need additional research to inform:
- Standards
- Quality control criteria
- Best practices

For laboratory models with these new technologies
Choose compounds to advance so we don’t lose promising new drugs

Replace imperfect clinical trials

Inform regulatory decision making

New Approach for Assessing Heart Safety of All New Drugs

1. Laboratory Cell-Based Models
2. Integrate in Computer Model
3. Predict Heart Safety in Patients

• 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
FDA Research Led to Update to International Regulatory Guidelines

- Systematic Process
  - FDA Applied Research
  - Collaborative Research
  - Workshops & White Papers
  - Guidance, Policy & Training

Prior FDA Research
- Nonclinical models
- Clinical biomarkers

FDA-Led International Regulatory Draft Guideline Released Sept 2020

Nonclinical Models Reduce Number of Clinical Studies

# Studies

Possible Risk? → Low Risk

Nonclinical Models Inform Approval Decisions & Labeling

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

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

However, Current Updates Focus on Limited Clinical Scenarios
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

FDA is performing preliminary studies on:

Liver
Heart
Interconnected Organs
Kidney (coming soon)

Example disease modeling areas:

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

Recent FDA Publications:

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

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**

- Kidney-Injury Biomarkers
- Vascular-Injury Biomarkers
- Pancreatic-Injury Biomarkers

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

- 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

Cellular + Computer Models and Biomarkers to Predict Patient Safety

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

More Drugs Approved for Broader Patient Populations at Less Cost
Links for Additional Information

Division of Applied Regulatory Science (DARS)


Rodney Rouse, DVM, MBA, PhD¹, Naomi Kruhlak, PhD¹, James Weaver, PhD¹, Keith Burkhart, MD¹, Vikram Patel, PhD¹, and David G. Strauss, MD, PhD¹

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)