Advancing Regulatory Science Through Innovation

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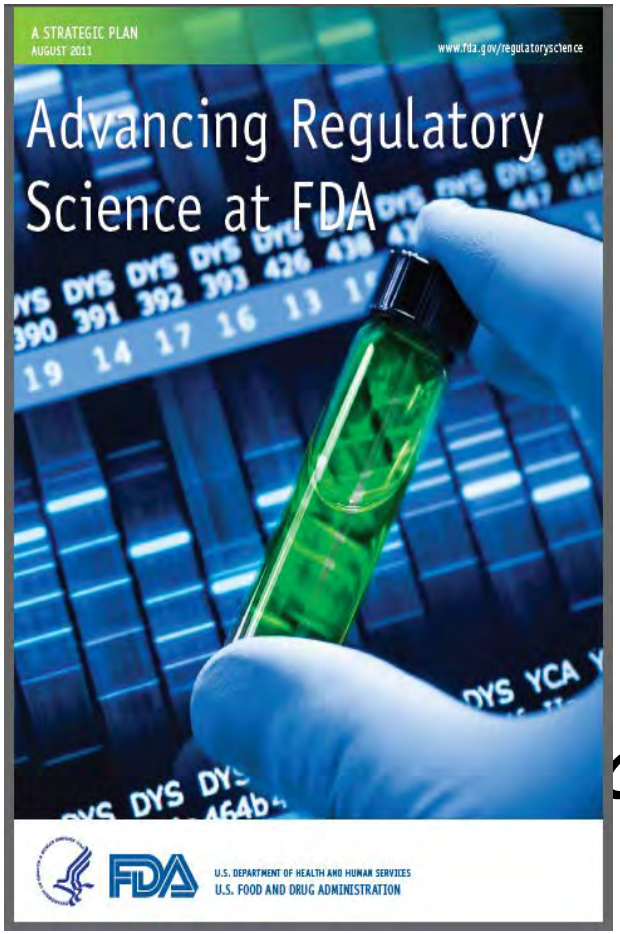
STRATEGIC PLAN: Vision



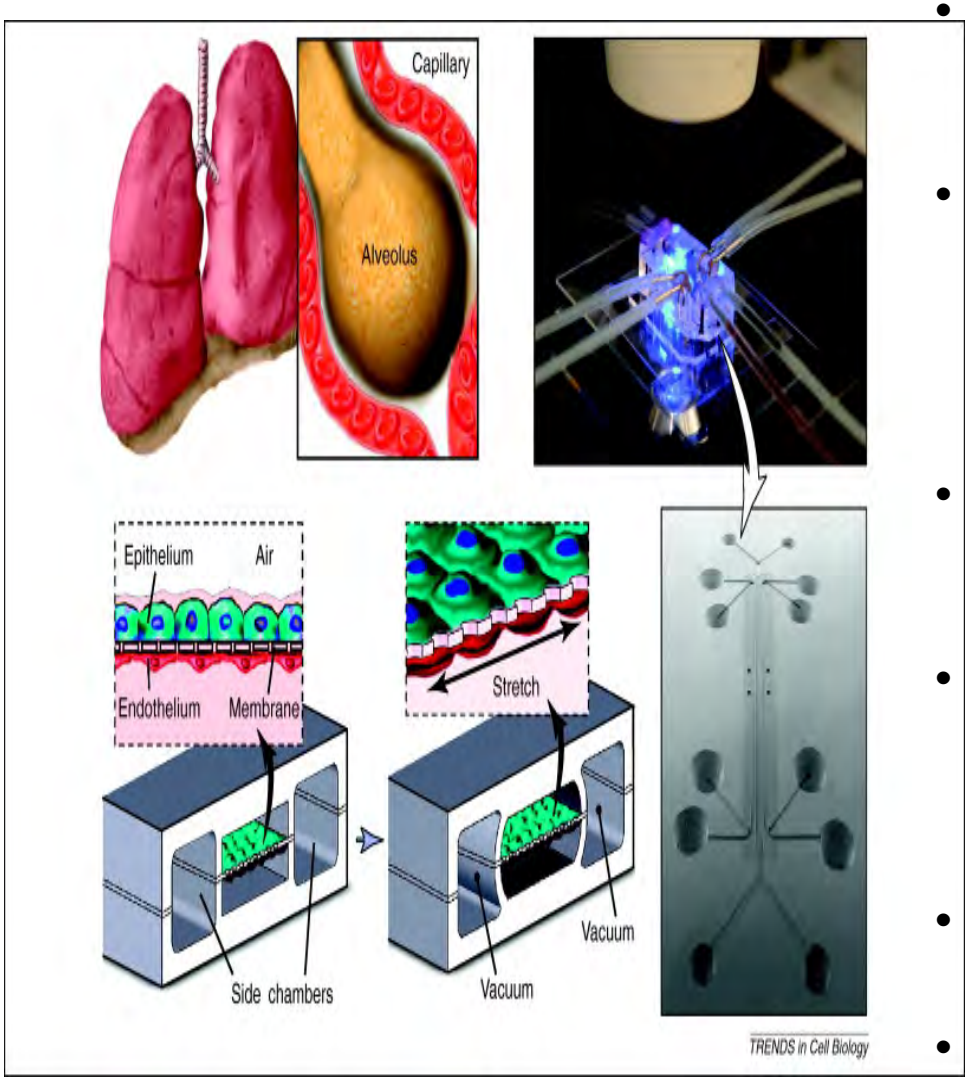
"FDA will advance regulatory science to speed innovation, improve regulatory decision-making, and get safe and effective products to people in need. 21st Century regulatory science will be a driving force as FDA works with diverse partners to protect and promote the health of our nation and the global community"

