# FDA Update on Advancing Alternatives for Regulatory Use

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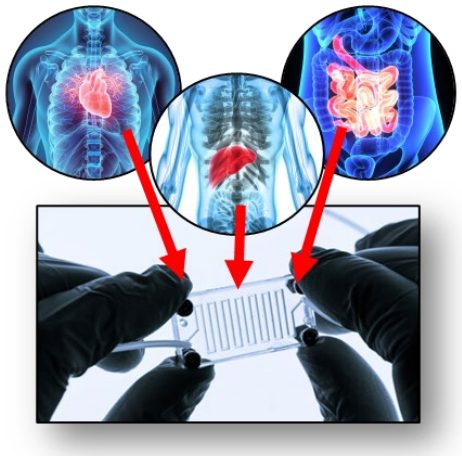


# Outline

- Background
- FDA's Proposed New Alternative Methods Program
- The Role of Qualification
- Alternative Methods Case Studies
- Product-Area Specific Considerations
- 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

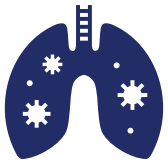
Regulating the manufacturing, marketing, and distribution of tobacco products

https://www.fda.gov/about-fda/what-we-do

# 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**

# Addressing the 3Rs – Successes to Date

- **Harmonizing drug/biologic regulatory requirements globally** to avoid repeat animal testing being performed in different countries
- **Leveraging toxicology studies from a reference product** for generic drugs/biosimilars

Comprehensive Review

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

Regulatory Toxicology and Pharmacology, 2021,123:104953

- ***In vitro* assays replacing animal studies for**
  - Certain biologics/vaccine product quality testing
  - Paralytic shellfish toxin detection

National Toxicology Program
U.S. Department of Health and Human Services

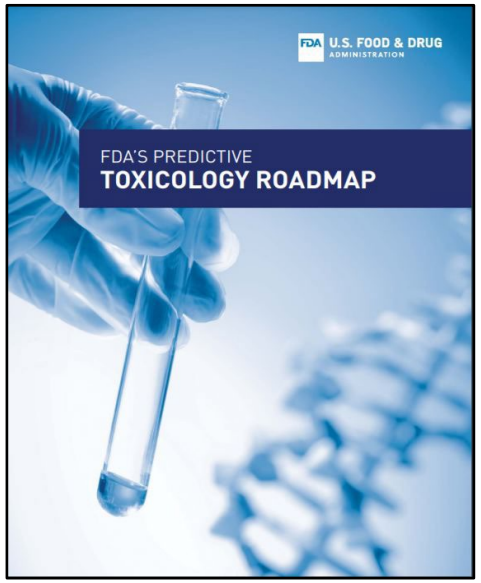
Alternative Methods Accepted by US Agencies

# 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:**

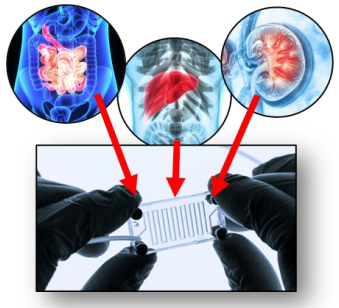
- Toxicology Working Group
- Alternative Methods Working Group
- Modeling and Simulation Working Group

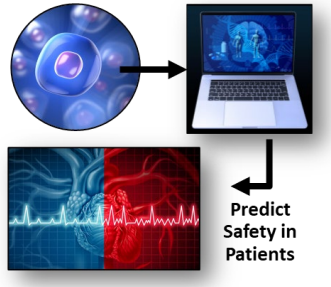
- **Regulatory Science Research**
- **National and International Collaborations**

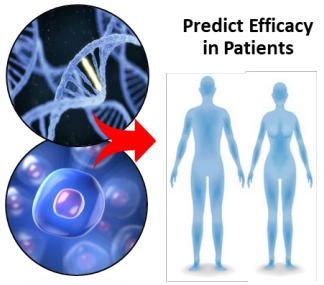
**Additional details:** [Advancing Alternative Methods at FDA | FDA]

# New Technologies: Promise and Challenges

**New technologies hold significant promise**






**However, multiple steps required to translate new technologies into regulatory use and maintain same standards of safety, efficacy and quality for FDA-regulated products**

