U.S. FOOD & DRUG ADMINISTRATION

Advancing Regulatory Science Through Innovation- In Vitro Microphysiological Systems

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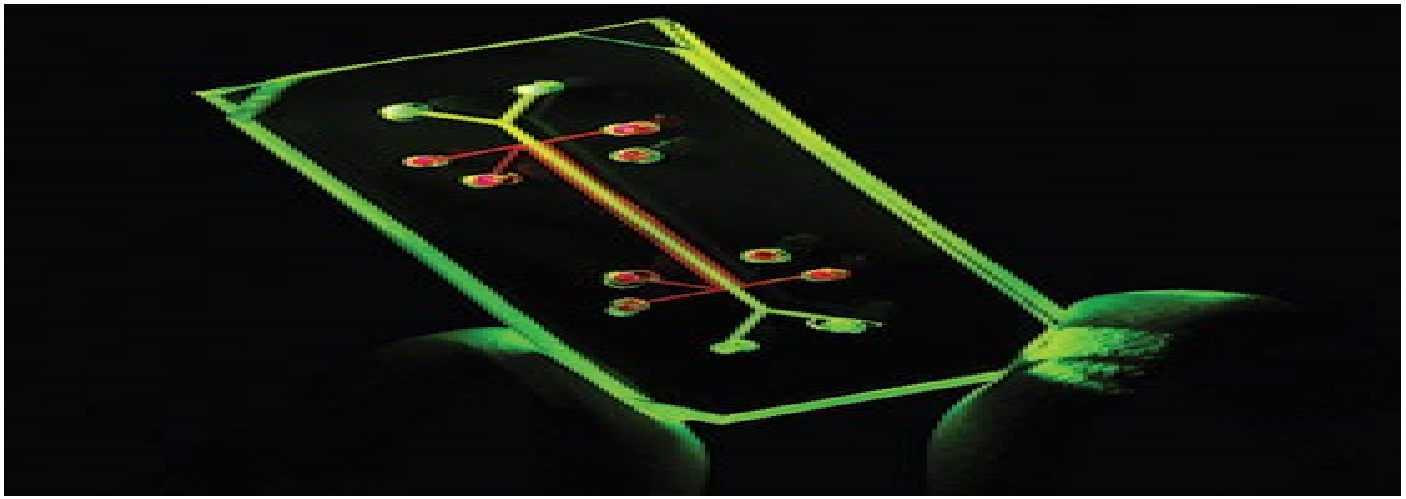
US Food and Drug Administration
Secretary's Advisory Committee on Advancing Test Methods
September 20, 2019



Overview

- FDA's Toxicology Working Group
- Roadmap
- *In* Vitro Systems Working Group

FDA Toxicology Working Group

- FDA has formed a FDA Senior Toxicologist Working Group to share information on new toxicology methods and to familiarize FDA Regulatory and Research Scientists on emerging toxicology tests and their usefulness in risk assessment.
- Consisted of Senior Toxicologists from all six FDA program offices plus NCTR and the Office of the Commissioner

Formation of a Roadmap Committee

- FDA Commissioner Gottlieb tasked FDA's Toxicology Working Group with development of a roadmap for integrating emerging predictive toxicology methods and new technologies into regulatory risk assessments.
- Rear Admiral Denise Hinton, FDA's Chief Scientist, Office of the Chief Scientist (supports all the agency's cross-cutting regulatory science initiatives)
- Suzy Fitzpatrick (CFSAN) chair

Why a Roadmap?

- Advances in systems biology, stem cells, engineered tissues, and mathematical modeling are creating opportunities to improve toxicology's predictive ability, potentially enhancing FDA's ability to predict risk.

- These advances are expected to help bring safer FDA-regulated products to the market faster.

