# FDA-ICCVAM 3Rs

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# Tox21 activities in the past year

- CDER was the lead center until 2014
- CFSAN and the FDA Foods program took over as the lead in 2014
- Strategy has been two-pronged:
  1. Reach out to FDA regulatory scientists to familiarize them with ToxCast/Tox21 data and its usefulness in risk assessment
  2. Conduct research in partnership with NIH and EPA

# Outreach to FDA Scientists

- NCCT scientists visited CFSAN to talk about the ToxCast data and dashboards (Spring 2014)
- FDA Chief Scientist Hosted a seminar by Dr. David Dix on EPA's Endocrine Disruptor Screening Program-*A Computational Approach for the Prioritization and Screening of Chemicals in the Endocrine Disruptor Screening Program (Fall 2014)*
- Agency Toxicology Group formed to update all agency scientists on emerging issues in Tox21

# FDA-DARPA-NIH Microphysiological Systems Program

Started in 2011 to support the development of human microsystems, or organ “chips,” to screen for drugs swiftly and efficiently (before human testing)

Collaboration through coordination of independent programs

- eering platforms and biological proof-of-concept
  PA-BAA-11-73: Microphysiological Systems)
- Underlying biology/pathology and mechanistic understanding
  -RM-12-001 and RFA RM-11-022)
- Advise on regulatory requirements, validation and qualification

# CFSAN Research

- A collaboration between FDA and NIH to carry out a high-throughput developmental tox screen developed by David Reese and Yanling Chen, OARSA/DMB, to identify chemicals that interfere with the retinol (vitamin A) signaling pathway.
- This pathway is essential for normal embryonic development; chemical interference with this pathway is toxic to the embryo and adult tissues.
- The rationale, cell system and initial test parameters were developed at CFSAN and the high-throughput screening protocol was developed and is being carried out on NCATS's robotic platform at NIH

# CFSAN Research on Toxicity Pathways

- The retinol signaling screen is the first of several developmental screens anticipated under this collaboration.
- This screen will provide the basis for a developmental toxin database that can be used for rapidly identifying potential teratogens in food contaminants and when reviewing petitions for premarket approval.

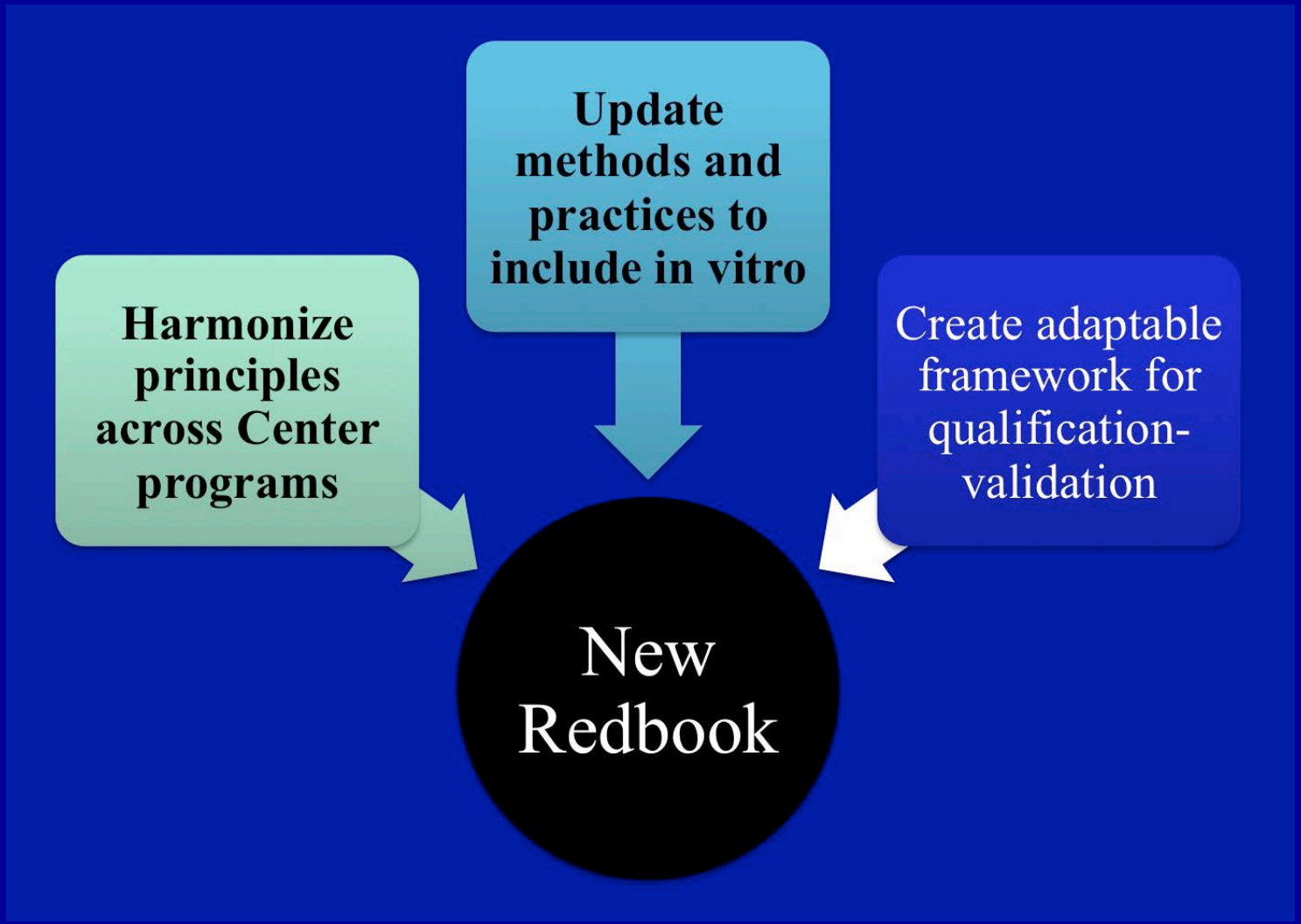
# Computational Tox: Analysis of Office of Food Additive Safety (OFAS)-regulated substances in the ToxCast database

