U.S. FOOD & DRUG ADMINISTRATION

Microphysiological Systems (MPS): Bridging Human and Animal Research

An FDA/CDER Perspective

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The content of this presentation represents the opinions of the speaker and does not necessarily represent the official position of CDER and FDA.

DISCLAIMER

New Approach Methodologies (NAMs): The CDER Definition

"CDER considers NAMs to include a broad range of methods such as in vitro, in chemico, and in silico methods. In vivo methods can also be considered NAMs when they improve predictivity, shift studies to phylogenetically lower animals, or otherwise help replace, reduce, and refine animal use (i.e., the 3Rs) in development programs."

Avila, *et al*. *An FDA/CDER perspective on nonclinical testing strategies: Classical toxicology approaches and new approach methodologies (NAMs).* Regulatory Toxicology and Pharmacology 114 (2020).

FDA Draft Definition

FDA Draft Definitions

Microphysiological System (MPS): A microphysiological system is an in vitro platform composed of cells; explants derived from tissues/organs; and/or organoid cell formations of human or animal origin in a micro-environment that provides and supports biochemical/electrical/mechanical responses to model a set of specific properties that define organ or tissue function.

Organ-on-a-chip: Organ-on-a-chip is a miniaturized physiological environment engineered to yield and/or analyze functional tissue units capable of modeling specified/targeted organ-level responses.

CDER experience with complex in vitro models in regulatory applications

Searched CDER's electronic document room for study reports in section M4 of IND/NDA/BLAs

- ***Microphysiological*: 15 results – but all are just in literature references**
- ***Liver chip*: 2 results – but just in a discussion about possible follow up studies**
- ***Reconstructed human epidermis*: 115 – mostly skin corrosivity and irritation**
- ***Organoids*: 83 results – mostly pharmacology; examples: bronchial epithelium, intestinal (including from patients with disease), retinal**
- ***Spheroids*: 760 results – many are histopath results; 78 in "other toxicity studies" – mostly hepatocyte, also thyroid, and angiogenic assays**
- ***iPSC*: 178 results – mostly pharmacology; hepatocytes, neurons, cardiomyocytes**

- **No hits for organ chip, tissue chip, brain chip, kidney chip, microbrain, microphysiological systems**

Code of Federal Regulations
21 CFR Part 312.23

- **(8)** ***Pharmacology and toxicology information.*** Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations.

- **(ii)** ***Toxicology. (a)*** An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

ICH Guidance

M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION. A. Objectives of the Guidance (1.1)

This guidance should facilitate the timely conduct of clinical trials, reduce the use of animals in accordance with the 3R (reduce/refine/replace) principles, and reduce the use of other drug development resources. Although not discussed in this guidance, consideration should be given to use of new in vitro alternative methods for safety evaluation.

Some Guidances Explicitly Describe Alternative Approaches

- ICH S3 Q&A - microsampling
- **ICH S5(R3)** - *in vitro*, *ex vivo* and nonmammalian embryofetal toxicity
- ICH S10 - *in chemico* and *in vitro* phototoxicity
- FDA Draft Nonclinical Immunotoxicity guidance– *in silico*, *in chemico*, and *in vitro* skin sensitization methods

Other alternatives routinely accepted

- Ocular irritation - OECD Guidelines 437, 438, 460, 491, 492, 494
- Skin irritation – OECD Guideline 439

