Update on FDA Activities on Alternative Methods
ICCVAM Public Meeting

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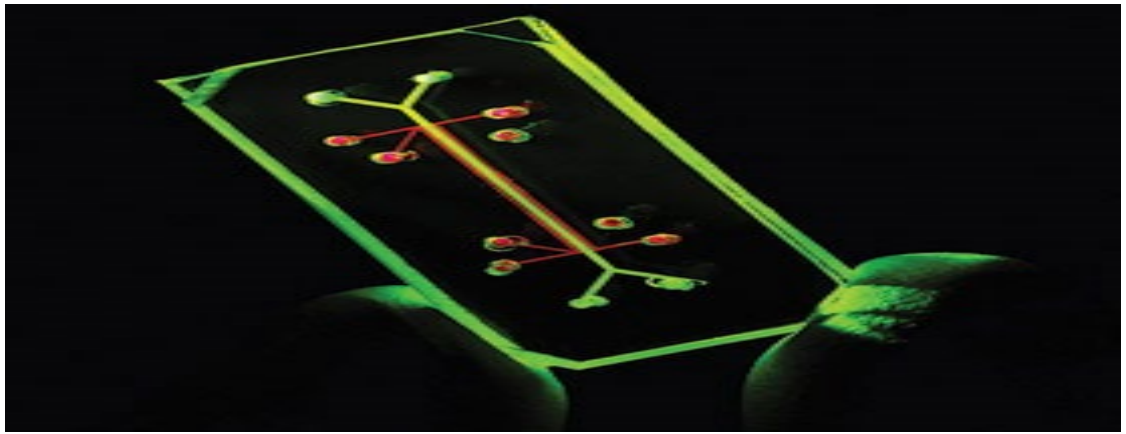
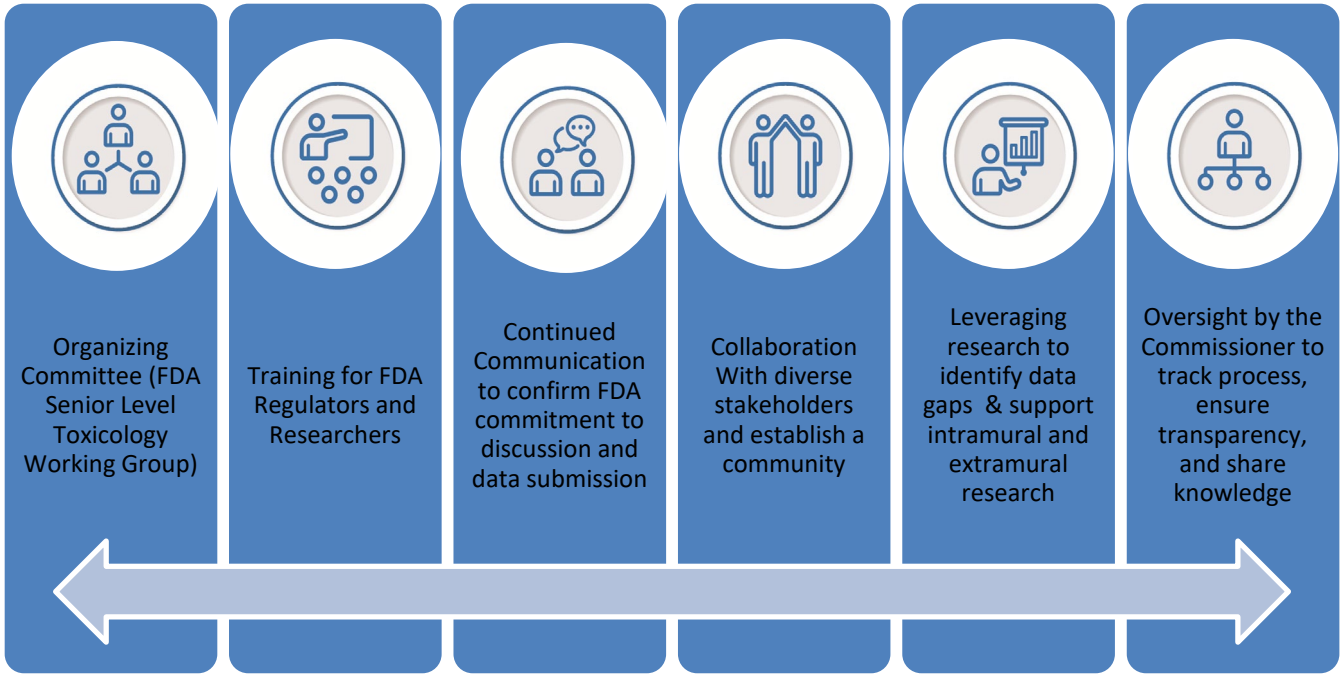


FDA's Roadmap: Framework for Incorporating Emerging Predictive Toxicology Methods in Regulatory Reviews

https://www.fda.gov/science-research/about-science-research-fda/fdas-predictive-toxicology-roadmap



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.