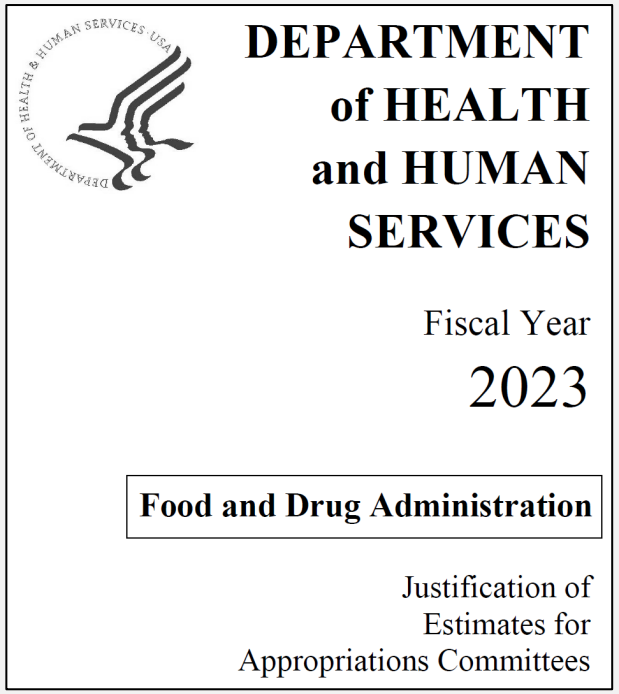

**While we are nowhere near being able to replace all animal testing …**

**… there are opportunities for alternative methods to make inroads in addressing the 3Rs for <u>specific contexts of use</u>**

# 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 them to US public and patients more rapidly and more efficiently
  - Assure they are safe, effective, and that patients can depend on them



# 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

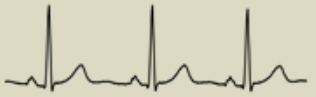
Medical Device Development Tools (MDDT) | FDA

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

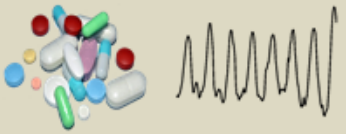
Case Study 1

# Fill information gaps with applied research to advance new policy and guidance development

**Normal Heart Rhythm**



**ABNORMAL Heart Rhythm!**



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

**New *in vitro-in silico* mechanistic approach**

**Systematic Process**


**ICH Guideline Adopted February 2022**

**Clinical and Nonclinical Evaluation of QT 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

**Publication Links:** *Assay standards, best practices, variability* *Human iPSC-cardiomyocyte assays* *In silico model* ICH Official web site : ICH

Case Study 2

# ICH Guideline Describing Regulatory Acceptance of Alternative Methods for Developmental Toxicity


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

**Acceptance of an alternative method into FDA/CDER Qualification Program**

- **Proposed context of use**: Safety biomarker for detecting human developmental toxicity potential *in vitro* using human pluripotent stem cells …as part of a weight-of-evidence assessment as described in the ICH S5(R3) guideline


Additional details: Biomarker Qualification Submissions | FDA

# Product Area-Specific Considerations

***Links to additional information***

| | |
|---|---|
| **Food** | State of the science on alternatives to animal testing and integration of testing strategies for food safety assessments: Workshop proceedings. Regulatory Toxicol and Pharmacol 2020. |
| **Cosmetics** | Paving the way for application of next generation risk assessment to safety decision-making for cosmetic ingredients. Regulatory Toxicol and Pharmacol 2021. |
| **Tobacco** | Nonanimal toxicology testing approaches for traditional and deemed tobacco products in a complex regulatory environment: Limitations, possibilities, and future directions. Toxicology in Vitro 2020. |
| **Medical Devices** | New Approach Methodologies for Medical Devices Workshop. 2021. |
| **Biologics** | Report of the 2019 NIST-FDA workshop on standards for next generation sequencing detection of viral adventitious agents in biologics and biomanufacturing. Biologicals 2020. |
| **Drugs** | An FDA/CDER perspective on nonclinical testing strategies: Classical toxicology approaches and new approach methodologies (NAMs). Regulatory Toxicol and Pharmacol 2020. |
| **Veterinary Medicines** | Center for Veterinary Medicines. Advancing New Alternative Methodologies at FDA report 2020. |

