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
- Fostering development of medical products to respond to deliberate and naturally emerging public health threats
- Ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices
- Regulating the manufacturing, marketing, and distribution of tobacco products

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

Alternative Methods Accepted by US Agencies
Transforming Toxicology is a Key FDA Goal

2011

Priority 1: Modernize toxicology to enhance product safety

Office of the Chief Scientist Sponsored Cross-Agency Working Groups:
- Toxicology Working Group
- Alternative Methods Working Group
- Modeling and Simulation Working Group

2017

- 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 specific contexts of use
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
Fill information gaps with applied research to advance new policy and guidance development

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 website: ICH
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**

- **Cosmetics**

- **Tobacco**

- **Medical Devices**

- **Biologics**

- **Drugs**

- **Veterinary Medicines**
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
- 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
- Characterizing the Reproducibility in Using a Liver Microphysiological System for Assaying Drug Toxicity, Metabolism and Accumulation
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**
  o Reproduced observed liver toxicity of other drugs
  o 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

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
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