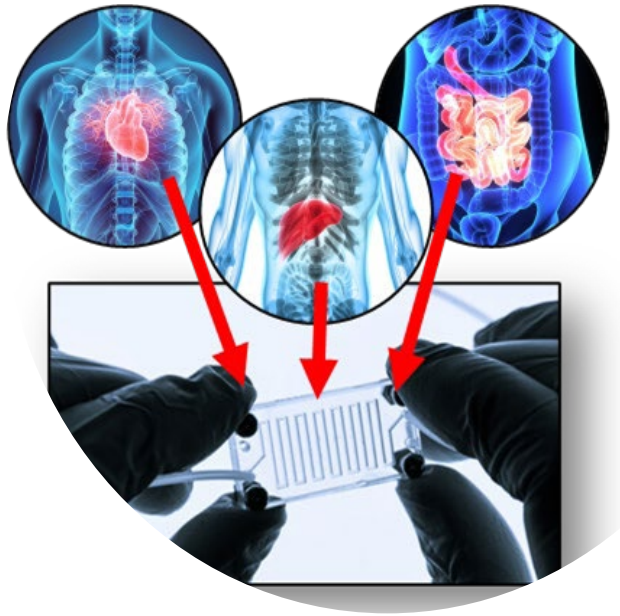
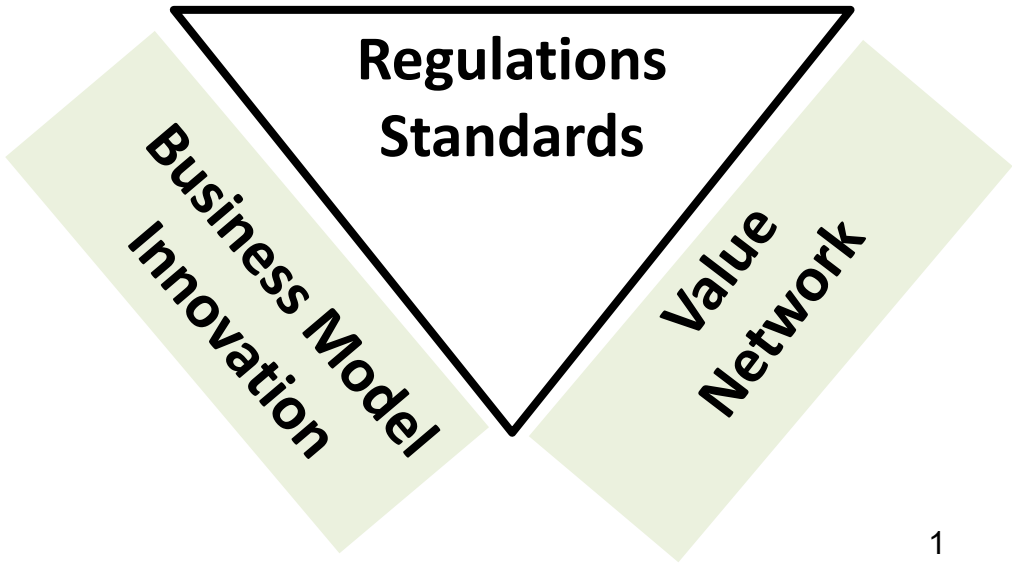
New Approach Methodologies
An FDA Perspective



ICCVAM Public Forum

Steven Kozlowski
Chief Scientist
Office of the Commissioner, FDA

NIH Neuroscience Center Building, Rockville, MD
July 30, 2026

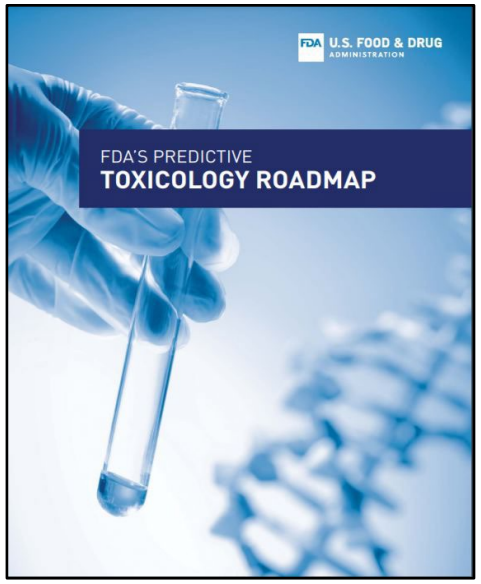


Transforming Toxicology is a Key FDA Goal

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
- New Alternative Methods Group
- Modeling and Simulation Working Group

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

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

MOUs

MOU 225-22-005

Between
NIH/NIEHS/DNTP
NIH/NCATS/DPI
EPA
FDA

Concerning Research to Advance Toxicity Testing (Tox21)

MOU 225-23-003

Between
NIH/NCATS
FDA

To promote the advancement of Microphysiological Systems

Regulations Standards

Section 3209 of the **Consolidated Appropriations Act, 2023** amended section 505 of the FD&C Act to add and define the term "nonclinical test," which clarifies that drug application sponsors can submit results from alternative methods to animal testing to support INDs for human drugs.

Guidance on assessing specific types of alternative methods

Guidance on qualification process

Topical guidance on specific safety or development areas

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
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Roadmap to Reducing Animal Testing in Preclinical Safety Studies

Executive Summary

This roadmap outlines a strategic, stepwise approach for FDA to reduce animal testing in preclinical safety studies with scientifically validated new approach methodologies (NAMs), such as organ-on-a-chip systems, computational modeling, and advanced *in vitro* assays. By partnering with federal agencies like NIH and VA through ICCVAM, FDA can accelerate the validation and adoption of these human-relevant methods, improving predictive accuracy while reducing animal use. This transition will enhance public health by streamlining drug development and ensuring safer therapies reach patients faster, while positioning FDA as a global leader in modern regulatory science and innovation.