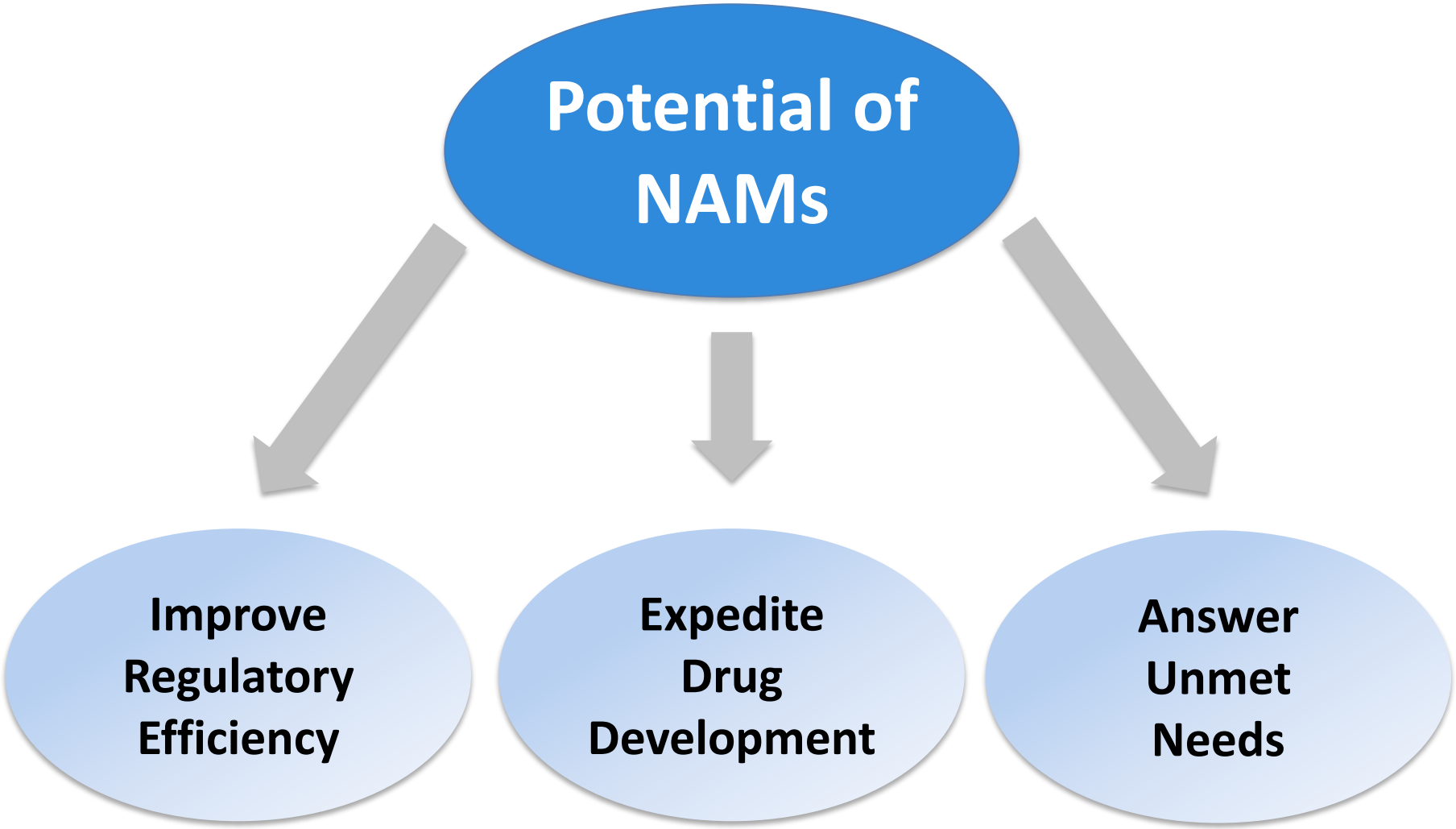
Guidances Allow Justified Use of Alternative Methods

Example FDA guidance wording:

"FDA supports the principles of the 3Rs (replace/reduce/refine) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, and feasible. FDA will consider whether the alternative method is adequate to meet the nonclinical regulatory need."

FDA Draft Guidance for Industry: Nonclinical Safety Evaluation of the Immunotoxic Potential of Drugs and Biologics (Feb 2020)

The CDER Perspective



Current safety testing paradigm (CDER)

Key Issues Addressed by Pharmacology and Toxicology Studies Supporting Pharmaceutical Development

- Pharmacological effects and mechanism(s) of action
- Risk attributes of drug ADME
- Safe “first in human” starting dose
- Safe maximum exploratory doses in early clinical trials
- Possible consequences of chronic exposure
- Risks for special populations (e.g., pediatrics)
- Specific parameters to monitor more closely in clinical trials
- Risks that are difficult or unethical to assess in humans
- Mechanistic understanding of an adverse biological change observed in animals or humans

General Considerations for a NAM

Scientific Evidence

- Is the assay fit for its intended purpose?
- Does the method improve the current testing strategy?