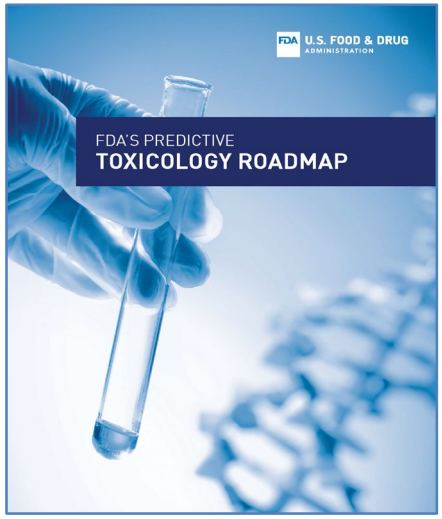
- Also critical is the potential of these advances for replacing, reducing, and/or refining animal testing.

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's Predictive Toxicology Roadmap



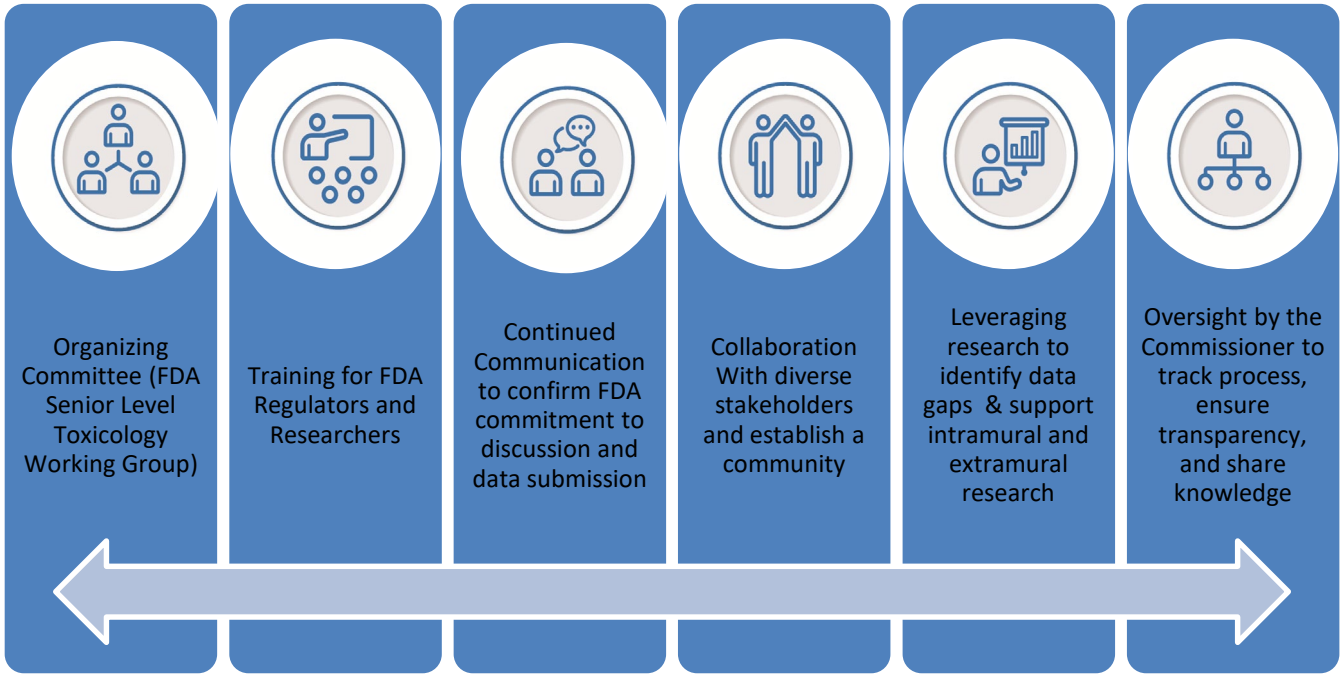
FDA thought on viable ways to:

- Foster the development and evaluation of emerging toxicological methods and new technologies, and
- Incorporate these methods and technologies into regulatory review, as applicable.