roadmap link

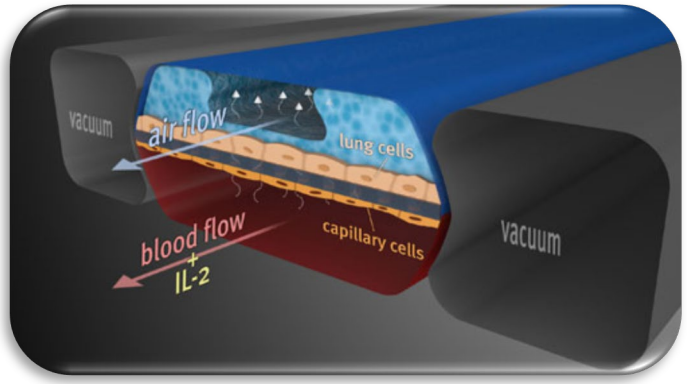
A NEW CALL FOR ACTION

New Alternative Methods ← NAMS → **New Approach Methodologies**

FDA should invest in the development of NAM models (through research collaborations with NIH and other venues)

Select ORES/OCS Supported NAMS-Related Research

- Organs-on-Chips for Radiation Medical Countermeasures – Extramural (Wyss Institute for Biologically Inspired Engineering)



- Extended Longevity of 3D Tissues and Microphysiological Systems for Modeling of Acute and Chronic Exposures to Stressors – Extramural (NASA)

The Roadmap specifically lists chronic toxicity

In Silico

To minimize animal testing, it will be essential to use an integrative strategy

FDA

Digital Twin

Rat Study Design:
- Chemical structure
- Treatment duration
- Dose

Animal GAN

Rat Study Results:
38 clinical pathology measurements

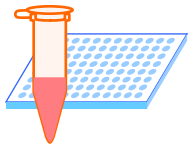
Weida Tong NCTR

DeepDILI versus

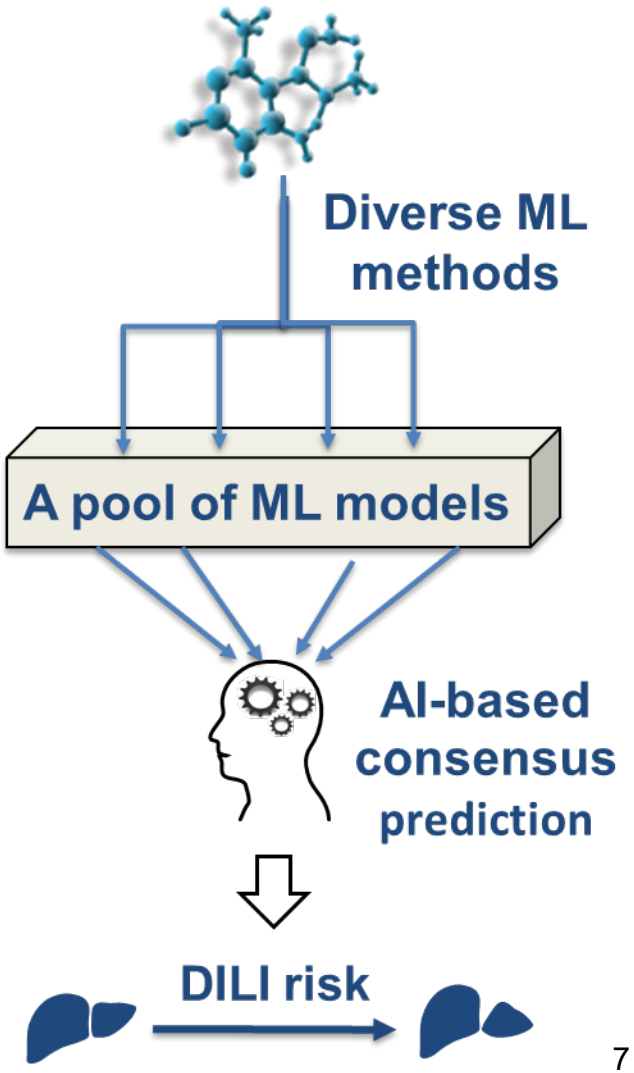
Animal Models: ~50% accuracy in predicting human DILI –past literature review

DeepDILI Model: ~70% prediction accuracy using chemical structure
Trained pre-1997, Tested post-1997

DeepDILI +

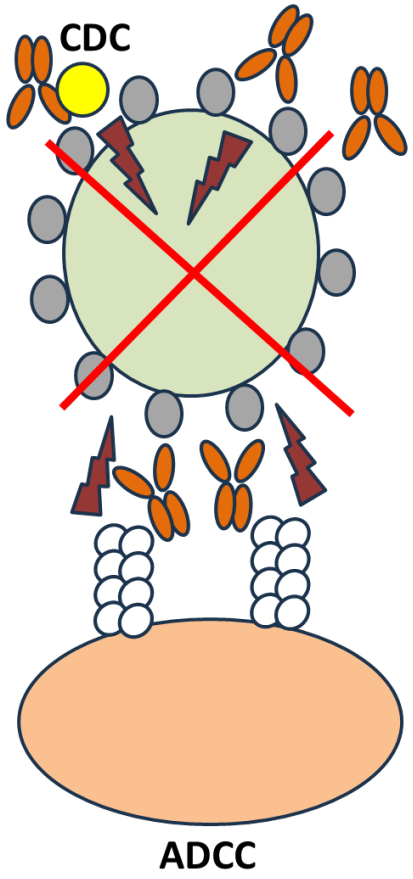


[Integrating in vitro and in silico NAMs for enhanced prediction of drug-induced liver injury, ScienceDirect]



This Roadmap was intended to begin with monoclonal antibodies…

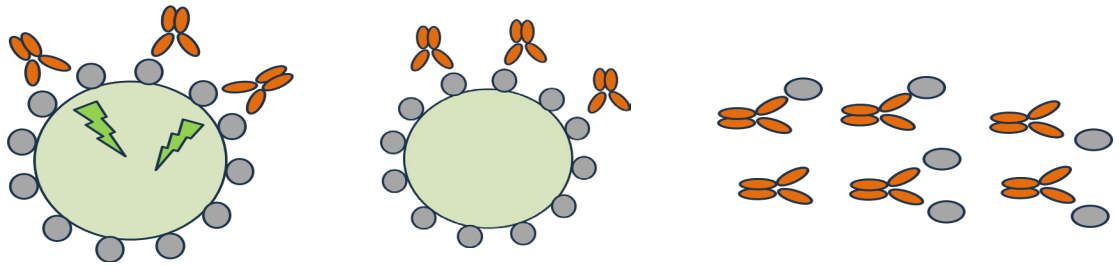
Often On-target Toxicity; Challenge to find relevant animal models