One goal is more predicative models for safety assessment

Advancing Regulatory Science

- FDA-NIH Joint Leadership Council formed in 2010
- Issued RFA for Advancing Regulatory Science through Novel Research & Science-Based Technologies Program ($7M, 4 awards):
  - Accelerating Drug & Device Evaluation through Innovative Clinical Trial Design
  - Replacement Ocular Battery
  - **Heart-Lung Micromachine for Safety and Efficacy Testing**
  - Characterization/Bioinformatics-modeling of Nanoparticle: Complement Interactions

Wyss Lung on a Chip



- Complex, 3-D model of a living, breathing human lung on a microchip.
- Two layers of living human tissues—the lining of the lung's air sacs and the blood vessels that surround them—across a porous, flexible boundary.
- Air delivered to the lung lining cells, a rich culture medium flows in the capillary channel to mimic blood,
- Cyclic mechanical stretching is generated by a vacuum applied to the chambers adjacent to the cell culture channels to mimic breathing.
- http://www.sciencemag.org/content/328/5986/1662.full
- http://vimeo.com/22999280

Pulmonary Edema Model- Lung on a Chip

- Device used to reproduce drug toxicity–induced pulmonary edema observed in human cancer patients treated with interleukin-2 (IL-2) at similar doses and over the same time frame.
- Studies revealed that mechanical forces associated with physiological breathing motions play a crucial role in the development of increased vascular leakage that leads to pulmonary edema, and that circulating immune cells are not required for the development of this disease.
- http://www.sciencemag.org/content/338/6108/731.summary

Using Lung on a Chip in Drug Discovery

- Working with the institute, drug maker GlaxoSmithKline tested a potential drug's effect on the diseased human lung on a chip, and found that it replicated the response seen in dog, mice and rat models of pulmonary edema.
- GlaxoSmithKline is now exploring how to use the device to assess the safety and efficacy of other respiratory compounds, says Kevin Thorneloe, a senior Glaxo scientist.
- http://online.wsj.com/article/SB10001424127887324049504578545154163286708.html?mod=WSJ_business_LeftSecondHighlights

