

FDA Activities

ICCVAM Public Meeting

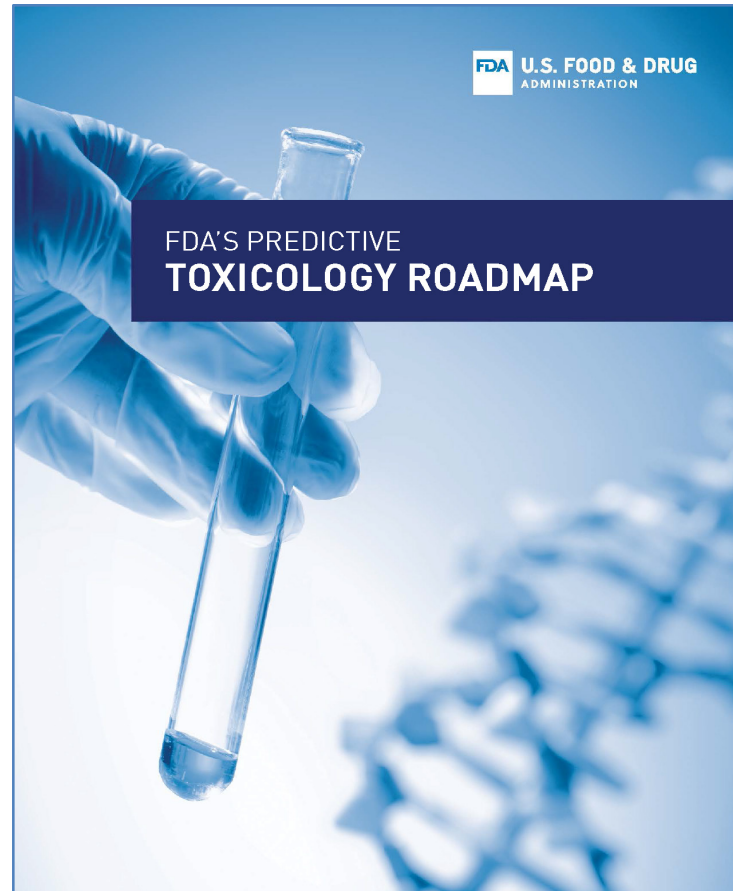
Suzanne C Fitzpatrick, PhD, DABT, ERT

CFSAN/FDA

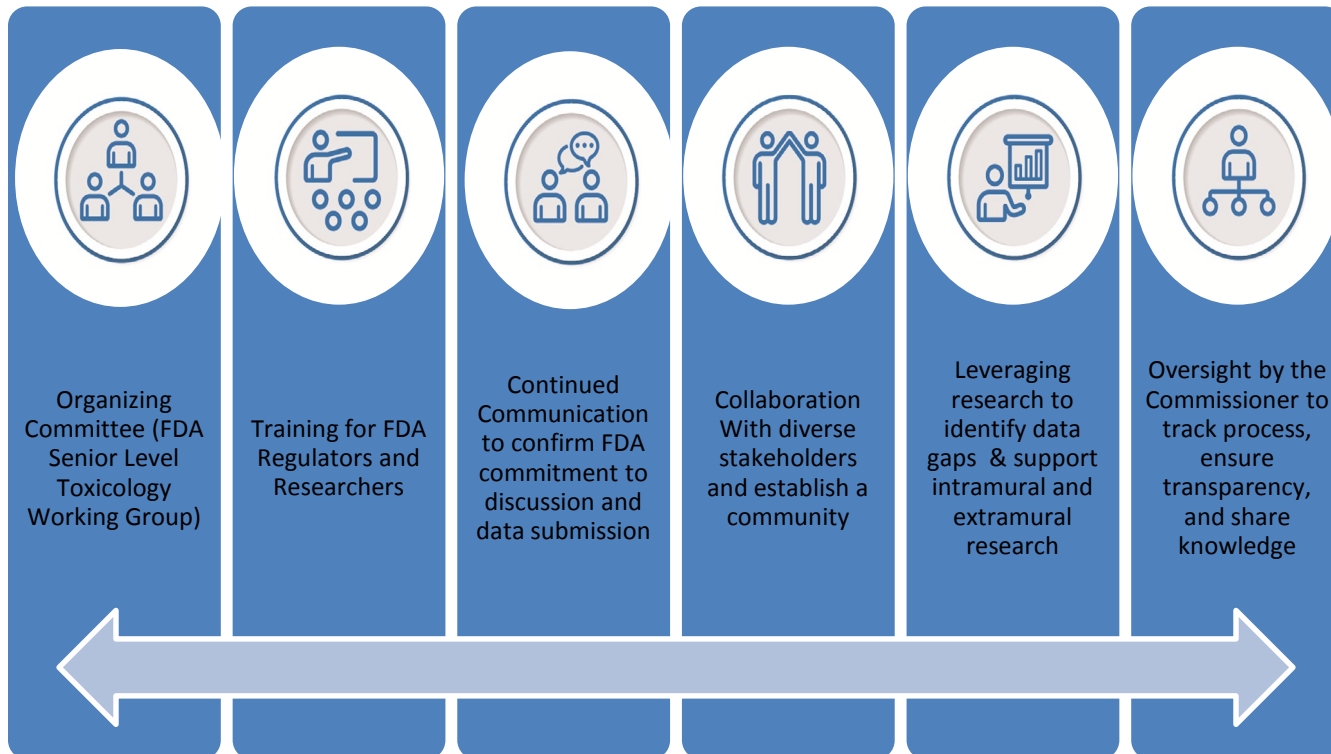
May 23, 2019

FDA Predictive Toxicology Roadmap Announced December 6, 2017

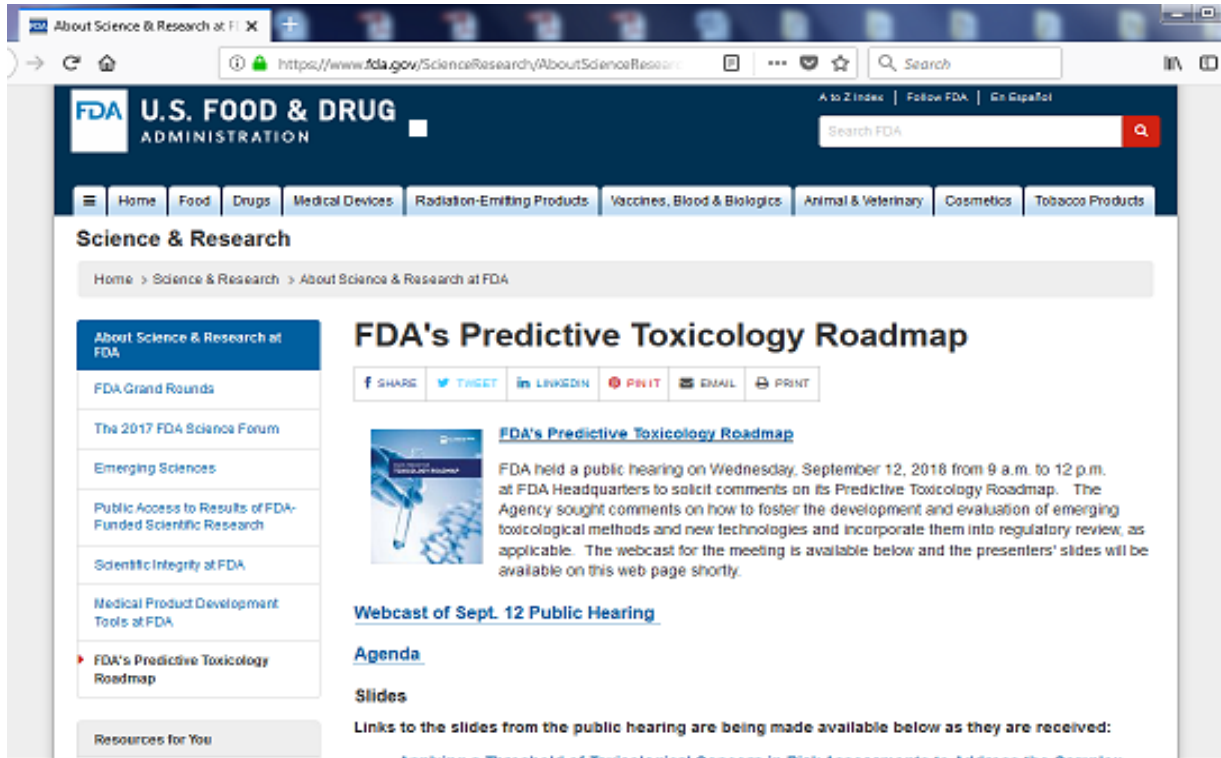
- <https://blogs.fda.gov/fdavoice/index.php/2017/12/fda-launches-predictive-toxicology-roadmap-to-enable-advances-in-toxicity-testing/>



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



Public Hearing on the Roadmap



The screenshot shows the FDA website's 'Science & Research' section. The main heading is 'FDA's Predictive Toxicology Roadmap'. Below the heading are social media sharing options for Facebook, Twitter, LinkedIn, Pinterest, Email, and Print. A small image of a laboratory flask is visible. The text states: 'FDA held a public hearing on Wednesday, September 12, 2018 from 9 a.m. to 12 p.m. at FDA Headquarters to solicit comments on its Predictive Toxicology Roadmap. The Agency sought comments on how to foster the development and evaluation of emerging toxicological methods and new technologies and incorporate them into regulatory review, as applicable. The webcast for the meeting is available below and the presenters' slides will be available on this web page shortly.' Below this text are links for 'Webcast of Sept. 12 Public Hearing', 'Agenda', and 'Slides'. A note at the bottom says: 'Links to the slides from the public hearing are being made available below as they are received:'. A partially visible link at the bottom of the page reads: '...ing a Threshold of Technological Progress in Risk Assessments to Address the Complex'.