Re-evaluating the need for chronic toxicity studies with therapeutic monoclonal antibodies, using a weight of evidence approach

Regulatory Toxicology and Pharmacology 138 (2023) 105329

Isotype and mutations, effector functions, valence, half-life , and half molecule exchange



MABS
2018, VOL. 10, NO. 1, 1–17
https://doi.org/10.1080/19420862.2017.1389364

Taylor & Francis
Taylor & Francis Group

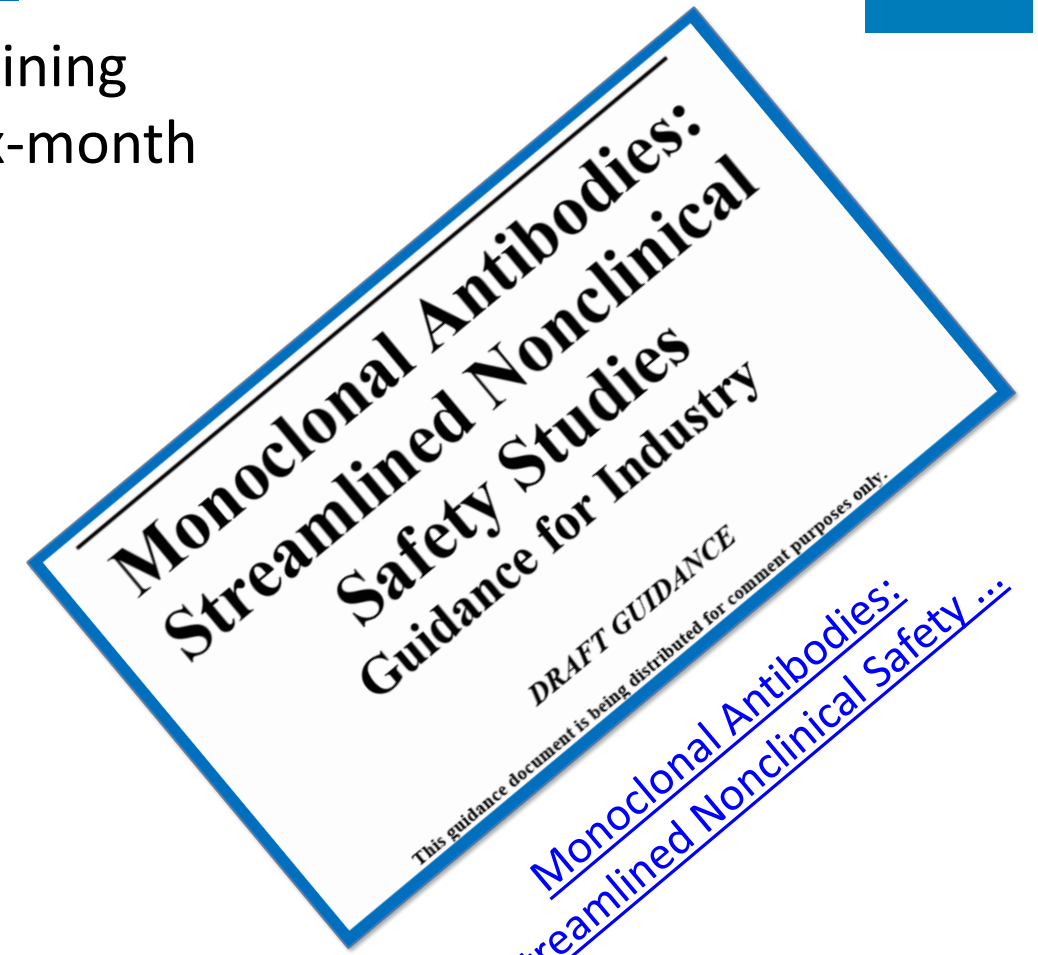
PERSPECTIVE

Check for updates

Safety testing of monoclonal antibodies in non-human primates: Case studies highlighting their impact on human risk assessment

Progress with monoclonal antibodies… Draft Guidance (1)

CDER draft guidance issued December 02, 2025,outlining specific product types for which the FDA believes six-month NHP toxicity testing can be eliminated or reduced.



3-month toxicology and **Weight of Evidence** risk assessment will generally be sufficient for non-rodent chronic toxicology studies. **WoE** includes:

- Mechanism of action and pharmacology data
- Literature… potential toxicities… molecular target
- …toxicology and pharmacokinetic (PK) data in relevant species
- …off-tissue binding and potential 2nd effects
- Tox findings in animals and humans, … the same target
- Other nonclinical data as scientifically justified (e.g., NAMs, transgenics, surrogates).

Progress with validating all NAMs…

Draft Guidance (2)

FDA published a draft guidance document "General Considerations for the Use of New Approach Methodologies" on March 18, 2026.