December 6, 2017

https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM587831.pdf

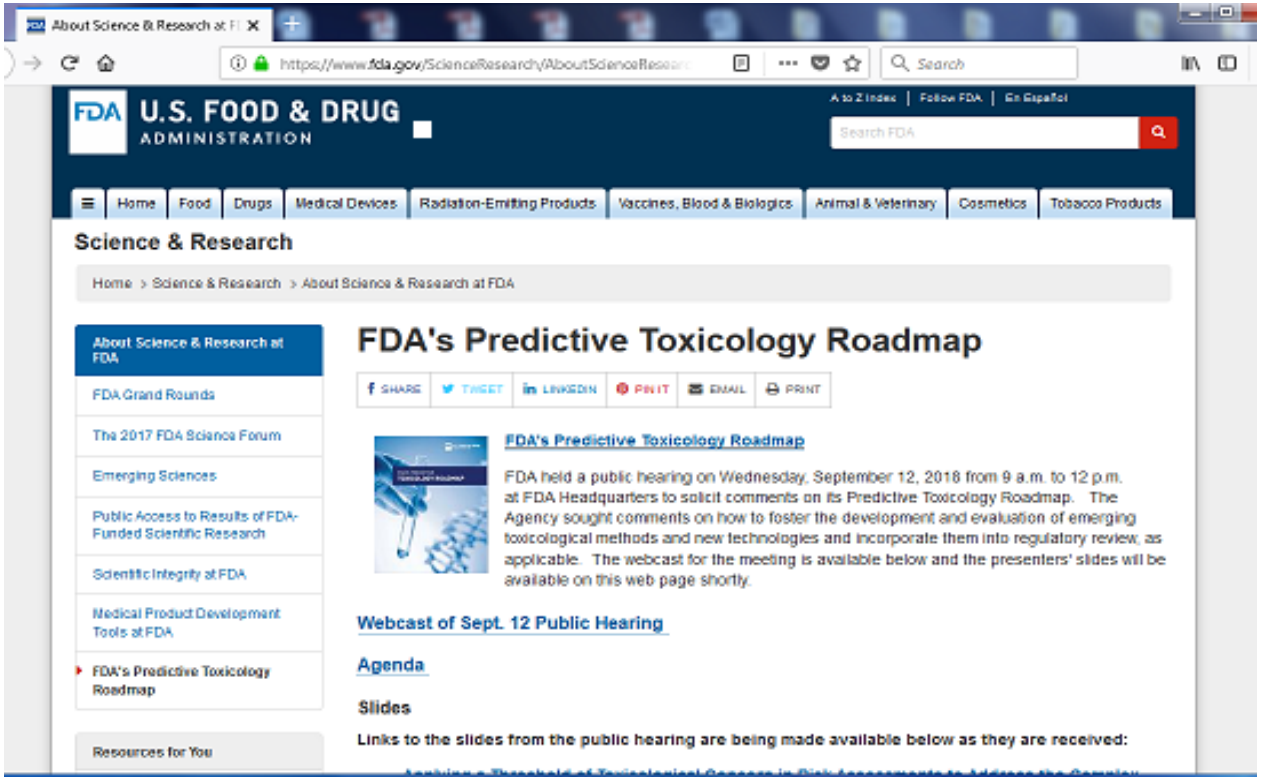
FDA's Roadmap: Framework for Incorporating Emerging Predictive Toxicology Methods in Regulatory Reviews



Important to Remember-
Role of Regulators in Predictive Toxicology

- Recognized that regulators had to be included up front in new method development.
- New toxicology methods of interest must answer regulatory questions.
- Regulators should delineate what tools were needed.
- Regulators needed to identify gaps for additional research.
- Continued ongoing training for regulators in new methods is required.

Public Hearing on the Roadmap



Federal Register Notice: https://www.federalregister.gov/documents/2018/06/29/2018-14052/the-food-and-drug-administration-predictive-toxicology-roadmap-and-its-implementation-public-hearing

Webcast: https://www.fda.gov/ScienceResearch/AboutScienceResearchatFDA/ucm601090.htm

What Did We Hear From Our Stakeholders?