Using Lung on a Chip in Drug Development

- At Merck Co.'s labs in Boston, researchers are looking at using microchips engineered to resemble a diseased lung in their hunt for a new asthma treatment.
- Company scientists want to see whether these "lungs on a chip" can help them better understand the biology behind asthma and identify promising candidates for medicines, says Don Nicholson, who oversees Merck's respiratory drug research.
- http://online.wsj.com/article/SB10001424127887324049504578545151416328670 8.html?mod=WSJ_business_LeftSecondHighlights

FDA-DARPA-NIH Microphysiological Systems Program

- Started in 2011 to support the development of human microsystems, or organ "chips," to screen for safe and effective drugs swiftly and efficiently (before human testing)
- Collaboration through coordination of independent programs

Engineering platforms and biological proof-of-concept (DARPA-BAA-11-73: Microphysiological Systems)

Underlying biology/pathology and mechanistic understanding (RFA-RM-12-001 and RFA RM-11-022)

Advise on regulatory requirements, validation and qualification

Microphysiological Systems DARPA –BAA-11-73

- Reconfigurable platform
- Ten or more in vitro physiological systems
- Able to monitor resident tissues for up to 4weeks
- Uses human cells
- Commercial availability
- Includes plan for validating integrated platform performance
- 70 million over 5 years
- Applications jointly reviewed by DARPA, FDA, and NIH
- Contracts were awarded to Wyss and MIT

Stem/Progenitor Cell-Derived Human Micro-organs and -tissues (U18)
Integrated Microphysiological Systems for Drug Efficacy and Toxicity Testing (UH2/UH3)

- *GOAL U18:* Develop stem- and progenitor-derived cell resources to seed circulatory, endocrine, gastrointestinal, immune, integumentary, musculoskeletal, nervous (including eye), reproductive, respiratory and urinary microsystems.
- *GOAL UH2/UH3:* Develop *in vitro* microphysiological systems representative of major organs/tissues in the human body, that will facilitate the assessment of biomarkers, bioavailability, efficacy, and toxicity of therapeutic agents prior to clinical trials.

Tissue Chip Program Overview

U18 generated cell resources
UH2 generated organ systems

24 months

DARPA bioengineering
Platform + 2 systems

Base period

4 systems

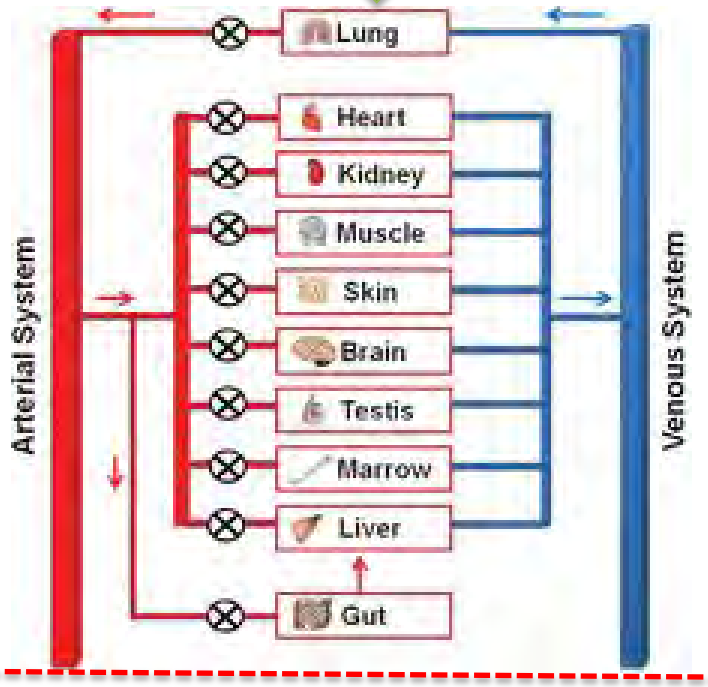
Period 1

7 systems

Period 2

Integration & validation

UH3 phase:
- Incorporation of differentiated stem- and progenitor-derived cells
- Integration of various organ systems