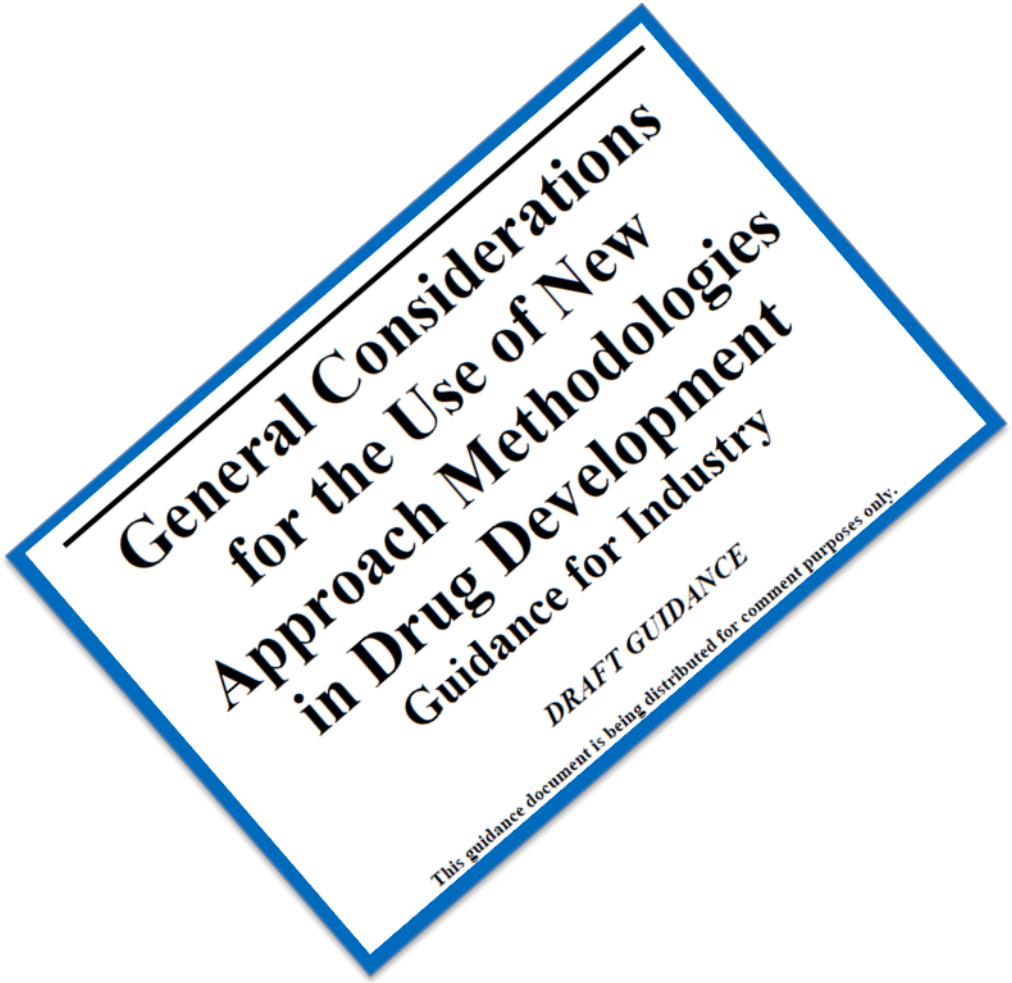
This guidance document establishes four core validation principles… for demonstrating an alternative method is acceptable.

(1) Context of Use

(2) Human Biological

(3) Technical Characterization

(4) Fit-for-Purpose



FDA Advances Drug Development Innovation - Establishing ISTAND as Permanent Qualification Program 7/31/2025

Drug Development Tool Qualification Process

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[FDA Advances Drug Development Innovation by Establishing ISTAND as Permanent Qualification Program | FDA]

By partnering with federal agencies…

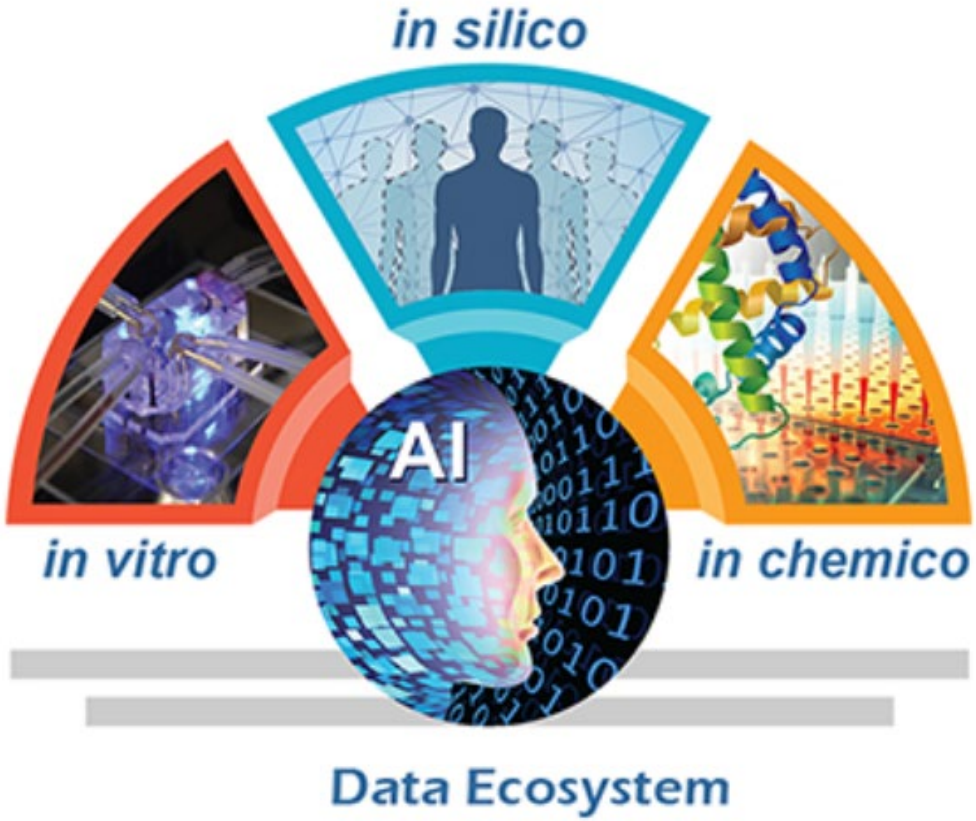
Collection of Alternative Methods for Regulatory Application (CAMERA)

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

UNITED STATES ICCVAM
Advancing Alternatives to Animal Testing

FDA

FDA-NIH Workshop: Reducing Animal Testing 7/7/2025



MOU 225-25-012

DHHS, NIH and FDA
CONCERNING
Coordinated Efforts
NIH COMPLEMENT-ARIE
8/27/2025

- [New Approach Methodologies (NAMs) | FDA]
  Integrated website with the one-year progress report with many of these accomplishments

