

FDA Predictive Toxicology Road Map

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CFSAN/FDA

ICCVAM Public Forum

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Formation of a Roadmap Committee



- Commissioner tasked the FDA Toxicology Working Group with development of a roadmap for integrating emerging predictive toxicology methods and new technologies into regulatory risk assessments
- Each of FDA's product centers has very different legal authorities for evaluation of product safety
- Nevertheless, greater cross-center collaboration can help accelerate the use of emerging predictive toxicology methods

Roadmap Emphasizes Qualification and Context of Use

- Qualification is a conclusion that the results of an assessment using the model or assay can be relied on to have a specific interpretation and application in product development and regulatory decision-making
- Context of use refers to a clearly articulated description delineating the manner and purpose of use for the tool



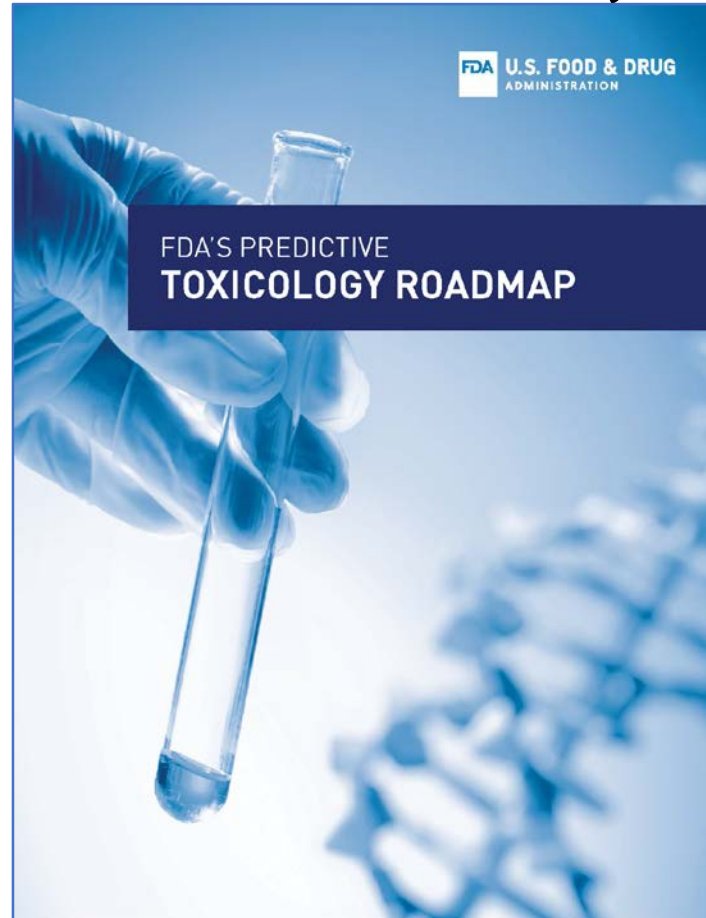
Roadmap Emphasizes the Importance of Partnerships for Accepting New Technologies

- Fostering collaborations between government researchers and regulators and between government regulators, industry , stakeholders and academia to ensure the most promising technologies are identified, developed, validated and integrated into regulatory risk assessment.

FDA Predictive Toxicology Roadmap

Announced December 6, 2017

- <https://blogs.fda.gov/fda/voice/index.php/2017/12/fda-launches-predictive-toxicology-roadmap-to-enable-advances-in-toxicity-testing/>



FDA Senior Level Toxicology Working Group



- Foster enhanced communication among FDA product centers and researchers
- Leverage FDA resources to advance the integration of emerging predictive toxicology methods and new technologies into regulatory safety and risk assessments.

Training of FDA regulators and researchers



- Continuing ongoing education in new predictive toxicology methods is essential for FDA regulators.
- Established an Agency-wide education calendar of events and a Toxicology Seminar Series to introduce concepts of new toxicology methodologies and updates in toxicology-related topics.

Continued Communication



- Reaffirm FDA's commitment to incorporate data from newly qualified toxicology methods into regulatory missions
- Encourages discussions with stakeholders as part of the regulatory submission process.
- Encourage sponsors to submit a scientifically valid approach for using a new method early in the regulatory process

Collaborations with Stakeholders



- Foster collaborations across sectors and disciplines nationally and internationally.
- Pivotal to identifying the needs, maintaining momentum, and establishing a community to support delivery of new predictive toxicology methods.

Leveraging Research



FDA's research programs will identify data gaps and support intramural and extramural research to ensure that the most promising technologies are identified, developed, validated, and integrated into the product pipeline.

Oversight by Office of the Commissioner



- Track the progress of these recommendations and report to the Chief Scientist annually.
- Ensure transparency, fostering opportunities to share ideas and knowledge, showcase technologies, and highlight collaborations on developing and testing new methods

RoadMap Goals

- Roadmap identifies the critical priority activities for energizing new or enhanced FDA engagement in transforming the development, qualification, and integration of new toxicology methodologies and technologies into regulatory application
- Implementing the roadmap and engaging with diverse stakeholders will enable FDA to fulfill its regulatory mission today while preparing for the challenges of tomorrow.

