Overview of Qualification and Application to CIVM

Jeffrey Siegel, MD
Director, Office of Drug Evaluation Sciences (ODES)
OND / CDER / FDA
Complex in vitro Models (CIVM) Workshop
September 28, 2023
Disclaimers

- Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position.
Overview

- Types of drug development tools (DDTs)

- Qualification process for DDTs, including complex in vitro models (CIVMs)

- Challenges for defining context of use (COU)

- Examples of potential COUs
Complex *in vitro* models (CIVMs) have demonstrated potential to become drug development tools (DDTs).
Potential uses of CIVMs in drug development

- Screening compounds for efficacy
- Preclinical safety screening
- Understanding drug mechanism of action
- Drug metabolism, disposition
- Replacing, reducing, refining animal use in preclinical studies

*Some uses are for internal company decision making and out-of-scope for FDA to qualify; others may serve regulatory purposes*

- For use in regulatory setting, CIVM follow similar process as other DDTs
21st Century Cures: Drug Development Tool Qualification

Drug Development Tools (DDTs)

- Biomarkers
- Clinical Outcome Assessments (COAs)
- Any other method, material, or measure that the Secretary determines aids drug development and regulatory review

An Act

Public Law 114–255
114th Congress

To accelerate the discovery, development, and delivery of 21st century cures, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the “21st Century Cures Act”.

Animal Models for use under Animal Rule

ISTAND: Pilot for novel DDTs not addressed by other programs

**Mission:** Accelerate use of novel Drug Development Tools through agency-wide coordination, effective communication, and efficient regulatory review.

**Vision:** To enable the timely incorporation of innovative science and technology approaches into drug development for the benefit of public health.
ISTAND Pilot Process

ISTAND Submission or Referral

ISTAND Continuous Engagement

3-Step Qualification Process

Qualified DDT

Public Meeting
White Paper
Guidance

1Potential outcomes
Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program

Drug Development Tools (DDTs) are methods, materials, or measures that have the potential to facilitate drug development. As described in the 21st Century Cures legislation, DDTs include biomarkers, clinical outcome assessments, and other methods, materials, or measures that aid drug development and regulatory review. To support DDT development efforts, FDA has established qualification programs for biomarkers, clinical outcome assessments, and for animal models for use under the Animal Rule.

The Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program is designed to expand DDT types by encouraging development of DDTs that are out of scope for existing DDT qualification programs but may still be beneficial for drug development.

Examples of submissions that might be considered for ISTAND include, but are not limited to:

- Assessment of use of Clinician-reported outcomes (ClinROs) or measures of patient performance through remote (e.g., telemedicine) study visits rather than collection at clinical sites.

ISTAND@fda.hhs.gov
Accepted LOIs in ISTAND

Two LOIs have been accepted into ISTAND pilot:

- Specificity Screening of Biotherapeutics for Improved Safety Profiling in IND Applications Using the Membrane Proteome Array (MPA)
- Local tolerance of epidurally/intrathecally administered leachables in vitro

LOI submissions for CIVMs have been received by ISTAND but none accepted to date
Qualification is a conclusion that **within the stated context of use**, the DDT can be relied upon to have a **specific interpretation** and application in drug development and regulatory review. Once qualified, DDTs will be publicly available to be used in any drug development program for the qualified context of use.

Additionally, the qualified DDT generally can be included in IND, NDA, or BLA submissions without needing FDA to reconsider and reconfirm its suitability.
The Specific Context of Use for a DDT Drives the Extent of Evidence Needed for Qualification

Analytical Validation
(establish performance and acceptance characteristics of the biomarker assay)

- Reference Ranges/Decision Points
- Pre-Analytical and Assay Performance Characteristics
- Analytical Rigor/Reproducibility
- Sample Handling/Stability

Clinical Validation
(establish that the DDT acceptably identifies, measures, or predicts the concept of interest)

- Study Design Acceptability
- Clinical Meaningfulness/Decision Points
- Benefit/Risk Assessment
Interconnected paths to DDT validation

Drug approval process (IND)

DDT qualification program

Scientific community consensus
DDT Qualification and 21st Century Cures DDT Legislation*

Biomarker Qualification Process

- **Letter of Intent**: Is a request for the qualification of a specific biomarker for a proposed context of use (COU) in drug development.
- **Qualification Plan**: Describes biomarker development plans for the COU and provides data on analytical validation of the biomarker measurement.
- **Full Qualification Package**: Contains all accumulated data to support the qualification of the biomarker for the proposed COU.
- **Qualification Determination**: Is FDA’s determination on qualification of the biomarker for the proposed COU based on a comprehensive review of the full qualification package.

* Similar process for biomarkers and other DDTs
For use as potential drug development tools, CIVMs must:

• yield reproducible results
• perform under well-defined quality control criteria
• be developed for a specific context of use (COU) and demonstrate to improve or be equivalent to the outcome of currently used techniques or provide novel insight
Considerations for CIVMs

- CDER recognizes the need to evaluate and utilize new approach methodologies (NAMs) to improve our ability to predict safety risks in humans.
- CDER is committed to the principles of the “3Rs” (replace, reduce, and refine) of animal testing.
- Evidence required to replace an existing method greater than to supplement existing methods.

However:
- Methodologies that pertain to internal decision-making by pharmaceutical companies are generally out-of-scope for qualification program.
- Context of use can address a gap pertinent to regulatory decision-making, e.g., where current models leave uncertainty.
- An acceptable context of use may provide the same information as obtained with a current method if it addresses the “3Rs” or is better in some other way.
FDA surveyed CDER review staff to determine toxicology knowledge gaps that could be potentially addressed by new methodologies, such as CIVMs.

Example:

• Drug-induced seizures in humans are a significant safety concern. Animal models can detect risk but not levels of exposure associated with risk.
  • New alternative methods with specific COUs to predict human-relevant seizure risk of a drug, including cross-species relevance, could be developed to inform the safety of a drug’s effect on the central nervous system.
  • A potential COU statement might read, “Use of a battery of in vitro ion-channel functional assays to predict in vivo human Cmax levels of small molecule drugs associated with increased risk of seizures (or absence of seizures).”

AM Avila. Reg Tox and Pharm. 139 (2023) 105345
Detection of risk of rare and idiosyncratic toxicities:

- CIVM could aid in predicting the potential of a drug to induce rare and idiosyncratic toxicities, e.g., drug-induced liver injury (DILI), immune-mediated toxicity, CNS toxicity.
- A potential COU statement for DILI might address use of a CIVM as part of a weight of evidence assessment to predict a drug’s risk for liver toxicity.
Example of potential COU – assessing risk of embryofetal toxicity

International Council for Harmonization (ICH) guidance S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals (ICH S5R3, 2021) provides examples for which an alternative method could be acceptable for regulatory use in CDER:

• “for pharmaceuticals that are expected to adversely affect embryofetal development based on mechanism of action, pharmacologic class or target biology, it can be appropriate to confirm this activity in a qualified alternative assay(s)”

• A COU could be written that enables the use of a CIVM capable of detecting the potential for malformations or embryofetal lethality to reduce animal testing within in vivo embryofetal development studies.

AM Avila. Reg Tox and Pharm. 139 (2023) 105345
• CDER recognizes the need to evaluate and utilize CIVM and other novel methodologies to improve our ability to predict safety risks in humans
• Validation of CIVM for a specific COU involves rigorous validation for the specific context of use in drug development
• The COU for a CIVM could address gaps and challenges in nonclinical safety assessments
• Proposals for use of CIVM for regulatory purposes can be submitted as part of the IND process or through the FDA DDT qualification program ISTAND