Advancing Alternative Methods for Regulatory Use

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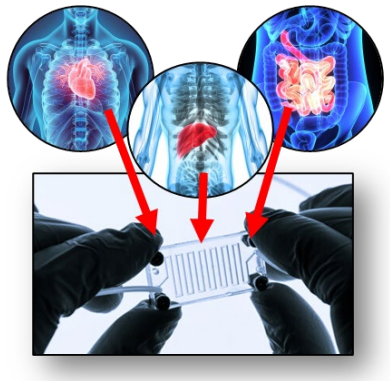
Presentation to the FDA Science Board on Behalf of FDA New Alternative Methods Group Members – June 14, 2022



Thank You to FDA New Alternative Methods Group Members

Office of the Chief Scientist: Jacqueline O'Shaughnessy, Chad Nelson, Rakesh Raghuwanshi

Centers

- **CBER**: Kyung Sung, Claudia Wrzesinski
- **CDER**: Paul Brown, Kevin Ford, Rodney Rouse, Nakissa Sadrieh
- **CDRH**: Edward Margerrison, Melissa Scales
- **CFSAN**: Suzanne Fitzpatrick
- **CTP**: Wanyoike Kang'ethe
- **CVM**: Jeffrey Ward
- **NCTR**: Donna Mendrick, Tucker Patterson
- **ORA**: Paul Howard, Selen Stromgren

CBER: Center for Biologics Evaluation and Research
CDER: Center for Drug Evaluation and Research
CDRH: Center for Devices and Radiological Health
CFSAN: Center for Food Safety and Applied Nutrition
CTP: Center for Tobacco Products
CVM: Center for Veterinary Medicine
NCTR: National Center for Toxicological Research
ORA: Office of Regulatory Affairs

Office of Commissioner

- **OP** (Office of Policy): Jean McCue, Jarilyn Dupont
- **OL** (Office of Legislation): Matthew Lockeed
- **OCET** (Office of Counterterrorism and Emerging Threats) Tracy MacGill

Why Are We Here?

GOAL	**FDA plans to seek input from the Science Board on how the agency can enhance its existing approaches to support the development, qualification, and implementation of alternative methods for regulatory use that can:** • **Replace, reduce, and refine animal testing (the 3Rs)** • **Improve predictivity of nonclinical testing**

- The purpose of today's presentation is to introduce the topic
- FDA is not seeking specific detailed feedback from the FDA Science Board today
- FDA plans to charge a Science Board subcommittee to work on this topic
- The subcommittee report would be presented at a future Science Board meeting

Outline

- Background
- FDA's Proposed New Alternative Methods Program
- Product-Area Specific Considerations
- New Alternative Methods Applied Research and Examples of Use in Regulatory Submissions
- Summary and Next Steps

FDA's Mission

Protect and advance public health by:

Ensuring the safety of our food supply, cosmetics, and products that emit radiation

Ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices

Fostering development of medical products to respond to deliberate and naturally emerging public health threats

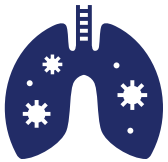
Regulating the manufacturing, marketing, and distribution of tobacco products

What We Do | FDA

Fulfilling FDA's Mission – Example Role of Animal Testing

FDA reviews medical product developer-submitted data to establish:

- Under what conditions (e.g., dose, population, patient monitoring) a new medical product can be safely administered to patients
- Whether some new medical product carries an increased risk for developmental and reproductive toxicity or an increased cancer risk



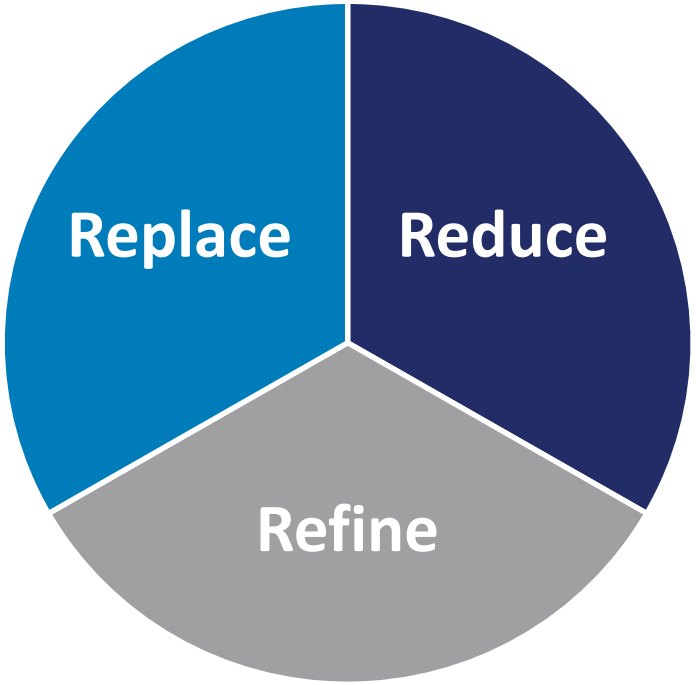
This includes endpoints that cannot ethically be obtained in humans, such as histopathological analysis of all major organs

- Animal studies play a critical role to meet this need and bring safe and effective therapies to patients

FDA has a long-standing commitment to replace, reduce and refine ("3Rs") animal testing

What are the 3Rs?