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>

Roadmap-Responsive Activities

- Each center developed its own plan to meet roadmap goals.
- Two goals for updating our toxicology toolboxes:
 - Reevaluate Existing Tools For Regulatory Use
 - Use of Dog for Chronic Testing
 - Use of Chronic Rodent Bioassays
 - Evaluate New Tools for regulatory Use
 - *C.Elegans*
 - Organs on Chips
 - Read Across



Reassessment of the Dog for Food and Color Additive Safety Assessments-

- Goal of the project
 - To determine the impact of studies conducted in dogs on decisions regarding the safe use of food and color additives that have been the subject of petitions submitted to OFAS.
 - To apply the knowledge obtained from these findings to update toxicology testing recommendations.
- Reviewed 162 food and color additive petitions containing one or more dog studies were submitted to FDA from 1950-2018. Since 2000, very few dog studies have been submitted.
- There were no unique toxicity that were seen only in the dog.
- Concluded that rodent studies combined with ADME data are could be sufficient to evaluate the safe use of food and color additives.



Redesigning the Rodent Bioassay for the 21st Century- Beginning the Discussion....

- FDA and SOT held a colloquia February 20, 2019
- The following presentations will be available on the SOT website.
 - **The Chronic Cancer Bioassay Is Frequently Conducted for Pesticides When It Is Not Always Needed to Protect Human Health** Doug Wolf, Syngenta
 - **Threshold-based Risk Assessment is the Same for Cancer and Non-cancer Endpoints for Non-DNA Reactive Carcinogens**-Samuel Monroe Cohen, University of Nebraska Medical Center,
 - **Is the Two-Year Rodent Bioassay Needed to Address Carcinogenic Risk for Human Pharmaceuticals?** Frank D. Sistare, Merck & Co Inc., West Point, PA
 - **Weight of Evidence Approach to Cancer Assessment**-Alan R. Boobis, Imperial College,

C. *Elegans* Model for DNT Assessment of Mixtures of metals

- FDA designed a novel worm Development and Activity Test (wDAT) that maps the timing of *C. elegans* developmental milestone acquisition as well as stage-specific activity levels.
- The wDAT was able to detect both developmental delay and hyperactivity for arsenic, lead, and mercury, developmental neurotoxins that have been associated with hyperactivity in children.
- The wDAT can be completed by a single technician in 4 days using a relatively inexpensive activity tracker, making it a cost-effective addition to integrated approaches to testing and assessment.
- A planned 20-compound, blinded qualification study will clarify the utility of the wDAT for human-predictive developmental neurotoxicity testing.

Goals of the Research Collaborative Agreement Plan between Underwriter's labs and FDA/CFSAN

- To provide CFSAN employees the option to use UL Cheminformatics Tool Kit.
- To provide UL with feedback on how well UL Cheminformatics Tool Kit performs in predicating specific toxicities of chemicals found in CFSAN-regulated products.
- To evaluate the usefulness of Read Across as a Regulatory Tool for use in safety/risk assessment.
- To share the results of our finding with members of the FDA Toxicology Working Group.

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.

Original Report

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

Johnny Lam¹, Ross A. Marklein¹, Jose A. Jimenez-Torres², David J. Beebe², Steven R. Bauer¹, and Kyung E. Sung¹



Human iPSC-based Cardiac Microphysiological System For Drug Screening Applications

Anurag Mathur^{1,2}, Peter Loskill^{1,2}, Kaifeng Shao¹, Nathaniel Huebsch^{4,5}, SoonGweon Hong¹, Sivan G. Marcus¹, Natalie Marks¹, Mohammad Mandegar^{4,5}, Bruce R. Conklin^{4,5}, Luke P. Lee^{1,3} & Kevin E. Healy^{1,2}



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



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**
- **Already receive a myriad of alternative assays from drug developers, used in drug discovery.**
- **Guidances offer opportunities for additional new approach methodologies**



ICH S3 Q and A on PK

Finalized May 2018

Microsampling

- A method to collect a very small amount of blood (typically $\leq 50 \mu\text{L}$) to measure TK parameters of the drug and/or its metabolites
- Matrices: blood and its derived plasma or serum, in liquid or dried form
- Can minimize pain and distress in animals (improvement of the animal welfare: refinement)
- Can reduce or eliminate the number of required animals in a TK satellite group for rodents (reduction), particularly for mice



ICH S5(R3)-Repro-Developmental

Draft – under revision in 2019

- Proposes to expand circumstances under which the outcome of “preliminary EFD studies” (per ICH M3(R2)) could support clinical trials – can lead to fewer definitive studies being conducted
- Proposes basic principles that would assist in the development and potential regulatory use of *in vitro*, *ex vivo* and non-mammalian assays



ICH S7B/E14 Questions and Answers

New working group November 2018

- Improve proarrhythmia prediction
- Standardization of multi-ion channel assays, *in silico* models, *in vitro* human primary and induced pluripotent cardiomyocyte assays and *in vivo* evaluations
- Describe how to use the proarrhythmia prediction algorithms or model results
- Supported by the Comprehensive *In Vitro* Proarrhythmia Assay (CiPA) initiative

Summary

- FDA continues to be committed to developing new predictive toxicology methods.
- Partnerships are Important 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.



U.S. FOOD & DRUG
ADMINISTRATION