- *FDA should make public the Annual reports by the FDA centers on activities that advanced predictive toxicology.*

- FDA agreed and make the first report to the Office of the Commissioner public. This report includes activities from all FDA Offices and can be found at https://www.fda.gov/media/128045/download

What Did We Hear From Our Stakeholders?

- *FDA should develop a clear implementation plan with specific goals for its roadmap and FDA should clearly define the goals of the roadmap and identify specific actions to reach those goals.*

- FDA agreed and has developed an agency implementation strategy. The Office of the Commissioner has formed an agency *In Vitro* Safety Working Group with representation from all parts of FDA.

What Did We Hear From Our Stakeholders?

- *FDA stakeholders would like one entrance point to FDA to present their new methods.*

- FDA agreed and is developing a webinar series entitled "New Predictive *in vitro/in vivo/ in silico* Methods' to allow sponsors of new technologies to present these to the FDA. Submissions to be sent to FDA at alternatives@fda.hhs.gov

Implementation of the FDA Predictive Toxicology Roadmap

- On Sept. 18, 2019, FDA hosted a public workshop to highlight the work FDA has been doing to support and implement FDA's Predictive Toxicology Roadmap.
  - https://www.fda.gov/science-research/about-science-research-fda/implementing-fdas-predictive-toxicology-roadmap-update-fda-activities-09182019-09182019
- FDA's Predictive Toxicology Roadmap

  2018 Annual Report Prepared by the Food and Drug Administration's Toxicology Working Group
  https://www.fda.gov/media/128045/download
- FDA has formed an *In Vitro* Systems Work Group (IVSWG)

Overall Objectives of IVSWG

- Discuss *in vitro* activities across FDA.
- Interact with U.S. federal partners and global regulatory partners to facilitate discussion, development, and acceptance of regulatory performance criteria for such assays.
- Establish a dialogue and develop partnerships with FDA stakeholders to explore regulatory science applications for such technologies.
- Leadership Council and:
  - Research Group (User Group)
  - Performance Criteria Group (Regulatory Group)

IVSWG Leadership Council

- Consists of one representative from each FDA Center/Office.
- Responsible for ensuring that IVSWG's goals are moving forward in a timely and transparent manner.
- Ensure FDA scientists are updated on new emerging *in vitro* methods and models.
- Inform FDA scientists on seminars, site visits, hands-on training, and other learning opportunities.
- Contact point for outside scientists wishing to present new technology to FDA.
- Develop proposals for potential public–private partnerships or applicable mechanisms to advance the development of *in vitro* technologies for regulatory science use.

Researcher WG Responsibilities

- Meet at least bi-monthly to discuss technical designs, issues, and complexities and facilitate information-sharing about the pros and cons of different approaches

- Propose criteria and questions that address issues concerning the quality of data from new predictive regulatory tools, including issues related to qualification

- Membership consists of 4–5 FDA researchers per product center involved in developing and/or qualifying *in vitro* technologies

Performance Criteria Development WG Responsibilities

- Collaborate with the Researcher WG to translate proposals into draft performance criteria.

- Discuss draft performance criteria within FDA and with FDA stakeholders to obtain broad feedback and refine the draft criteria.

- Membership is limited to 1–2 members from each FDA center.
  - Suzy Fitzpatrick (Chair)

Office of the FDA Chief Scientist

- Provide scientific, administrative, and logistics support to help IVSWG achieve its objectives, including:
  - Arranging an annual update to the SSC, FDA senior management, and the Commissioner on IVSWG activities.
  - Arranging and organizing large group meetings.
  - Providing budgetary support, if needed.
  - Creating/Maintaining a sharepoint site for communication across the Agency.

IVSWG First Case Study

- Focus on coordinating, developing, and evaluating *in vitro* Microphysiological Systems (MPS) for regulatory use.
- This will be the first IVSWG case study on the viability of its implementation plan for *FDA's Predictive Toxicology Roadmap.*
- IVSWG program will be evaluated, and if needed, refined, after completion of its goals.