Replacing: Test method that substitutes traditional animal models with other test systems



Reducing: Test method that decreases the number of animals required for testing

Refining: Test method that eliminates pain or distress in animals, or enhances animal well-being

New Alternative Methods Incorporate the 3Rs

3R Successes: Internationally Harmonized Guidelines and Standards

ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use	ICH harmonisation for better health	Prior to these guidelines, separate animal studies were often required for developing drugs/biologics in different countries/regions

Creation of ICH and implementation of harmonized guidelines has reduced animal testing by decreasing repeat animal studies and standardized timing of when studies should be conducted

Additional information: Implementation of the principles of the 3Rs of animal testing at CDER: Past, present and future

Organizations relevant to other FDA product areas

Veterinary Medicines

VICH

International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

Cosmetics

ICCR

International Cooperation on Cosmetics Regulation

Medical Devices and Other Product Areas

ISO

International Organization for Standardization

3R Successes: Interagency Coordination & Collaboration

FDA plays an active role in the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

Member Agencies:

- Agency for Toxic Substances and Disease Registry
- National Cancer Institute
- National Institute for Occupational Safety and Health
- National Institute of Environmental Health Sciences
- National Institute of Standards and Technology
- National Institutes of Health
- National Library of Medicine
- Occupational Safety and Health Administration
- U.S. Consumer Product Safety Commission
- U.S. Department of Agriculture
- U.S. Department of Defense
- U.S. Department of Energy
- U.S. Department of the Interior
- U.S. Department of Transportation
- U.S. Environmental Protection Agency
- U.S. Food and Drug Administration

- Coordinates activities within the federal government relevant to new test method evaluation, acceptance, and use
- ICCVAM-coordinated activities have led to acceptance of alternative methods for testing some FDA-regulated products

  (examples to follows)

About ICCVAM

Addressing the 3Rs – Successes to Date – Product Quality

Paralytic shellfish toxin detection

- *In vitro* assay listed as approved method in National Shellfish Sanitation Program Guide for Control of Molluscan Shellfish in place of animal test (2013)

Botulinum neurotoxin type A product stability and potency testing

- FDA accepted an *in vitro* method (2012) for testing the stability and potency of the drug products in place of the median lethal dose (LD_{50}) method in rodents

Pyrogen testing

- FDA guidance (2012)* discussed approaches that could reduce animal use and indicated an *in vitro* method may be used instead of an animal test with appropriate product-specific validation

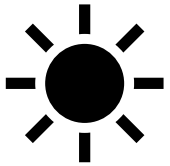
**See Guidance for details and considerations by FDA product area*

Additional details and examples:

ICCVAM database on accepted alternative methods; search for "FDA"

ICCVAM resources on: Alternative Methods for Biologics and Vaccine Testing; In Vitro Pyrogen Test Methods

Addressing the 3Rs – Successes to Date – Toxicology



Photosafety evaluation of pharmaceuticals

- ICH S10 Guidance (2015) has a step-wise process employing physiochemical and *in vitro* methods, that can be completed without the use of any animal studies

Assessing eye irritation and skin sensitization for pharmaceuticals

- Reconstructed human cornea-like epithelium and 3D reconstructed human epidermis models replaced rabbit tests for for eye irritation and skin sensitization (2019)

Multiple other ICH/FDA guidance documents with 3Rs principles

- Decrease certain stand-alone animal studies, delay certain studies until later in drug development, and discuss role of *in vitro*/*in silico* methods (see below)

Additional details and examples:

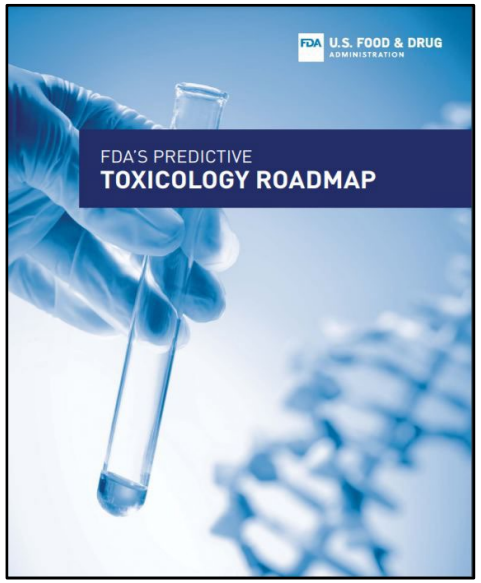
- Implementation of the principles of the 3Rs of animal testing at CDER: Past, present and future
- An FDA/CDER perspective on nonclinical testing strategies: Classical toxicology approaches and new approach methodologies (NAMs)

Transforming Toxicology is a Key FDA Goal

2011

Priority 1:
Modernize toxicology to enhance product safety

2017



2021

Office of the Chief Scientist Sponsored Cross-Agency Working Groups:

- Toxicology Working Group
- Alternative Methods Working Group
- Modeling and Simulation Working Group

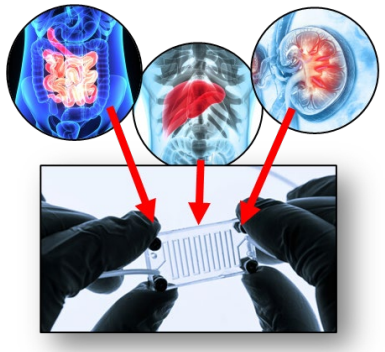
- **Regulatory Science Research**
- **National and International Collaborations**

Additional details: Advancing Alternative Methods at FDA

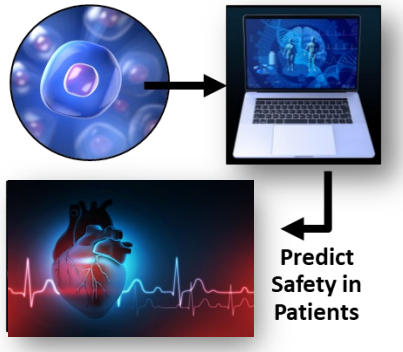
The Promise of New Technologies

- Advances in systems biology, stem cells, engineered tissues, and mathematical modeling present new opportunities to improve our ability to predict risk and efficacy