Reducing Animal Testing in Nonclinical Studies

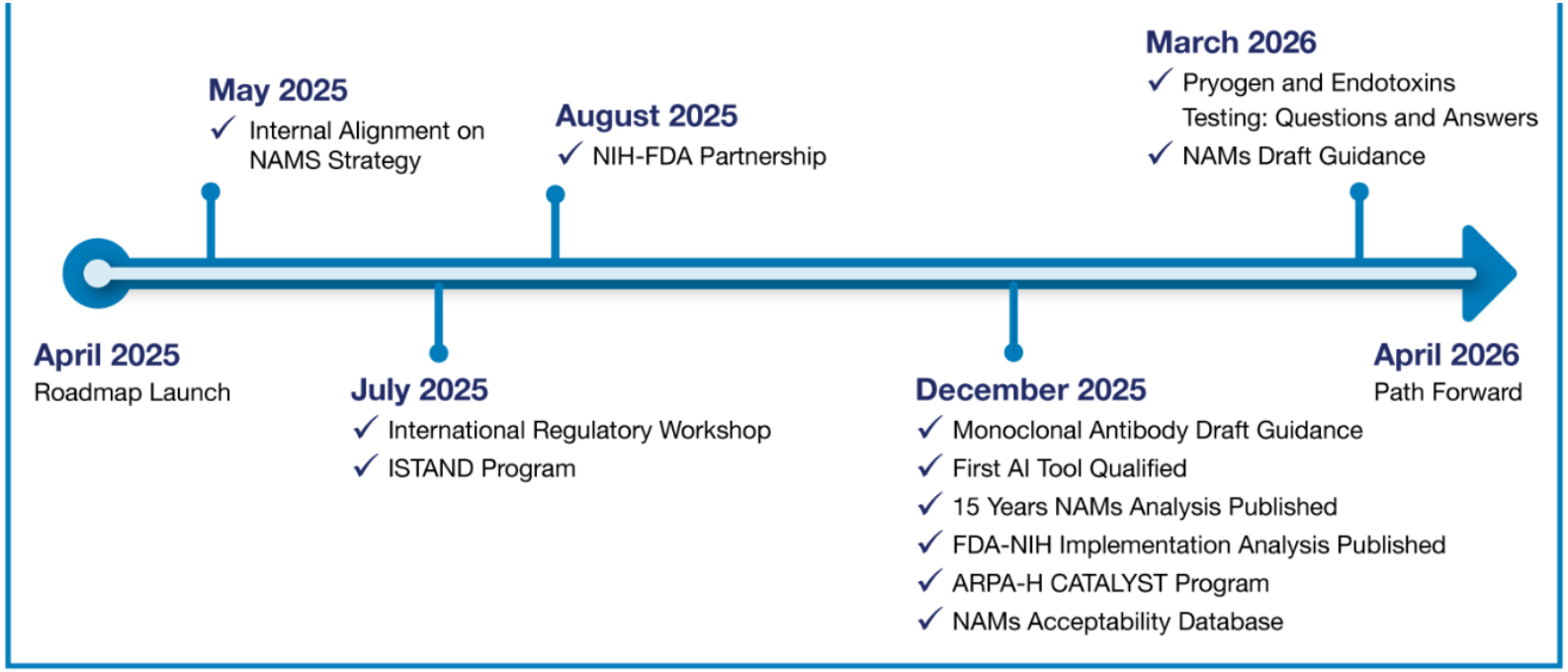
Year One Progress and the Path Forward

APRIL 2026

- Eliminating Unnecessary Animal Testing | Public Health | JAMA | JAMA Network

CDER/Office of New Drugs Streamlined Nonclinical Studies and Acceptable NAMs

A Year of Progress



Post Year 1 Roadmap

Oncology Pharmaceuticals: Streamlined Nonclinical Safety Studies for Biologics and Conjugated Products: Draft Guidance (May 2026, OCE)

Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing Draft Guidance (June 2026, CBER) [NAMs mentioned]

- 5/13/2026, FR Notice -Biomarker Incubator: Urinary Kidney Safety Biomarkers; RFI
- 5/26-5/29/2026- 2026 MPS World Summit
- 6/22-6/25, 2026 BIO International Convention (NAMs was a topic)
- 6/29/2026, Triangle CERSI: 2026 NAMeRS Summit,
- 6/3/2026- FDA Accepts First In Silico DDT Under ISTAND to Help Predict DILI
- 7/15/2026, Advancing Biomarker Use in Regulatory Review: (by Duke-Margolis)
- 7/28/2026, Hybrid Workshop: ICH S7A and New Approach Methodologies (NAMs) in Safety Pharmacology (hosted by FDA, HESI, and SPS)
- 7/28/2026 Data Request (DR001): pH Cycling Model for Fluoride OTC Dentifrice Products

Microphysiological Systems (MPS) Training Course (Module I & II) - now public.

Two prior WGs → NAM Program WG and Steering Committee established

Collaboration with the Advanced Research Projects Agency for Health (ARPA-H)

- ARPA-H – the HHS "moonshot" agency for health research – has awarded multiple R&D teams through its CATALYST program to link advanced*in vitro* data generation and *in silico* models (e.g., PBPK, QSP/QST, AI/ML-enhanced) to improve safety and toxicity prediction and eliminate animal testing in the non-clinical package
- ARPA-H is sponsoring research at CDER to 1) harvest toxicology data within FDA, 2) develop *in silico* models, 3) create data sharing mechanisms, and 4) develop pathways for submission and assessment of these combinatorial NAMs
- CDER will also engage directly with CATALYST awardees to provide regulatory perspective

Research

- CTP is researching physiologically relevant human bronchial airway air-liquid interface in vitro models to assess cytotoxicityand genotoxicity of ENDS exposures

- MOU: Coordinated Efforts on NIH-FDA Nutrition Regulatory Science Program ("PROJECT") **MOU 225-26-002** | FDA - NAMs for evaluating complex food matrices
- NCTR work on dermal models to support cosmetics