10 systems

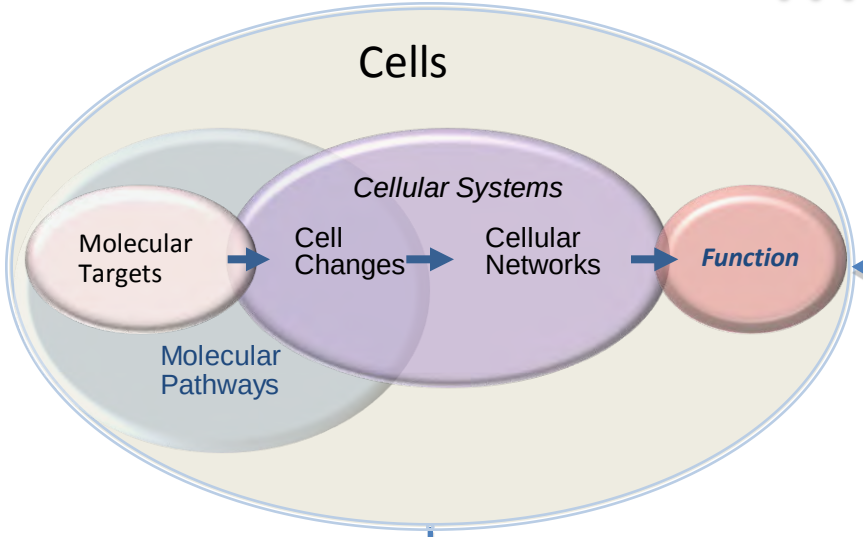
- Multicellular architecture
- Vascularization, innervation, hormonal, humoral and immunological signaling
- Genetic diversity and pharmacogenomic capacity
- Representation of normal and disease phenotypes

- Cell viability for 4 weeks
- Integrated system predicts human in vivo efficacy, toxicity, and pharmacokinetics:
  - safe and effective
  - safe and ineffective
  - unsafe, but effective
  - unsafe and ineffective

60 months

Period 3

A Chemical Testing Paradigm for MPS



Test Compounds # 1

Evaluate and optimize cell response

3D organ structure assemblies

Test Compounds # 2

Evaluate and optimize organ response

Linked multiple organ systems

Test Compounds # 3

Evaluate and optimize system response

Criteria for Selecting Test Compounds

- Do individual organ models respond to test compounds with the expected organ-specific effects?
- Do linked organ system models respond to test compounds with the expected systemic effects?

- Selection of test compounds should consider:
  - Individual organ function → linked organ functions
  - Direct organ toxicities → dependent organ toxicities
  - Study read-outs? → health outcomes of interest?

Drug Development Tool Qualification

- FDA program that provides a mechanism for formal review by CDER to qualify new tools that would benefit drug development
- Currently, 3 programs have been implemented:
  - Biomarkers
  - Clinical outcome assessments
  - Animal models
- But the concept should be applicable to any tool proposed for use in regulatory decision making

Can the concept of "qualification" help to position MPS assays for eventual regulatory use?

Context of Use

- Key concept in the qualification process
- Refers to a clearly articulated description delineating the manner and purpose of use for the tool (when and how will it be used?)
- Also defines the boundaries the available data adequately justify the use of the tool

- Models and assays are inevitably associated with limitations: important to define:
  - The context in which results are intended to be used
  - The specific human outcomes that will be predicted