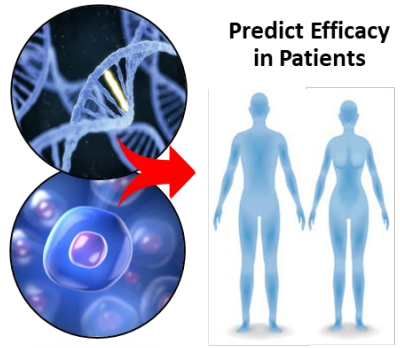
Microphysiological Systems



Combined *in vitro* and *in silico* Models



Genetically-engineered Cellular Models



- Advances may help bring products to market faster, with improved efficacy, or prevent products with increased toxicological risk from reaching the market

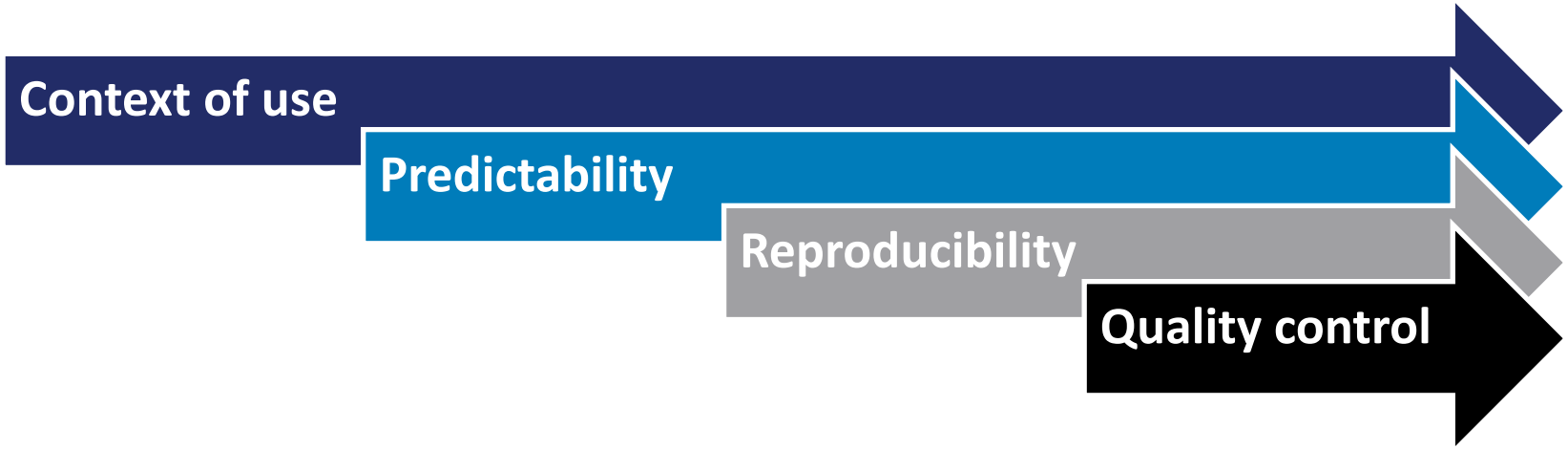
Efficacy ↑

Toxicological Risk ↓

Speed to market →

However, …

Multiple steps are required to translate these new technologies into regulatory use and maintain the same standard of safety, efficacy and quality of FDA-regulated products



While we are nowhere near being able to replace all animal testing …

… there are opportunities for alternative methods to make additional inroads in addressing the 3Rs for specific contexts of use

Outline

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- **FDA's Proposed New Alternative Methods Program**
- Product-Area Specific Considerations
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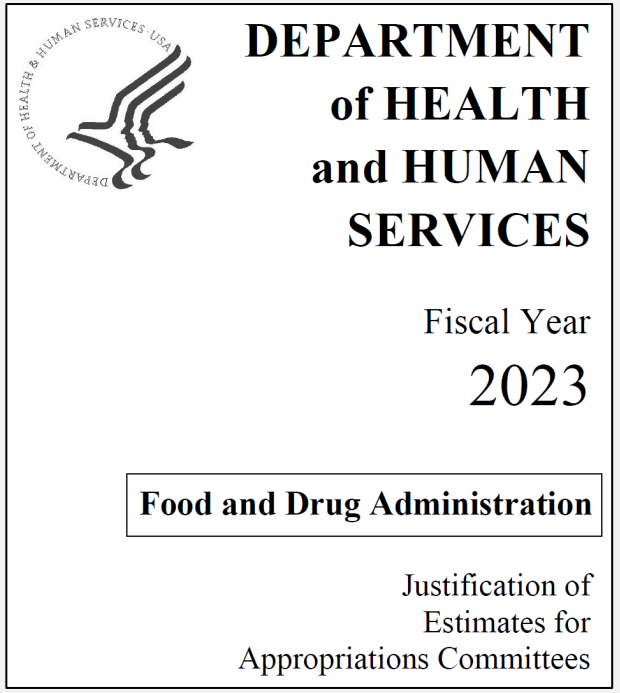
FDA's Proposed New Alternative Methods Program

The FY2023 President's Budget proposes new funding to implement a cross-agency New Alternative Methods Program to:

- **Spur the adoption of new alternative methods for regulatory use that can replace, reduce and refine animal testing and improve predictivity of nonclinical testing to**:
  - Streamline development of FDA-regulated products
  - Bring products to US public and patients more rapidly and more efficiently
  - Ensure products are safe, effective, and that patients can depend on them



Link

FDA's Proposed New Alternative Methods Program

- **Centrally coordinated through FDA's Office of the Chief Scientist with FDA Centers implementing Agency-wide programmatic objectives**

- **FDA cannot develop and implement alternative methods alone, so through this initiative FDA will**
  - Expand processes to qualify alternative methods for regulatory use
  - Provide clear guidelines to external stakeholders developing alternative methods
  - Fill information gaps with applied research to advance new policy and guidance development

- **Collaborations with external stakeholders are vital**
  - Federal partners, public-private partnerships, international regulators

Why Qualification?