History of FDA's Involvement with MPS

- In 2011 DARPA funded MPS research. "DARPA involved the FDA from the beginning of the MPS program to help ensure that regulatory challenges of reviewing drug safety and efficacy are considered during development of the MPS platform"
  - https://www.darpa.mil/program/microphysiological-systems

- In 2012 NCATS funded the Tissue Chip Development Program. FDA has been a partner throughout the program
  - https://ncats.nih.gov/tissuechip/about

- Critical to have regulators at the table from the beginning if aim is to use method for regulatory use

FDA Internal Research

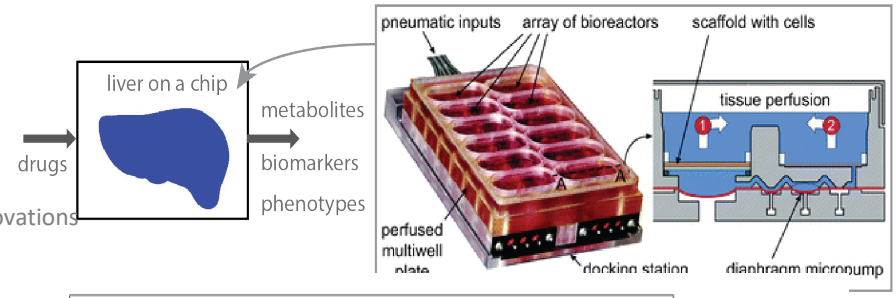
- FDA scientists are developing in-house MPS and collaborating with several external partners