- One year project with JIFSAN
- Develop database of OFAS-regulated substances in ToxCast containing: 1) their bioactivity profiles, and, 2) the HTS assay platforms used to produce these data;
- Evaluate the bioactivity profiles of OFAS-regulated substances in ToxCast;
- Examine the in vivo and in vitro toxicity data submitted by sponsors to OFAS to support the safety of substances added to food.

# CFSAN: GRAS Chemicals

- Running a list of the “96 GRAS” chemicals against the ToxCast phase II results
- Comparing the entire Tox21 list  of GRAS compounds against the CERES version 1.0, COSMOS and Leadscope Databases
- Purpose is to compare the results of traditional toxicity testing have been conducted on these chemicals and the ToxCast results

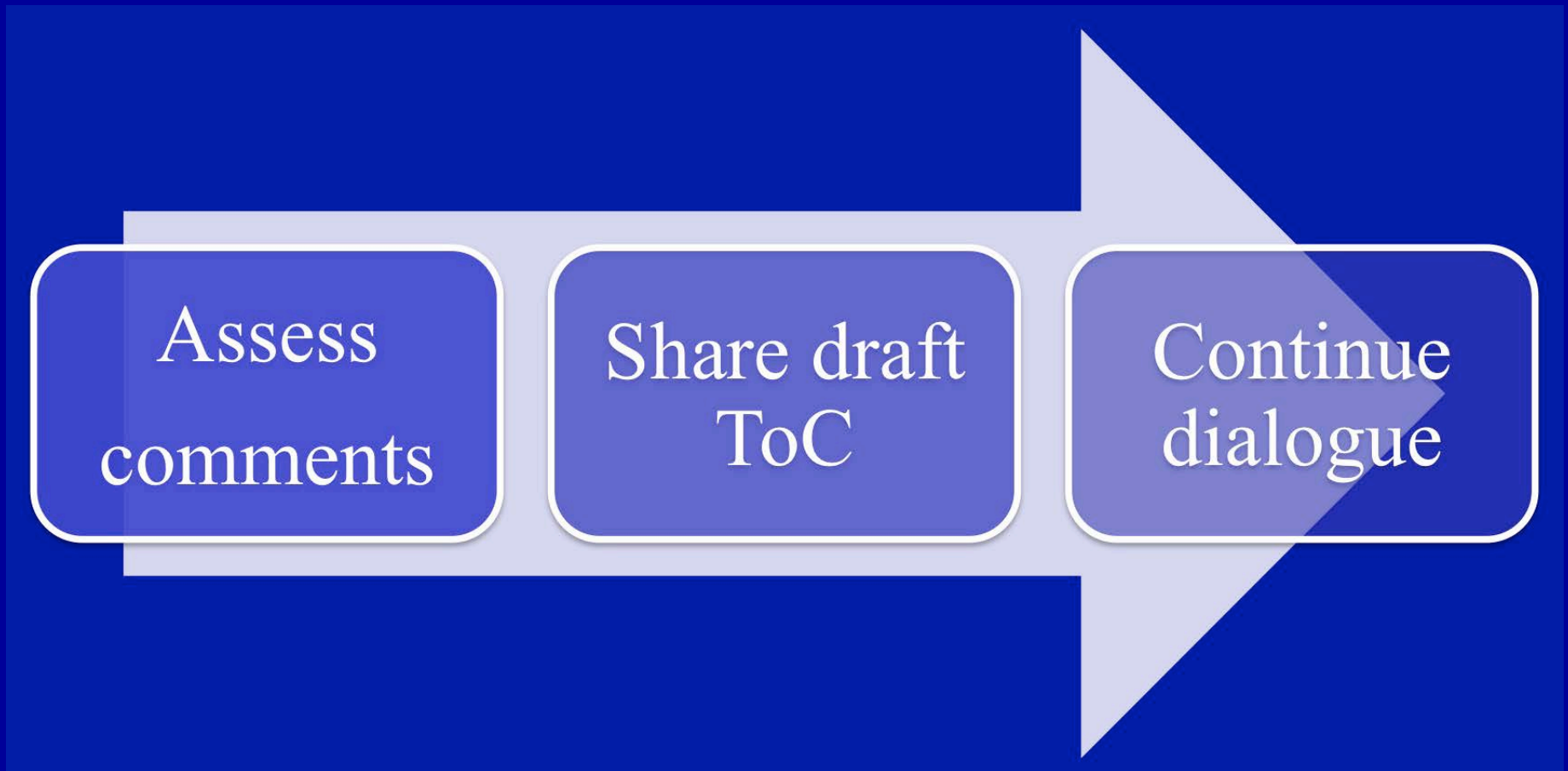
# CFSAN Redbook Project Update Goals



# Milestones

- January 2014 Project Launch
- Summer 2014 Internal Suggestions and Recommendations Collection
- December 2014 Public Meeting; 1st Public Comment Period Open
- May 2015 1st Public Comment Period Closes
- Late 2015 Draft Table of Contents (ToC)
- Future – More Public Meetings And Comments As Documents Are Drafted

# Next Steps



# To Learn More and Stay Informed:

- Email jeremiah.fasano@fda.hhs.gov
- http://www.fda.gov/Food/NewsEvents/ConstituentUpdates/ucm442415.htm (**http://tinyurl.com/ltog6qk**)

# NCTR-Tox21 Drug Induced Liver Injury (DILI) working group

- Agreed upon a definition of DILI to cover environmental chemicals, as well as drugs.
- Presentations from multiple participants to share ongoing work, provide feedback, and to identify areas of future collaboration
- Dr. Tong's division is working on a collaborative proposal to expand their liver toxicity knowledge base (LTKB) and develop new computational model
- Dr. Tong presented a recent study of evaluating an integrated approach of Tox21 data with in silico approach for an enhanced DILI prediction in humans

# Other NCTR Research

- In collaboration with EPA, etc. NCTR used multiple approaches to develop computational models for endocrine active agents. Data from ToxCast and Tox21 were used
- Dr. Beger is working with NCATS on hERG and phospholipidosis data to build computational models. (This builds on work they have done with CDER.)