Example of medical product development tool qualification programs

Medical product developers can submit data from alternative methods in investigational drug/device applications or marketing applications

- However, if it comes from an alternative method, the suitability of the alternative method would need to be evaluated in parallel
- There typically is not time to do this and it introduces significant uncertainty for the submitter

Qualification is a process that allows for an alternative method to be endorsed by FDA in advance for a specific context of use

- The qualified context of use defines the boundaries within which the available data adequately justify use of the tool
- Similar concept to a drug or medical device's indications for use

Medical product developers can then use the alternative method for the qualified context of use with confidence that it is an acceptable method

Current FDA Qualification Programs

CDER/CBER Drug Development Tools Qualification Programs

- **Biomarker Qualification**
- Clinical Outcome Assessment Qualification
- **Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program**

CDRH Medical Device Development Tools Qualification Program

- Clinical Outcome Assessment
- Biomarker Test
- **Nonclinical Assessment Model**

Additional information – including qualified tools

Drug Development Tool (DDT) Qualification Programs | FDA

Medical Device Development Tools (MDDT) | FDA

Role for qualification programs in other FDA product areas?

CDER/CBER Qualification Process and Pilot Program

Drug Development Tool Qualification Process

Letter of Intent (LOI)	Initiates the qualification process of a biomarker for a proposed context of use (COU) in drug development
Qualification Plan (QP)	Defines the intended development to generate the necessary supportive data to qualify the biomarker for the proposed COU
Full Qualification Package (FQP)	Contains all accumulated data to support the qualification of the biomarker for the proposed COU
Qualification Recommendation	Contains FDA's determination on whether the biomarker is qualified for the proposed COU based on a comprehensive review of the FQP

The Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program

Designed to expand drug development tool types to those outside of scope of other programs – examples:

- Microphysiological systems to assess safety or efficacy questions
- Development of novel nonclinical pharmacology/toxicology assays

ISTAND Pilot Program | FDA

CDRH Qualification Programs and Medical Device Development Tool Example

CDRH Qualification Program – Nonclinical Assessment Model

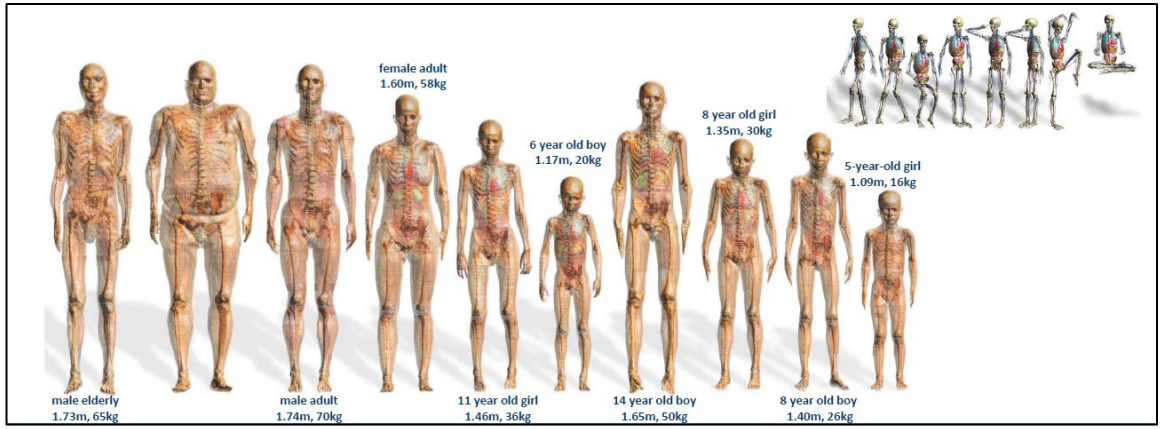
A non-clinical test model or method that measures or predicts device function or *in vivo* device performance – can be used to:

- ↓ Reduce or replace animal testing
- ↓ Reduce test duration or sample size

Medical Device Development Tools (MDDT) | FDA

Example Medical Device Development Tool

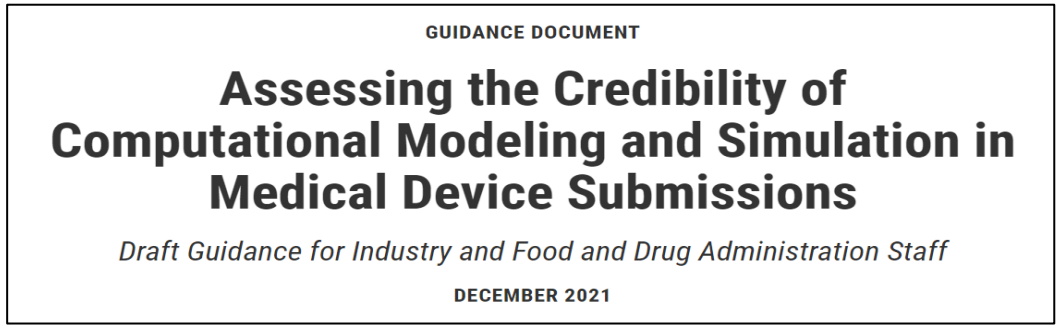
The Virtual Population is a set of anatomically correct whole-body models for thermal, electromagnetic and fluid dynamic simulations



Virtual Family | FDA

What are Potential Guidance to Stakeholders Developing Alternative Methods?