Liver Systems Evaluated in CDER's Integrated Cellular Systems Laboratory

Primary hepatocytes used by the developers

LiverChip

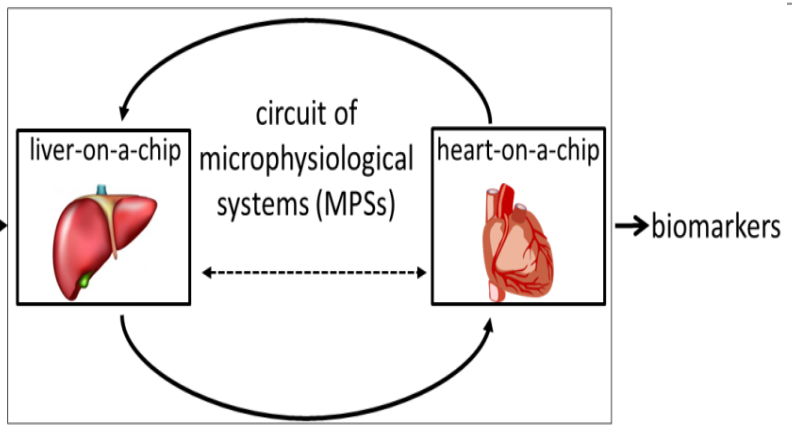
Collaboration with CN Bio Innovations



All iPSC-derived cells

Heart-Liver System

Collaboration with Kevin Healy



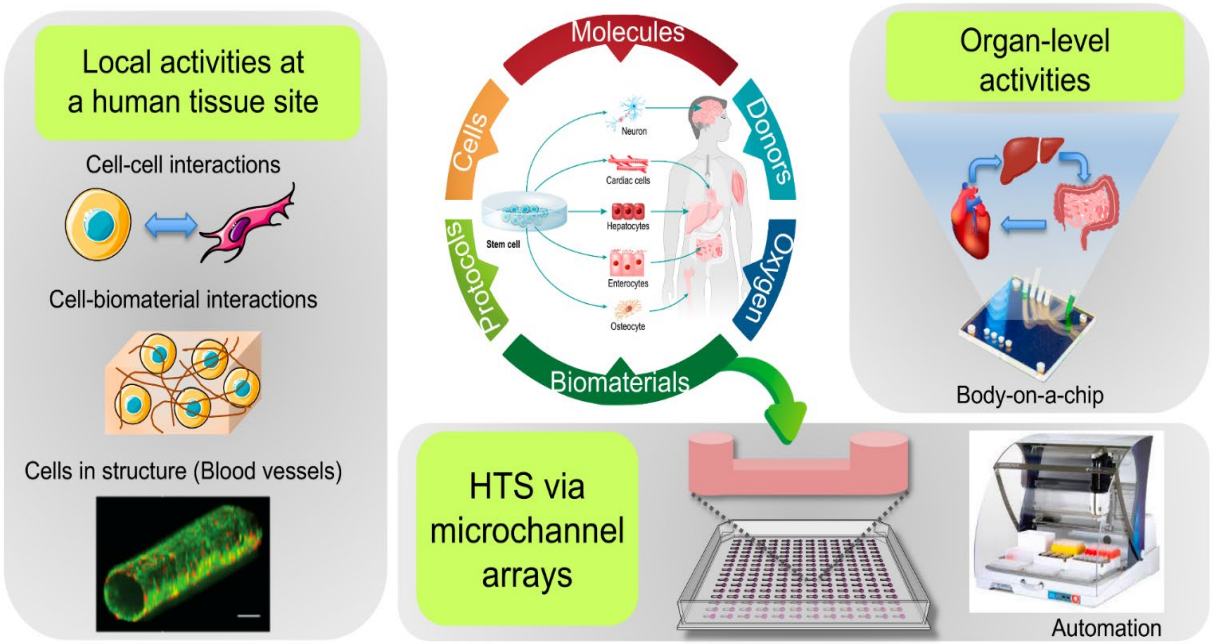
CBER: Practical Microscale Biomimetic Models

Tools to help understand the complexity of regenerative medicine products

Manufacturing & Regulatory challenges

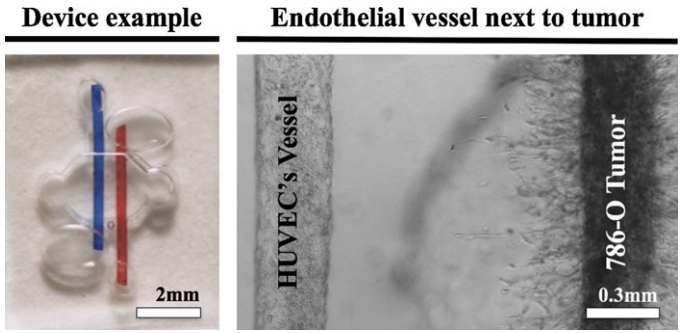
- Cellular heterogeneity
- Patient to patient variability
- Limited shelf life/limited sample volume
- Limited availability of starting material for test method development
- A wide range of manufacturing protocols

New methods and **quality attributes** are necessary to reliably predict biological functions of manufactured products.

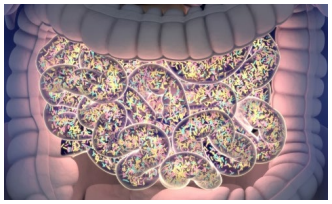


CBER

- In-house MPS and microscale organoid models and working with Curiosis and academics
- *In vitro* models of complex interactions
  - tumor microenvironment, reproductive toxicology (with NCTR), blood vessel generation, etc.



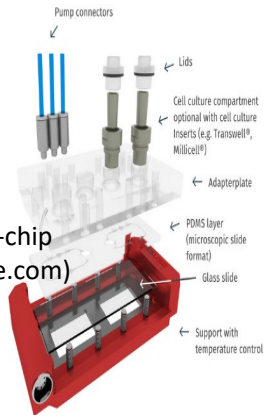
CVM's MPS Initiative



- Focus: Gut-on-a-Chip
- Short term goal
  - Develop a gut-on-a-chip model for determining the impact of antimicrobial drug residues on the human intestinal microbiome, including the development of antimicrobial resistance.
- Long term goal
  - Develop performance standards for qualification of the model to fill a gap in tools needed to support the evaluation of antimicrobial drug products intended for use in food-producing animals.
- Collaborations: outside government collaboration, CFSAN, NCTR, and other FDA Centers as needed