# CDER

- Participant in ICH guidance development:
  - International harmonization reduces repetition of studies and reduces animal use in overall drug development
  - No acute lethal tox
  - Combine endpoints-no stand-alone assays for local tox
  - Exposure and dose limits for tox studies
  - Exploratory clinical studies section reduces use of animals needed to support clinical studies
  - Defer reprotox studies until later in development for biologics

# CDER-Phototox

- Use 3T3 photocytox assay instead of animals
- Eliminated any photocarc testing

# CDER-Carcinogenicity

- Waive carc studies for most biologics
- Working on criteria for waiving carc for small molecules
- For Impurities: use SAR

# CDER-Reprotox

- Considering an alternative (in vitro) battery to sometimes replace one species for regulatory use (already used as screens in drug discovery)
- Considering reuse of animals normally discarded before pre-postnatal studies

## CDER Practice

- No need for Draize test for skin or eye (e.g., in vitro/in vitro alternatives-- accept BCOP assay)
- Accept nonanimal pyrogenicity assays (if applicable to product)

# CDER ICCVAM Activities

- Contributes to DARPA and NCATS initiatives on “human on a chip” programs
- Supports work on a dermal sensitization nonanimal battery
- Supports work on pathway-based assays
- Supports work on ocular assays for no ocular irritation

# CBER Vaccines (a)

- The International Working Group for Alternatives to HIST
- Multi-national consortium of interested stakeholders representing government, industry, animal welfare organizations, research and regulatory institutions
- Review and discuss implementation of in vitro assays as alternatives to the HIST (an animal-based method) for the testing of residual pertussis toxin (PTx) activity in acellular pertussis vaccines

# CBER Vaccines (b)

- CBER led the organization of the “Alternatives to HIST Workshop (London): What is Possible and Practical?” (March 4-5, 2015) held and sponsored by NC3Rs and supported by NICEATM and ICCVAM.
- Review of  the results of a collaborative study of the CHO cell assay (an in vitro, cell-based alternative to HIST) sponsored by EDQM
- CBER developed one of two methods (Direct) in the collaborative study

# CBER Vaccines-London Workshop Recommendations: (c)

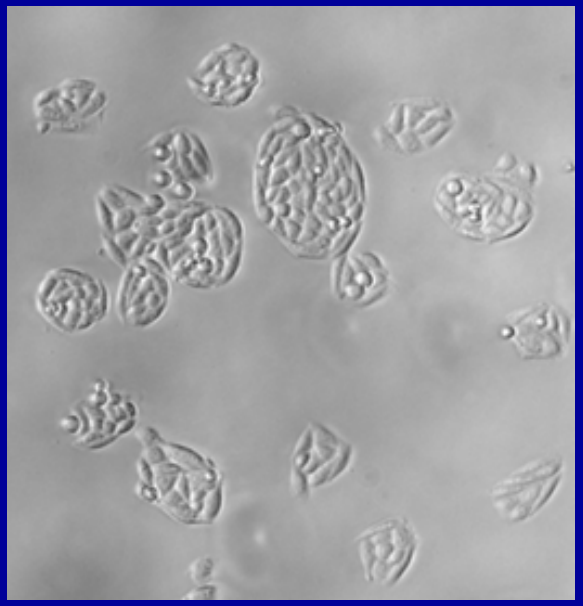
- The CHO cell assay is a suitable alternative to HIST – Measures PTx whole function
- The CHO cell assay is reasonably well developed to be considered suitable for regulatory purposes (protocol transferability demonstrated)
- Each manufacturer will have to optimize the method for their specific product & regulatory requirements

# CBER Vaccines-London Workshop Recommendations: (d)

- Implementation of the alternative method - Stepwise approach, initially used for release then extend to stability testing after a period of demonstrated performance
- In certain cases, waiving of the HIST altogether is an option (based on science & manufacturing history)
- Other in vitro assays (i.e. measuring PTx binding & enzymatic activity) have utility as supplemental manufacturing control information, but not for final lot release on their own

# CBER Vaccines-London Workshop Recommendations: (e)

- Publication of the collaborative study results should facilitate international regulatory acceptance (PharmEurpa BIO)



Pertussis toxin induction of characteristic morphologic patterns, or ‘clustering’, in CHO-K1 cells

This is the basis for the CHO cell test used in acellular pertussis vaccine control of the toxoiding process.