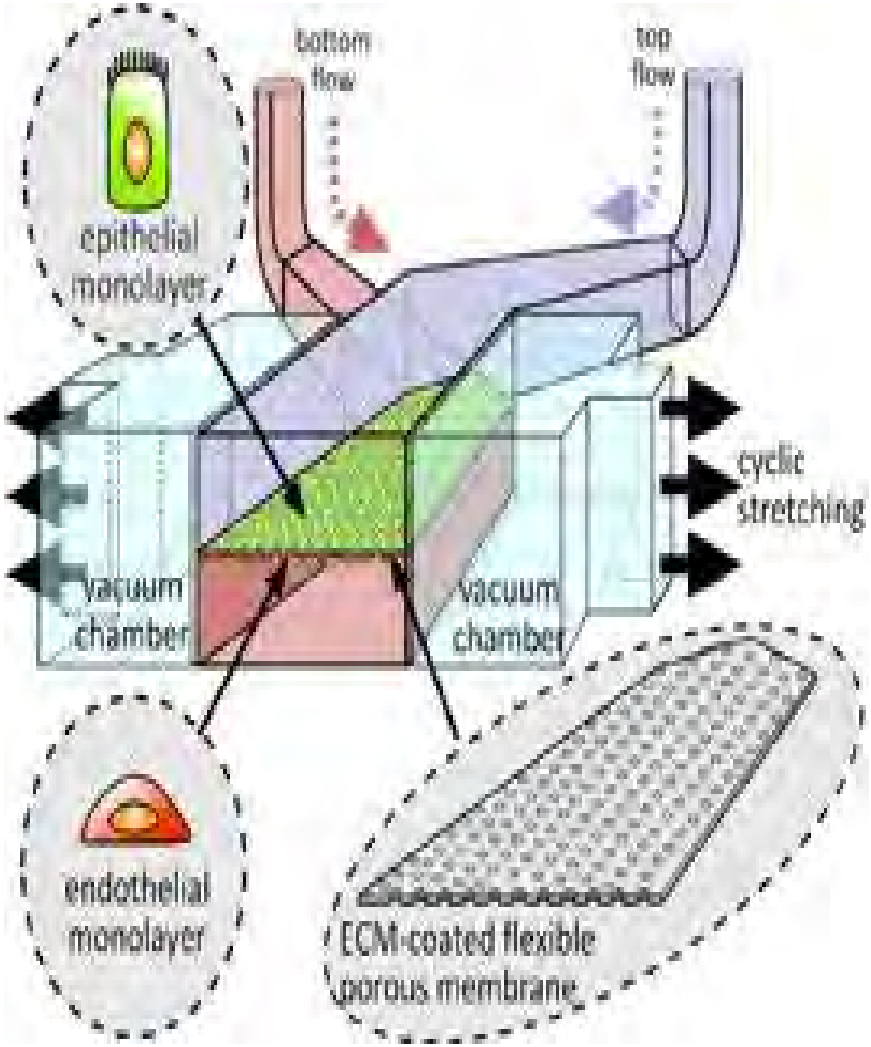
Qualification of a Drug Development Tool (DDT)

- The qualification of DDT begins with a meeting of CDER personnel and the biomarker sponsors
- Consultation on information need to compile a comprehensive evidence to support the application for qualification of a DDT
- CDER and other appropriate FDA scientists undertake a multi-disciplinary formal review of the DDT submission from the sponsor
- Decision reached regarding qualification of DDT
- If positive, decision is publically communicated in form of a guidance