# Cross-Cutting FDA Applied Research on MPS

## Lung MPS

### Tobacco Focused

Assessing the respiratory toxicity of dihydroxyacetone using an in vitro human airway epithelial tissue model

Toxicology in Vitro, 2019, 59:78-86

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

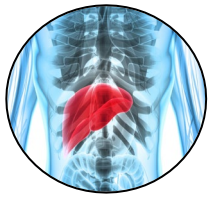
Toxicity of Ortho-phthalaldehyde Aerosols in a Human *In Vitro* Airway Tissue Model

Chem Res Toxicol, 2021, 34(3):754-766

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

International J Molec Sci, 2022, 23(5):2593

## Liver MPS



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

Food Chem Toxicol, 2022,161:112828

### Drug Focused

Liver Microphysiological Systems for Predicting and Evaluating Drug Effects

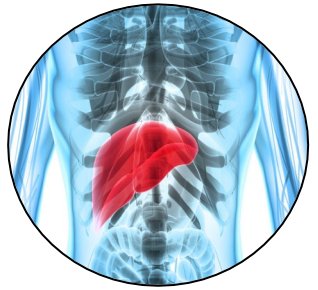
*Clin Pharmacol Ther 2019, 106:139-47.*

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

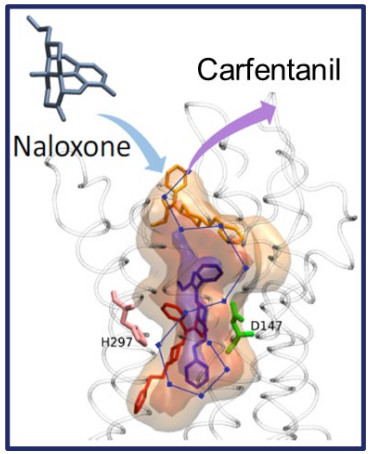
Clin Trans Sci, 2021, 14(3):1049-1061

# Alternative Methods Data Used to Support Regulatory Decision Making

## Safety



## Effectiveness

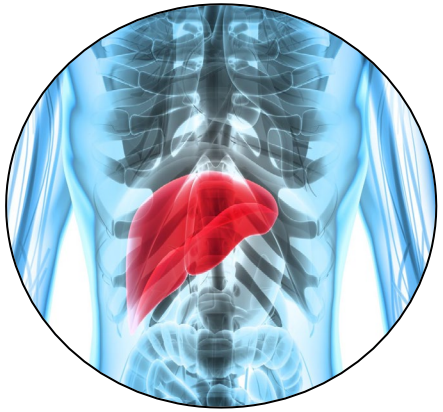


# Alternative Methods Data to Support Drug Approval

- Other drugs in class discontinued from clinical development due to liver toxicity
- Some liver enzyme elevations in rat studies
- **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

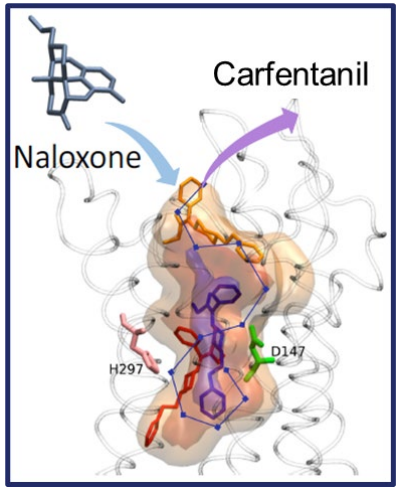
**Nonclinical NDA Review Link**

**Liver Safety**



Additional information: Mechanistic Investigations Support Liver Safety of Ubrogepant | Toxicological Sciences

# 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 to demonstrate efficacy

**FDA-Developed Model Used to Support Approval**

**----------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**

# Summary

- 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

# Next Steps: FDA Science Board Meeting

The FDA Science Board will hear about the Agency's enhanced efforts to spur the development, qualification, and adoption of new alternative methods for regulatory use


Federal Register Notice of Meeting

**June 14, 2022**

# Thank You to Working 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

**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

Additional support: Richard White, Dylan Bruckner

# Thank You