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. Criteria for being considered for selection are listed below. Submissions to be sent to FDA at alternatives@fda.hhs.gov

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.

What Have We Heard 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 Alternatives Methods Working Group with representation from all parts of FDA.

Alternative Methods Working Group (AMWG)

- Under Office of Chief Scientist, Office of Commissioner
  - Chaired by Drs. Fitzpatrick (CFSAN) and Mendrick (NCTR), members from each Center and OCS
- Strengthen FDA's long commitment to promoting the development and use of new technologies and to reduce animal testing
- Discuss new alternative *in vitro/in silico/in vivo methods* across FDA
- Interact with U.S. Federal partners and other global stakeholders to facilitate discussion and development of draft performance criteria for such assays.
- https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda

AMWG First Case Study – *In vitro* Micro physiological Systems

- 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 mechanisms to request information from MPS developers and end users

History of FDA's Involvement with MPS

- In 2010 FDA and NIH Common Fund awarded grant money to Wyss to develop a heart-lung micromachine.
- In 2011, DARPA approached the FDA Office of the Chief Scientist requesting to work together to develop a human body on a chip for medical countermeasures.
- 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
- In 2012 NCATS funded the Tissue Chip Development Program. FDA has been a partner throughout the program
- And the rest is MPS history!
- IMPORTANT LESSON-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

FDA signs collaborative agreement with CN Bio Innovations to use Organs-on-Chips to improve drug development and evaluation

POSTED OCT 2017

London, UK, October 26 2017: CN Bio Innovations Limited announced today that it has entered into a Research Collaboration Agreement with the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research.

Center for Drug Evaluation and Research

TISSUSE Emulating Human Biology

National Center for Toxicological Research

Human iPSC-based Cardiac Microphysiological System For Drug Screening Applications

Anurag Mathur[1,2], Peter Loskill[1,2], Kaifeng Shao[1], Nathaniel Huebsch[4,5], SoonGweon Hong[1], Sivan G. Marcus[1], Natalie Marks[1], Mohammad Mandegar[4,5], Bruce R. Conklin[4,5], Luke P. Lee[1,3] & Kevin E. Healy[1,2]

Center for Food Safety and Applied Nutrition

Original Report

Adaptation of a Simple Microfluidic Platform for High-Dimensional Quantitative Morphological Analysis of Human Mesenchymal Stromal Cells on Polystyrene-Based Substrates

Johnny Lam[1], Ross A. Marklein[1], Jose A. Jimenez-Torres[2], David J. Beebe[2], Steven R. Bauer[1], and Kyung E. Sung[1]

Center for Biologics Evaluation and Research

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

April 11, 2017

FDA Draft Definition

Microphysiological System (MPS) is an in-vitro platform composed of cells, explants derived from tissues/organs, and/or organoid cell formations of human or animal origin in a micro-environment that provides and supports biochemical/electrical/mechanical responses to model a set of specific properties that define organ or tissue function.

Organ-on-a-chip (OoC) is a miniaturized physiological environment engineered to yield and/or analyze functional tissue units capable of modeling specified/targeted organ-level responses.

Comments- send to alternatives@fda.hhs.gov

ICH and Human Pharmaceuticals

- **Worldwide participation in ICH guidance development:**
- **Founding members: US, EU, and Japan; other members-**The Health Canada; The Swissmedic; The Agência Nacional de Vigilância Sanitária (ANVISA, Brazil);The Ministry of Food and Drug Safety (MFDS, Republic of Korea), etc.

- **International harmonization has already reduced repetition of studies and reduces and refines animal use in overall drug development**
- **Some Guidances incorporate alternative assays**
- **Guidances also allow sponsors to propose use of alternatives even if not explicitly already included**
- **Future Guidances or revisions offer opportunities for additional new approach methodologies**

CDER – Recent drug development guidances with alternative approaches

- ICH S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals – final adopted by ICH February 2020
  - Provides basic principles that will assist in the development and potential regulatory use of in vitro, ex vivo and nonmammalian embryofetal toxicity assays
- Draft Guidance: Nonclinical Safety Evaluation of the Immunotoxic Potential of Drugs and Biologics – published for public comment February 2020
  - For individual chemicals, allows consideration of a battery of studies (e.g., in silico, in chemico, in vitro) that have been shown to adequately predict human skin sensitization with an accuracy similar to existing in vivo methods.

Remember-Change Takes Time- But It will Happen If We All Work Together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U.S. FOOD & DRUG
ADMINISTRATION