NCTR: Development of Two-Organ MPS Models for Reproductive Toxicity Assessment

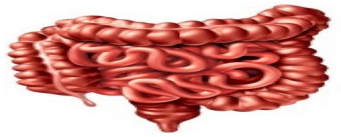
- Conventional tests are time intensive and require large numbers of rodents
- NCTR in partnership with TissUse will develop a MPS containing organoids
- for two tissues linked by a microfluidic circuit for drug toxicity testing
- Initial efforts will develop rat *in vitro* MPS models that approximate *in vivo* hepatic drug metabolism and spermatogenesis
- Future efforts will extend to
  - Rat-to-human extrapolation
  - Characterization and qualification of the MPS models for regulatory use



Two organ-on-a-chip platform (tissuse.com)

Medical Countermeasures: MPS Applications

- Radiation countermeasures project: Dr. Donald Ingber and the Wyss Institute (funded FY2013)
  - Project is developing models of radiation damage in lung, gut, and bone marrow organs-on-chips for candidate MCM testing
  - Recent publication: "Modeling radiation injury-induced cell death and countermeasure drug responses in a human Gut-on-a-Chip." Cell Death & Disease. 9.10.1038, 14 February 2018
  - For more information visit the FDA's Medical Countermeasures Initiative (MCMi) website: https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures



Objectives of the IVSWP MPS Program

- Define agreed-upon terminology for MPS and research/regulatory gaps for which MPS may be useful.
- Identify partnerships to advance MPS technology.
- Develop draft performance criteria for MPS and discuss internally and then with stakeholders
- Develop a Request for Information for MPS Developers and End Users

Developing a Working Definition for MPS

Some questions for our group:

- Are we including any 3D model (organoid) or only those with microfluidics, etc.?
- What term should we use for the FDA definition: MPS, Organ on a chip, tissue chip- or something else?
- Should we include only MPS with human cells or are we including those MPS that use animal cells?
- What should be included in the FDA definition, for example, microfluidics, flow, etc.?

FDA IVSWG User Group

- Researcher working group consists of FDA researchers in each Center/Office involved in using, developing and/or qualifying *in vitro* technologies

- Share internal research, discuss technical designs, issues, and complexities and facilitate information-sharing about the pros and cons of different approaches

- Propose criteria and questions that address issues concerning the quality of data from new predictive regulatory tools, including issues related to qualification

Performance Criteria Development Working Group

- Representatives from each FDA Center/Office
- Develop a request for Information from Developers and Users
- Collaborate with the Researcher Working Group to translate proposals into draft performance criteria
- Discuss draft performance criteria
- Share within FDA and with FDA stakeholders to obtain broad feedback and refine the draft criteria

FDA Office of the Chief Scientist Webinar Series on Emerging Predictive Methods and Methodologies

- Opportunity for developers to present new methods and methodologies to FDA.
- Webinars will be held monthly and advertised to all FDA scientists exclusively.
- If selected, developers' participation in FDA's webinar series would not constitute the agency's endorsement of a new method or methodology.
- Nor would it mean that FDA would assist the developer in qualifying his/her new method for regulatory use.

FDA Office of the Chief Scientist Webinar Series on Emerging Predictive Methods and Methodologies

- To be considered for selection, developers must submit the following information to FDA:
  - A description of their new method or methodology, including origin of cells (if appropriate), species of animal (if appropriate), etc.
  - A description of the proposed context of use of the new method or methodology.
  - A description of the regulatory issue/gap where it could have an impact on an important regulatory issue.
  - Data from use of your method, including any publications.

Change Takes Time

Questions

- Suzanne Fitzpatrick, PhD, DABT, ERT
- Please send comments/questions/suggestions to:
- Suzanne.Fitzpatrick@fda.hhs.gov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