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

This was a unique partnership because it involved regulatory scientists at the very beginning- was able to address identified gaps in knowledge need to regulate FDA products

Tissue Chip Program Overview

U18 generated cell resources
UH2 generated organ systems

DARPA bioengineering
Platform + 2 systems

24 months

Base period

Period 1

4 systems

UH3 phase:

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

Period 2

7 systems

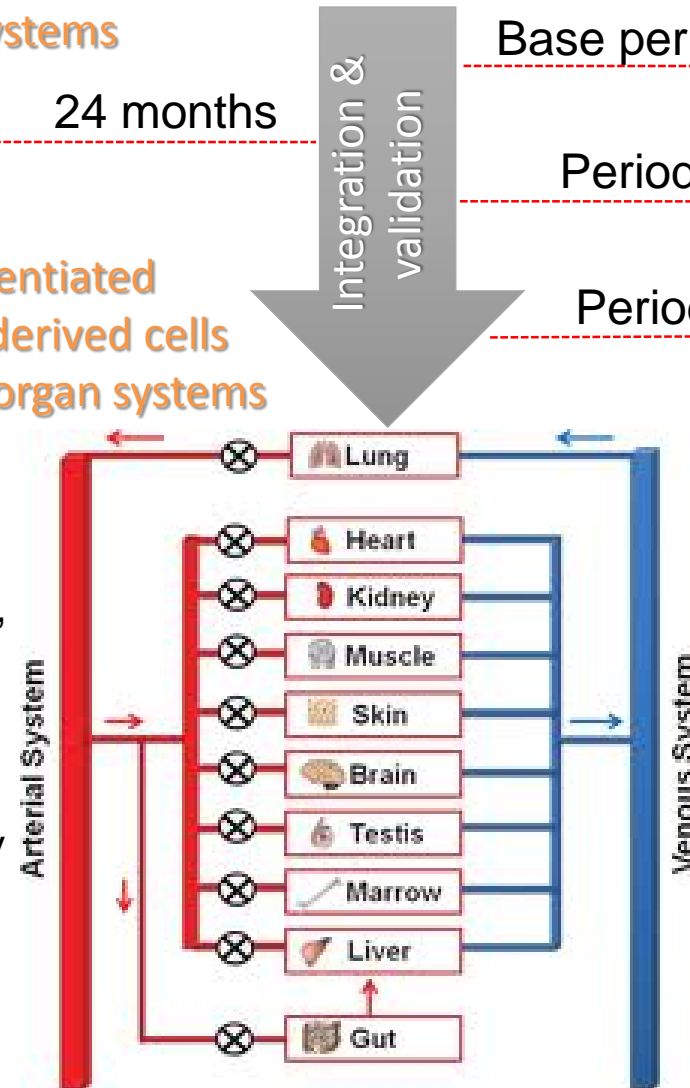
10 systems

- 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



The Tissue Chip Program

GOAL: Develop an *in vitro* platform that uses human tissues to evaluate the efficacy, safety and toxicity of promising therapies.



Phase 1:
Development



Phase 2: Cell incorporation &
organ integration



Liver



DARPA base periods: Organ integration



**FDA provides insight and expertise throughout the program

Current Goals:

- Integration
- Compound testing
- **Validation**
- **Partnerships**
- **Adoptions of the tech to the community**



FDA CRADA Press Release

Official Press Release

April 11, 2017

FDA Signs Collaborative Agreement with Emulate, Inc. to Use
Organs-on-Chips Technology as a Toxicology Testing Platform
for Understanding How Products Affect Human Health and
Safety

Cooperative Research and Development Agreement (CRADA)
to advance and qualify 'Human Emulation System' to meet
regulatory evaluation criteria for product testing

Link to Official Press Release

<https://emulatebio.com/press/fda-collab-agreement-emulate/>

Blog from FDA
 Voice

'Organs-on-Chips' Technology:
FDA Testing Groundbreaking
Science

By: *Suzanne Fitzpatrick, Ph.D.*



On April 11, 2017, FDA announced a multi-year research and development agreement with a company called Emulate Inc. to evaluate the company's "Organs-on-Chips" technology in laboratories at the agency's Center for Food Safety and Applied Nutrition

Link to FDA Blog

<https://blogs.fda.gov/fdavoices/index.php/2017/04/organs-on-chips-technology-fda-testing-groundbreaking-science/>

***NATURE* | NEWS**

Miniature liver on a chip could boost US food safety

- CFSAN
Researchers will be evaluating the effectiveness of this technology to better understand the effects of medicines, disease-causing bacteria in foods, chemicals, and other potentially harmful materials on the human body



CRADA Between EMULATE and FDA- Goals

- Begin with the Liver on a Chip
- Beta Test the Emulate System
- Look at concordance of chip data with in vivo, in silico and other in vitro (2-D) data on same compounds
- Begin to develop performance standards for organs on a chip-applicable to chips
- Resource for FDA regulators and researchers

FDA Using Platforms that Received DARPA/NCATS Funding

- CFSAN working with Emulate (spin-off from Wyss Institute)
- CDER working with CN Bio (spin-off from MIT) and Kevin Healy at UC Berkeley
- Both groups focusing first on liver



SOT Contemporary Concepts in Toxicology

November 14-16, 2018

Crystal City, VA



Predictive Toxicology for Healthy Children

<https://www.toxicology.org/events/shm/cct/FutureToxIV.asp>

Questions?

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