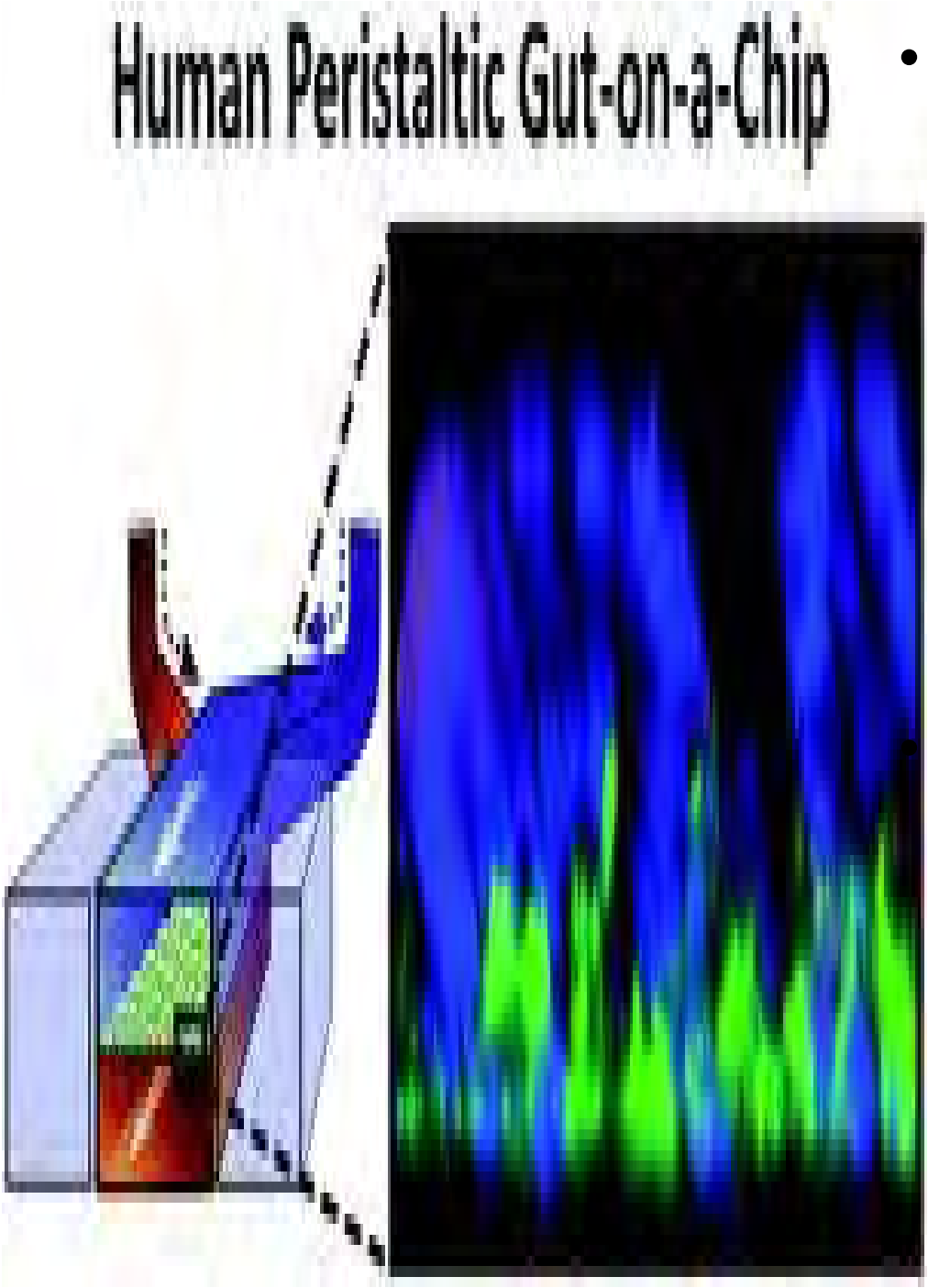
Qualification of a Drug Development Tool (DDT)

- Once qualification is granted, any drug sponsor can submit data obtained with the qualified DDT without being asked for further evidence in support of its suitability
  - FDA Draft Guidance on Qualification of Drug Development Tools- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf
- DDT Qualification is a complex process that requires significant time and resources
- Qualifying DDTs for regulatory purposes more feasible in collaborative approach with representatives from government, industry, academics

Wyss Gut on a Chip- mimics complex 3D features of the intestine



- Single layer of human intestinal epithelial cells on a flexible, porous membrane, recreating intestinal barrier.
- Mimic the wave-like peristaltic motions that move food along the digestive tract.
- Intestinal tissue-tissue interface, which allows fluids to flow above and below the intestinal cell layer, mimicking the luminal microenvironment on one side of the device and the flow of blood through capillary vessels on the other.
- Grow and sustain common intestinal microbes on the surface of the cultured intestinal cells, thereby simulating some of the physiological features important to understanding many diseases.



- Gut-on-a-chip has the potential to become a valuable in vitro diagnostic tool to better understand the cause and progression of a variety of intestinal disorders and to help develop safe and effective new therapeutics, as well as probiotics.
- The gut-on-a-chip could also be used to test the metabolism and oral absorption of drugs and nutrients.

http://pubs.rsc.org/en/Content/ArticleLanding/2013/IB/c3ib40126j

Thank You For Inviting Me

- Here is my contact information

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