- **Guidance on qualification process**
- **Topical guidance on specific safety or development areas**
- **Guidances on assessing credibility of specific types of alternative methods or what to include in regulatory submissions – examples:**


GUIDANCE DOCUMENT

Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions

Draft Guidance for Industry and Food and Drug Administration Staff

DECEMBER 2021

Link


GUIDANCE DOCUMENT

Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry

SEPTEMBER 2018

Link

Role for microphysiological systems-related general considerations guidance?

Case Studies Highlighting Components of the FDA New Alternative Methods Program Plan

1. Cardiac safety
2. Development and reproductive toxicity

Fill Information Gaps with Applied Research to Advance New Policy and Guidance

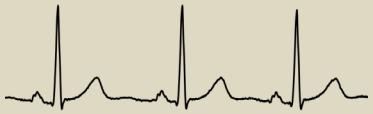
Example Highlights

Fill Information Gaps with Applied Research

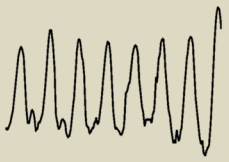
Policy & Guidance to Streamline Qualification & Implementation

Background

Normal Heart Rhythm



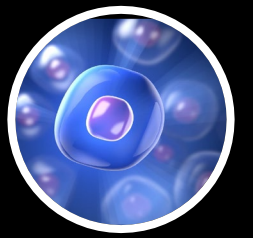
ABNORMAL Heart Rhythm!



Regulatory guidelines rely on non-specific test for predicting drug-induced abnormal heart rhythms

New Approach

1. Laboratory Cell-Based Models



2. Integrate in Computer Model

3. Predict Heart Safety in Patients

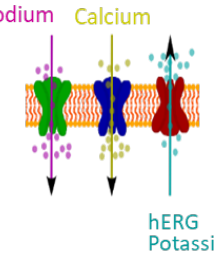
The Comprehensive in vitro Proarrhythmia Assay | FDA

CIPA (cipaproject.org)

Applied Research to Fill Information Gaps

Systematic Process

Assay standards, best practices, variability

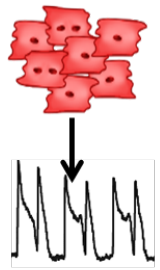


Link to research articles

Model development, optimization, validation

Link to research articles

Best practice considerations for human iPSC-cardiomyocyte assays



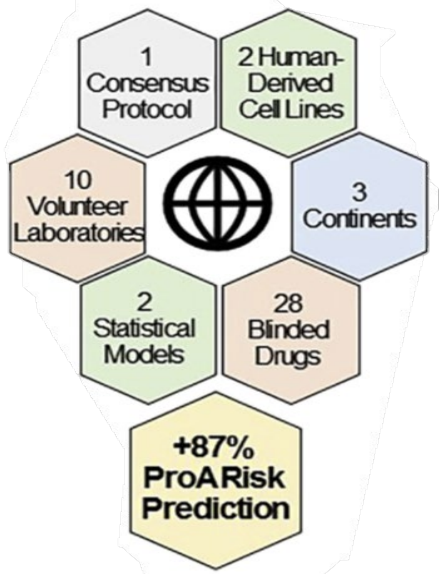
Link to research articles

Example of a collaborative multisite study:

Resource

International Multisite Study of Human-Induced Pluripotent Stem Cell-Derived Cardiomyocytes for Drug Proarrhythmic Potential Assessment

Cell Reports, 2018, 24(13):3582-3592



Case Study 1

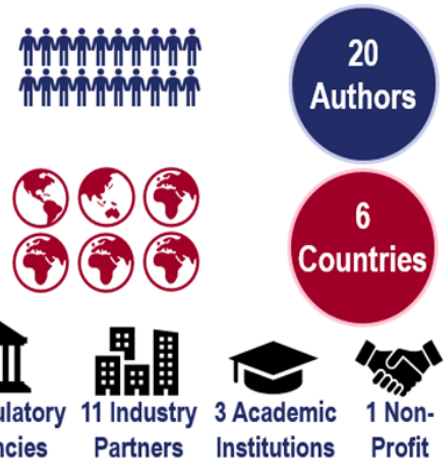
Collaborative Workshops, White Papers and Development of New International Regulatory Guideline

Comprehensive In Vitro Proarrhythmia Assay (CiPA) Update from a Cardiac Safety Research Consortium / Health and Environmental Sciences Institute / FDA Meeting

Ther Innov Regul Sci 2019;53(4):519-25

White Paper on Human Stem Cell-Derived Cardiomyocyte Assays

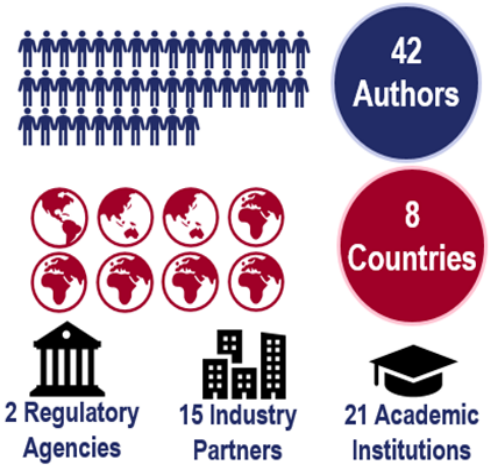
Regul Toxicol Pharmacol. 2020;117:104756.