OPERATION TRIALBLAZER

HHS Roadmap to Maintaining U.S. Leadership in Early Clinical Research and Development

FDA Actions to Accelerate and Modernize Early Clinical Development

FDA

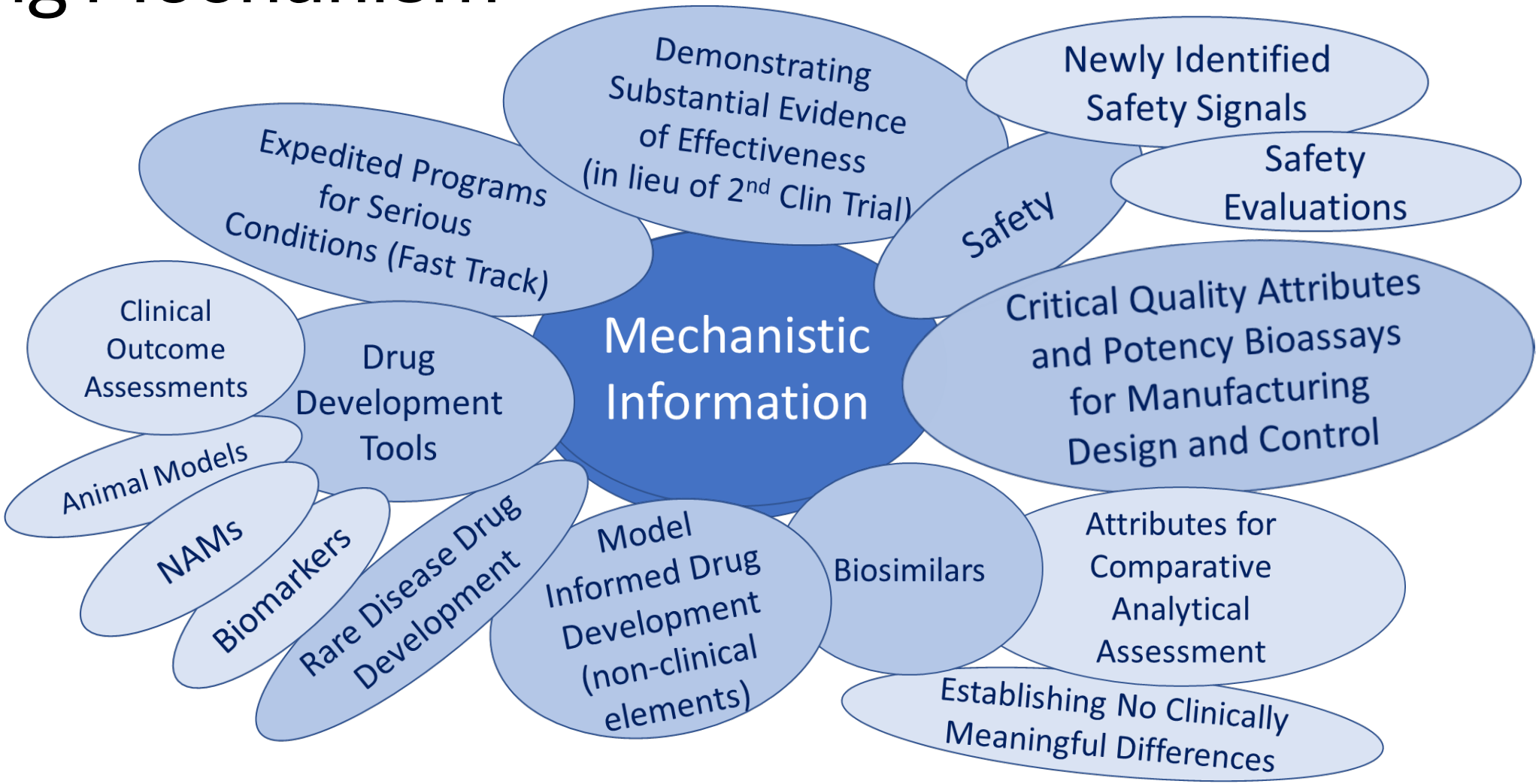
- Expedited Investigational New Drug Pilot Program Request for Information qualified research institutions to work with sponsors
- Phase 1 IND Navigator Webpage consolidates IND requirements, guidance documents, and practical examples
- Phase 1 IND Chemistry, Manufacturing, and Controls (CMC) Webpage generate and submit only the data that is needed
- New Approach Methodologies (NAMs)—including AI-powered models, human organ-on-a-chip systems, and real-world data—accelerating safer treatments to patients….

M15 General Principles for Model-Informed Drug Development (June 2026)

Quantitative Systems Pharmacology (QSP)-Based Dose Selection for Minimum Anticipated Biological Effect Level (MABEL) in First-in-Human (FIH) Trials
Draft Guidance (June 2026)