Link

White Paper on Proarrhythmia Model Validation

Clin Pharmacol Ther. 2020;107(1):102-111



Link

New ICH Guideline Adopted February 2022

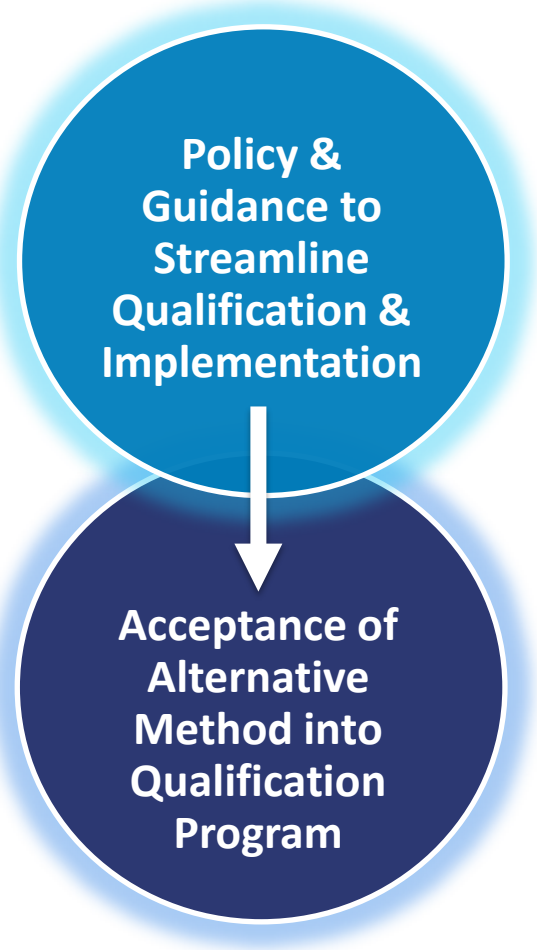
Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential - ICH E14/S7B Q&As

Includes:

- Best practice recommendations for *in vitro* ion channel and human induced pluripotent stem cell assays to enable use as follow-up studies in place of potential animal studies
- Principles for validating [*in vitro* and *in silico*] proarrhythmia models and qualifying them for regulatory use, which can reduce animal use

Link

ICH Guideline Describing Novel Testing Paradigms and Regulatory Acceptance of Alternative Methods



ICH Guideline on Detection of Reproductive and Developmental Toxicity (ICH S5[R3], 2020) contains a new section on novel testing paradigms and regulatory acceptance of alternative assays supporting the 3Rs

- Describes circumstances under which qualified alternative assays can be used
- No specific assays are recommended, but basic scientific principles are included to assist in assay qualification for regulatory use
- Includes reference compound list for assessing alternative assays

Link

Case Study 2

Alternative Assay Biomarker Accepted Into FDA/CDER's Biomarker Qualification Program

Letter of intent (LOI) submitted and accepted

Pending submission of qualification plan

Current status

LOI and FDA's response are public documents: Biomarker Qualification Submissions | FDA

Proposed context of use: Safety biomarker for detecting human developmental toxicity potential *in vitro* using human pluripotent stem cells at the nonclinical stage of drug development for small molecule drugs as part of a weight-of-evidence assessment as described in the ICH S5(R3) guideline

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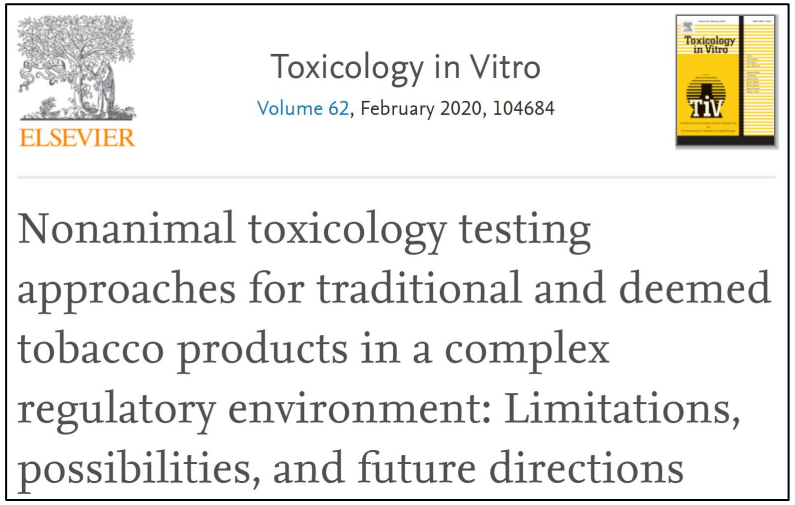
Tobacco-Specific Considerations

Regulates both traditional tobacco products and newer products such as e-cigarettes

Diversity of tobacco products to regulate

Disclaimer: These illustrations are intended to provide general examples of deemed tobacco products

FDA Article:



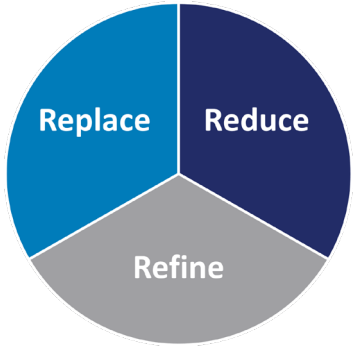
Toxicology in Vitro, 2020, 65:104684

Need alternative methods relevant to target tissues for tobacco product exposures

Veterinary Medicines-Specific Considerations

Animals are the patients, however there are opportunities to address the 3Rs

Developing generic animal drugs for non-systemically absorbed drug products (e.g., locally acting gastrointestinal or ophthalmic drugs) has required clinical endpoint bioequivalence trials for every indication



FDA's Center for Veterinary Medicines is developing roadmaps for alternative approaches for the bioequivalence evaluation of these various types of products

Includes understanding drug physicochemical properties, formulation-critical quality attributes, and use of physiologically-based pharmacokinetic models

See section on Center for Veterinary Medicines in Advancing New Alternative Methodologies at FDA.

Food and Cosmetics Products Safety

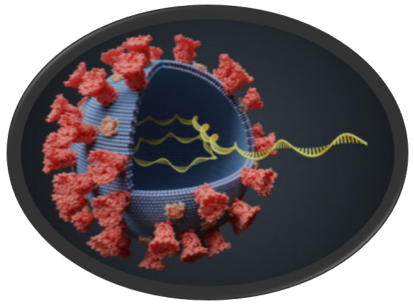
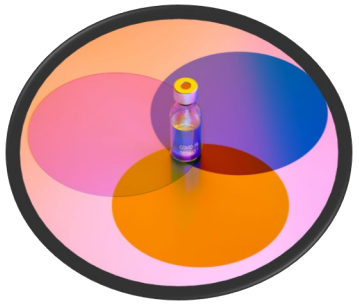
	Measuring botulinum neurotoxin in contaminated food
Standard Method	Mouse assay that can use large numbers of animals
Proposed Alternative	*In vitro* approaches to detect presence and potency of botulinum neurotoxin  Additional information

Article Link

Next generation risk assessment

- Exposure-led, hypothesis-driven approach
- Need to develop and test the *in vitro* and *in silico* approaches to enable confident application in a regulatory context

Biologics and Vaccines Product Quality (Human and Veterinary)

	Detecting viral adventitious agents in biologics and biomanufacturing	Potency testing of human and veterinary rabies virus vaccine
Standard Method:	Multiple animal-dependent assays	Relies on mice and is variable and time consuming
Proposed Alternative:	Next generation sequencing to detect viral adventitious agents 	Highly specific monoclonal antibodies to quantitate key part of vaccine 

Collaborative Workshop on Next Generation Sequencing

Article Link

Additional information: Alternative Methods for Biologics & Vaccine Testing

Human Medical Device- and Drug-Specific Considerations

Medical Devices

NAMs for Medical Devices:
Use of New Approach Methodologies for the Biological Safety Assessment of Medical Devices

FDA talks on:

- Medical Device Development Tools and Biocompatibility Considerations
- *In Vitro* Thrombogenicity Evaluation of Medical Devices – Regulatory Considerations and Research Efforts

NAMS for Medical Devices Workshop 2020 Link

Drugs

Article Link

Opportunities and challenges of using NAMs in drug development for regulatory purposes

Article Link

Events and activities that have had the greatest impact on animal use and ongoing efforts

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Cross-Cutting FDA Applied Research: Lung Microphysiological Systems

Tobacco Focused

FDA Centers: NCTR and CTP

Evaluating Mode of Action of Acrolein Toxicity in an In Vitro Human Airway Tissue Model

Toxicol Sci,2018, 166(2):451-464

Cigarette whole smoke solutions disturb mucin homeostasis in a human in vitro airway tissue model

Toxicology, 2018, 409:119-128

Device Focused

FDA Centers: NCTR and CDRH

Toxicity of Ortho-phthalaldehyde Aerosols in a Human *In Vitro* Airway Tissue Model

Chemical Research in Toxicology, 2021, 34(3):754-766

Evaluating the Sub-Acute Toxicity of Formaldehyde Fumes in an In Vitro Human Airway Epithelial Tissue Model

International Journal of Molecular Sciences, 2022, 23(5):2593

Drugs, Biologics and Medical Countermeasures Focused

FDA Centers:

CDER

Locally-acting inhaled generic drugs

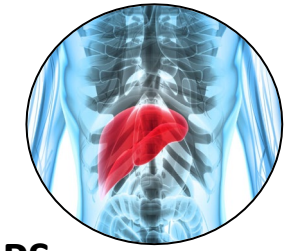
CBER

Lung infection model

OCS/Medical Countermeasures

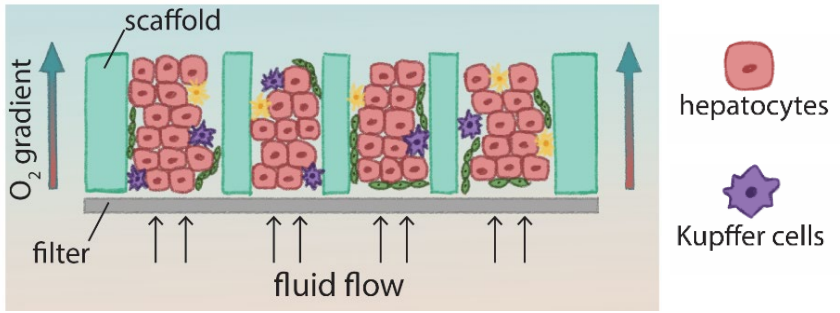
Radiation-induced lung injury

Cross-Cutting FDA Applied Research – Liver Microphysiological Systems



- Liver toxicity = major reason for discontinuation of drugs in development
- Chemical contaminants in food can also cause liver toxicity
- Liver critical for drug and food metabolism

Liver MPS



Clinical Pharmacology & Therapeutics 2019, 106:139-47.