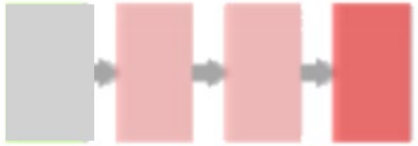
Leveraging Mechanism

The word mechanism appears ten times throughout the document



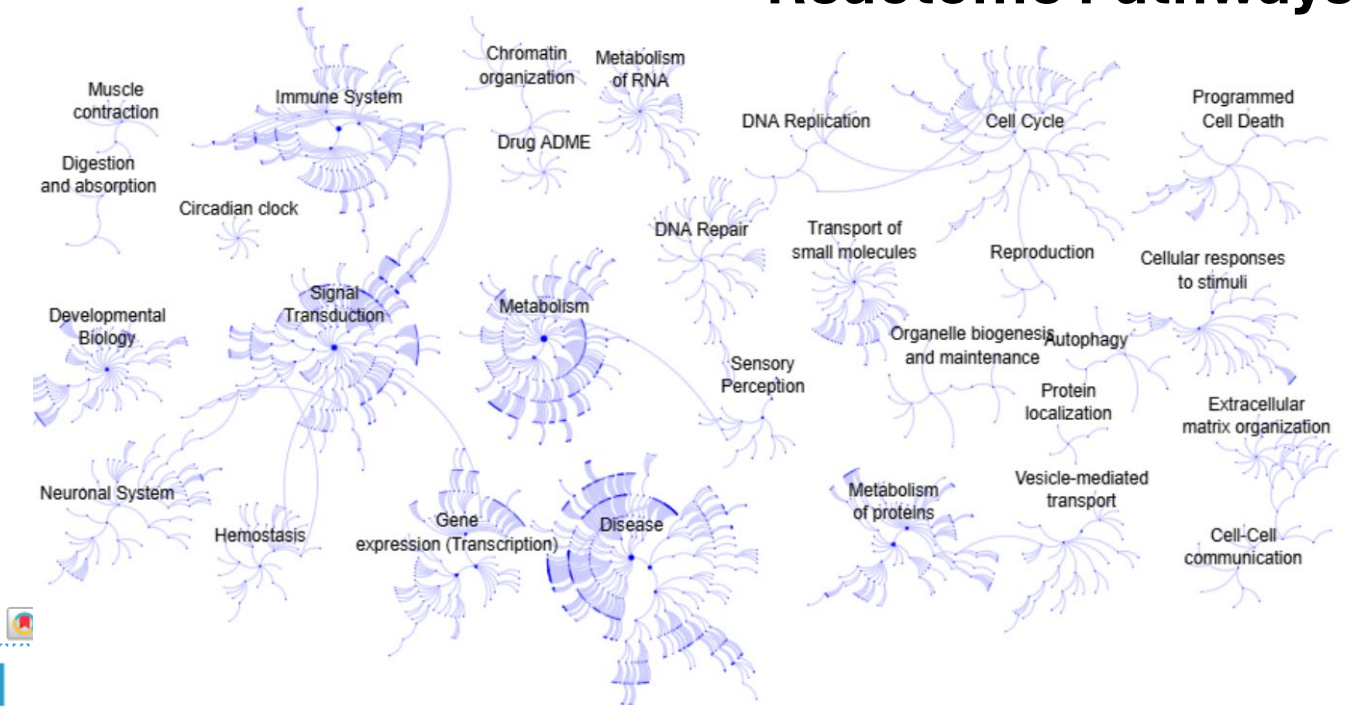
- *Common knowledge - information widely known and accepted [by relevant community]*
- *When Everyone Knows That Everyone Knows (S Pinker)*

Connecting & Annotating Pathway Information



AOP

Reactome Pathways



scientific **data**

OPEN

DATA DESCRIPTOR

A curated gene and biological system annotation of adverse outcome pathways related to human health

Laura Aliisa Saarimäki[1,2], Michele Fratello[1], Alisa Pavel[1], Seela Korpilähde[1], Jenni Leppänen[1], Angela Serra[1,2,3] & Dario Greco[1,2]✉

Genes

Gene Products

Pathways

Gene ontologies

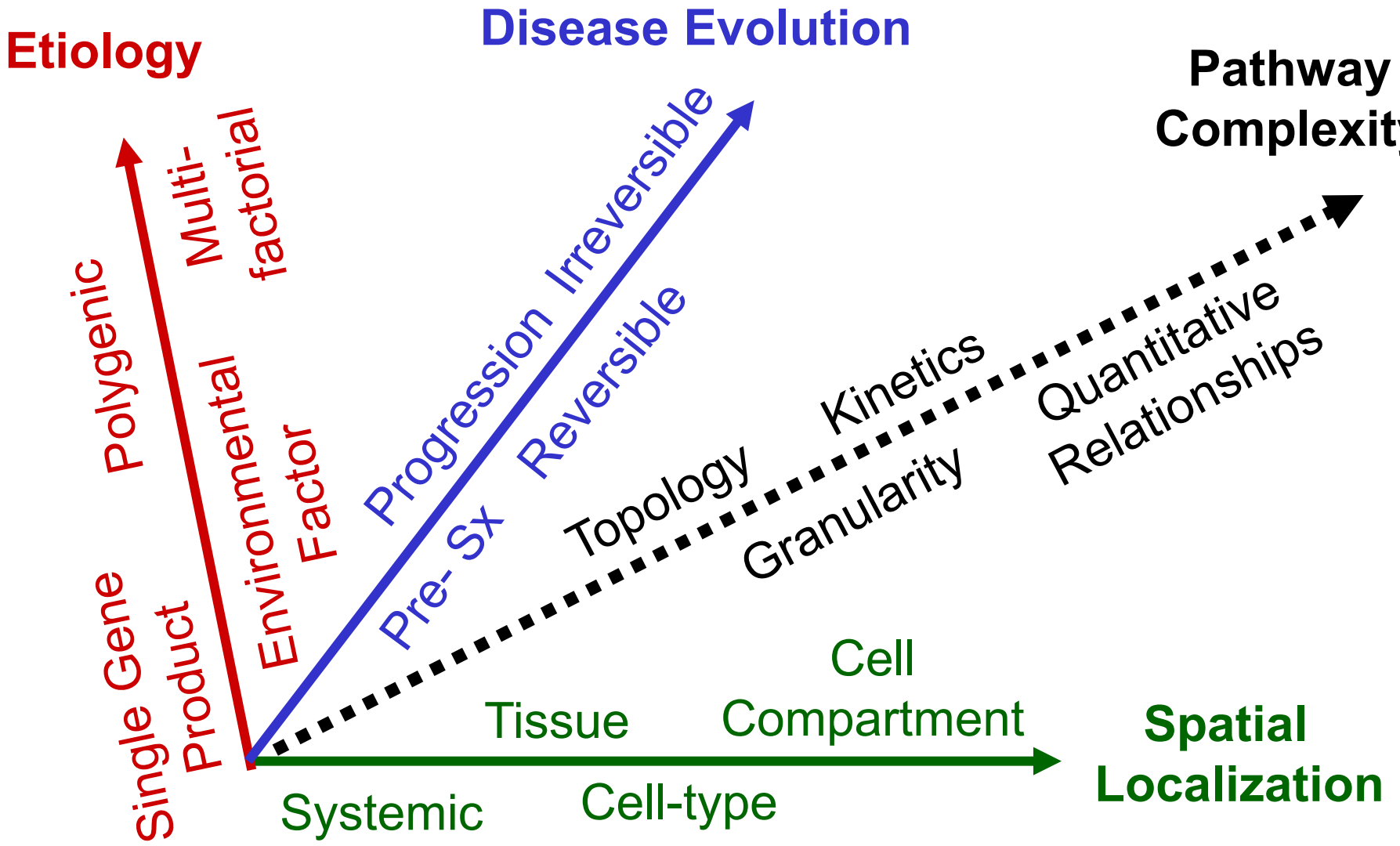
Phenotypes

Pathways are a topology within a space

Biological Atlases

- Organ Systems
- Organs
- Tissues
- Cells
- *Organelles*

Integrating Mechanistic Information



Lower Left Quadrant

Near Origin

- **Single Factor Etiology**
- **Reversible**
- **Understood Pathway**
- **Systemic**

Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause

Draft Guidance for Industry

This guidance document is being distributed for comment purposes only.

Scoring Evidence

GRADE: an emerging consensus on rating quality of evidence and strength of recommendations

Quality	Evidence
High	RCTs with no important limitations; very unlikely to change
Moderate	RCTs with limitations, or strong observational studies; may change
Low	Observational studies with limitations; likely to change the estimate
Very Low	Unsystematic clinical observations, effect is uncertain

- Results in several different experimental systems are consistent
- The overall mechanistic database is coherent
- Experiments showing that suppression of key mechanistic processes suppresses tumour development can be influential
- Typically, a substantial number of studies on a range of relevant end-points are available in one or more mammalian species

Mechanistic Data Can Play a Pivotal Role in *IARC Monographs* Evaluations When Human Data Are Less Than *Sufficient*

Are the mechanistic data "strong", "limited", or "inadequate"?

Claude Sonnet 4.6 – Mechanistic Evidence

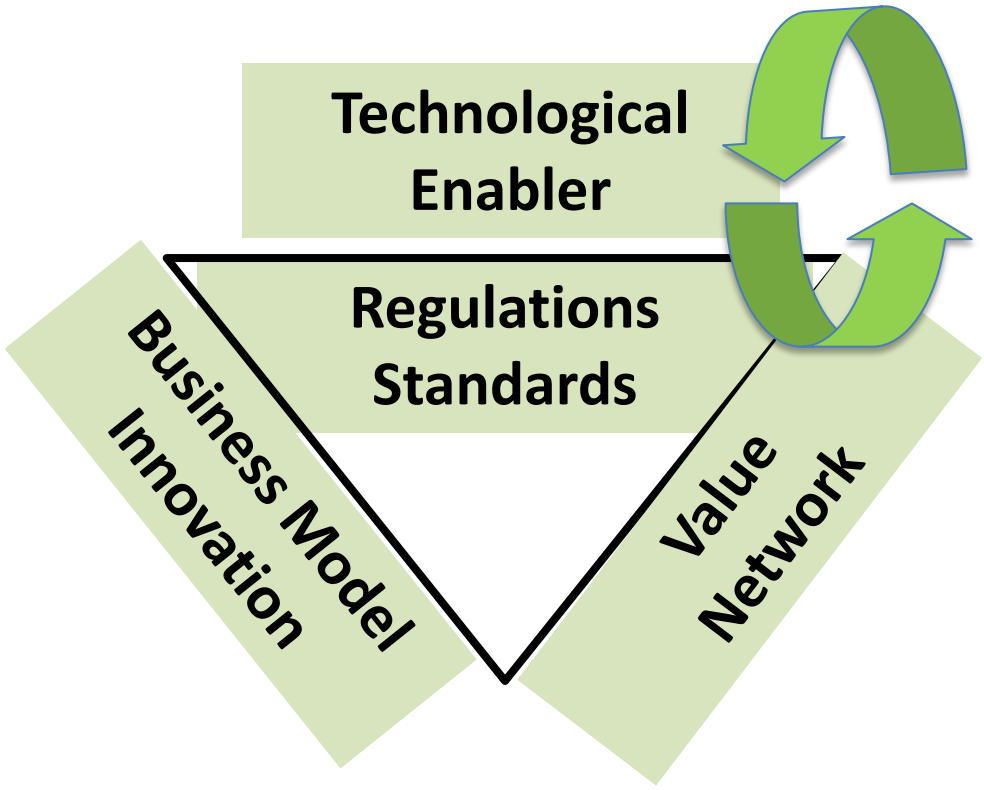
Framework	Best For	Mechanistic Evidence Role
GRADE	Clinical guidelines	Modifier/supporting factor
IARC Monographs	Carcinogen classification	Explicit, graded third stream
Navigation Guide	Environmental health	Explicit, graded third stream
OHAT/NTP	Toxicological hazard assessment	Explicit, graded stream
Bradford Hill	Causal inference, any domain	Plausibility as one criterion
Klimisch	Individual toxicology study quality	Primary rating tool

Mechanistic Framework

- Are there gaps between what we leverage from mechanistic information and what is possible to leverage?
- Is there a framework that can help close some of these gaps?
- Can a framework apply across the many different uses of mechanistic information (e.g., quality of information)?
  - Clearly **every COU and scenario are different** but are some aspects of information quality common to mechanistic data (the “g factor” of mechanism)?
- Can existing frameworks, such as AOP, be expanded or leveraged?
- Can get agreement on the principles to grade and integrate mechanistic information?
- Are we at a point in time when such a framework can be developed?

The Goal

- New "Approach" methodologies and validation
- Unstick the gears between technology capabilities and regulatory standards - advancing both.



Thank You!

- Tracy Chen
- Rodney Rouse
- Tracy Beth Hoeg
- Vanetha Sekar
- Jeff Siegel
- Weida Tong
- Dana van Bemmel
- Tucker Patterson
- & Others