FDA Applied Regulatory Science

ARTICLE | Open Access

Characterizing the Reproducibility in Using a Liver Microphysiological System for Assaying Drug Toxicity, Metabolism and Accumulation

Clinical & Translational Science, 2021,14(3):1049-1061

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

ELSEVIER

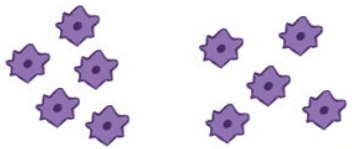
Evaluation of the utility of the Beta Human Liver Emulation System (BHLES) for CFSAN's regulatory toxicology program

Food and Chemical Toxicology, 2022,161:112828

- Similar results between two sites

- Similar results within a site when using different batches of cells

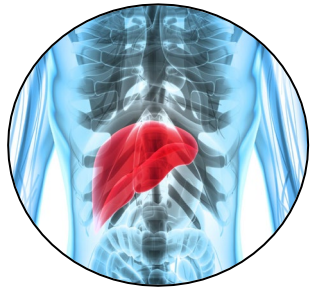
Batch 1 Batch 2



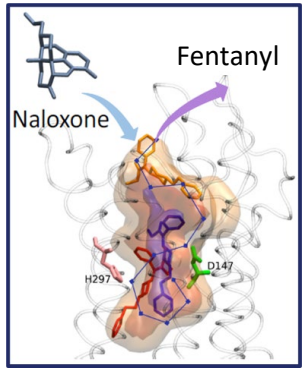
- Identified quality control criteria for cells

Alternative Methods Data Used to Support Regulatory Decision Making

Safety



Effectiveness

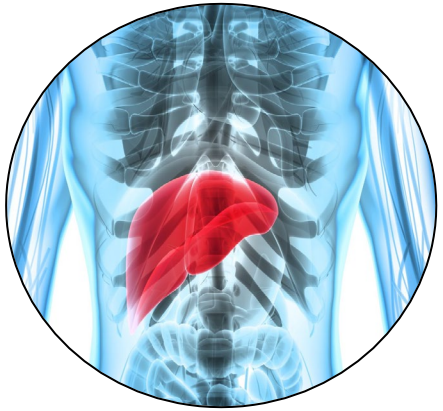


Alternative Methods Data to Support Drug Approval

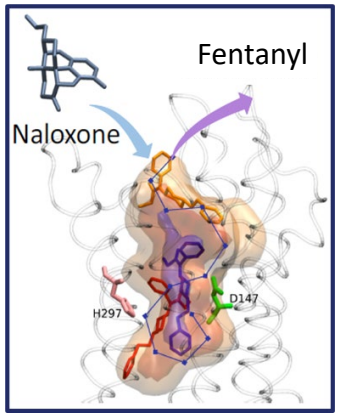
- Other drugs in class discontinued from clinical development due to liver toxicity
- Some liver enzyme elevations in rat studies at high doses
- **Complex *in vitro* models with 3D spheroids combined with *in silico* modeling**
  - Reproduced observed liver toxicity of other drugs
  - Suggested new drug has significantly reduced risk of liver toxicity
- **Regulatory Impact**: Data contributed to liver toxicity assessment as described in supervisory pharmacology-toxicology review for NDA

Drug approval review documents **link**

Liver Safety



Alternative Method Data to Support Drug Approval



- Certain fentanyl-derivatives have extremely high potency at the opioid receptor and have potential to be used as chemical weapons
- Department of Defense supported the development of a high-dose naloxone autoinjector to counter this purpose
- Instead of an animal model-based approach to demonstrate effectiveness, FDA recommended an *in vitro-in silico* quantitative systems pharmacology approach

FDA-Developed Model Used to Support Approval

Naloxone 10 mg autoinjector

----------INDICATIONS AND USAGE----------

NALOXONE HYDROCHLORIDE injection is an opioid antagonist indicated for use by military personnel and chemical incident responders for:

- Emergency treatment of patients 12 years of age and older where use of high-potency opioids such as fentanyl analogues as a chemical weapon is suspected. (1)

See the FDA approval package for details

Outline

- Background
- FDA's Proposed New Alternative Methods Program
- Product-Area Specific Considerations
- New Alternative Methods Applied Research and Examples of Use in Regulatory Submissions
- **Summary and Next Steps**

Summary – Background

- FDA's mission is to protect and advance public health with responsibility for regulating diverse products
- To ensure the safety, efficacy and quality of FDA-regulated products, animal studies have played a critical role
- FDA has a long-standing commitment to the 3Rs with successes to date
- New technologies hold substantial promise, however multiple steps required to translate into regulatory use and maintain the same standard of safety, efficacy and quality of FDA-regulated products

FDA's Proposed New Alternative Methods Program

Goal: spur the adoption of new alternative methods for regulatory use that can address the 3Rs and improve predictivity of nonclinical testing

FDA cannot develop and implement alternative methods alone, so through this initiative FDA will

Case studies highlighting components of the FDA New Alternative Methods Program plan

1. Cardiac safety
2. Developmental and reproductive toxicity

Critical role for collaborations and international harmonization

Product-Specific Considerations and Opportunities for Synergies

Product-Area Specific Considerations

Opportunities for Synergies

Alternative methods with contexts of use across multiple product areas

Lung and liver MPS

General considerations guidances for specific types of alternative methods?

Seeking Input from the FDA Science Board

GOAL	**FDA plans to seek input from the Science Board on how the agency can enhance its existing approaches to support the development, qualification, and implementation of alternative methods for regulatory use that can:** • **Replace, reduce, and refine animal testing (the 3Rs)** • **Improve predictivity of nonclinical testing**

- While today's presentation outlined FDA's proposed plan, we are interested in additional perspective from FDA's Science Board
- FDA is not seeking specific detailed feedback from the FDA Science Board today
- FDA plans to charge a Science Board subcommittee to work on this topic
- The subcommittee report would be presented at a future Science Board meeting

Thank You to FDA Working Group Members

Thank you to FDA Science Board

Questions?