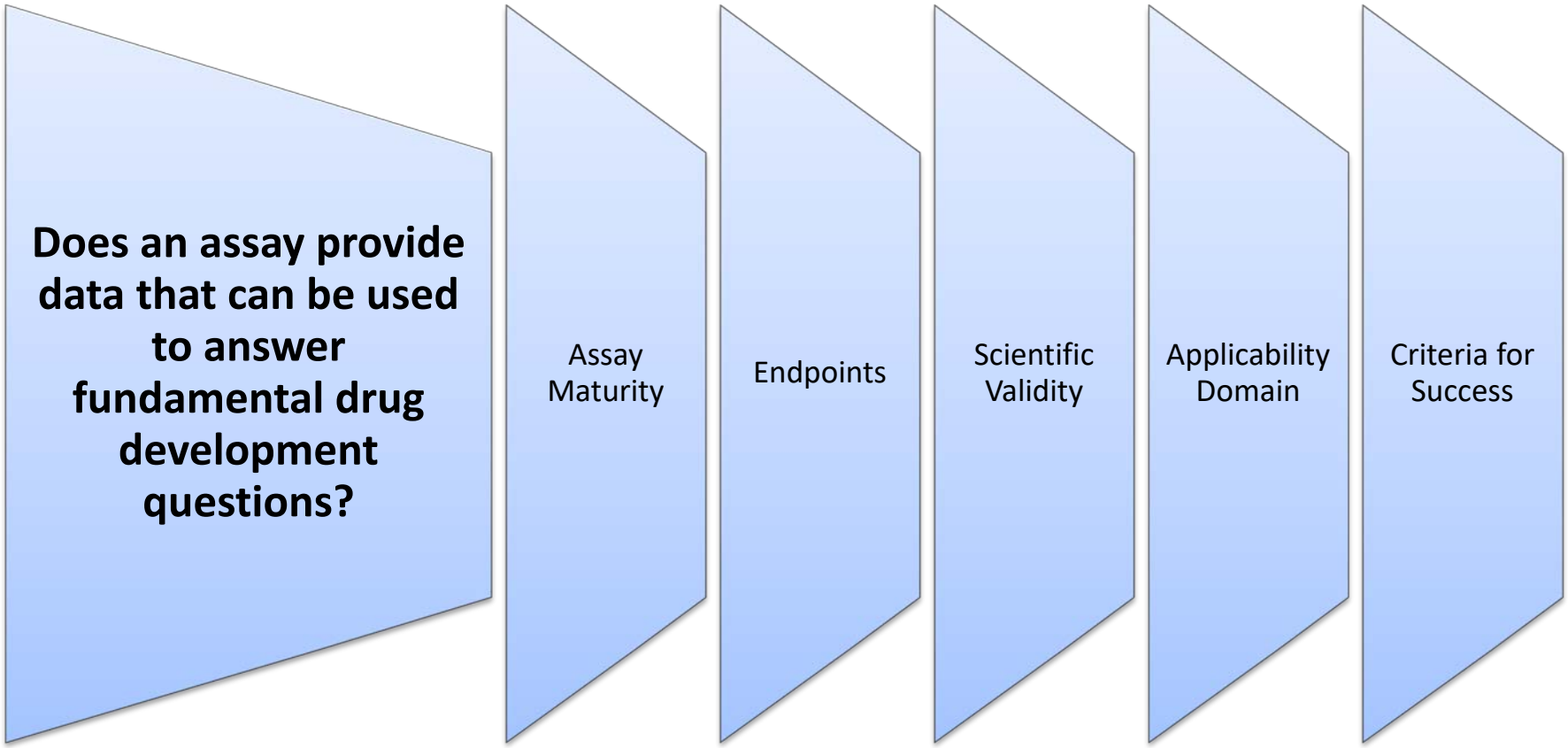
Scientific Confidence

- Does the scientific community agree the assay is suitable?
- Does the new method inform on the safe use of a drug?

Scientific Need

- Will the new approach add value?
- Is there a clear regulatory need for the assessment?

Moving Toward Regulatory Use



Context of Use

What Scientific Question Needs to Be Answered And For What Purpose?

- How much "validation/qualification" is needed for a particular assay will depend on the particular context of use.

- Helps define acceptable applicability domain and limitations
- Context could be expanded over time

Principles for Validation

1. Rationale for assay – need and purpose
2. Relationship of endpoint to in vivo effect of interest, also limitations
3. Detailed protocol
4. Intra-test variability, repeatability and reproducibility of the test method within and amongst laboratories
5. Test method's performance must have been demonstrated using a series of reference chemicals
6. Performance of a test method should be evaluated in relation to existing relevant toxicity data
7. Data supporting the validity must be available for review
8. Data should be obtained in accordance with GLPs

*ICH S5(R3) Annex 2: Qualification of Alternative Test Systems for Regulatory Acceptance

(adapted from OECD Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment)

How the Agency Supports NAMs

Partnerships with Scientific Organizations

- ICH
- ICCVAM
- CiPA/HESI
- IQ Consortium

Internal Scientific Working Groups

- Alternative Methods Working Group (AMWG)
- PTTC Subcommittees
- ISTAND
- Toxicology Working Group

Training and Seminars

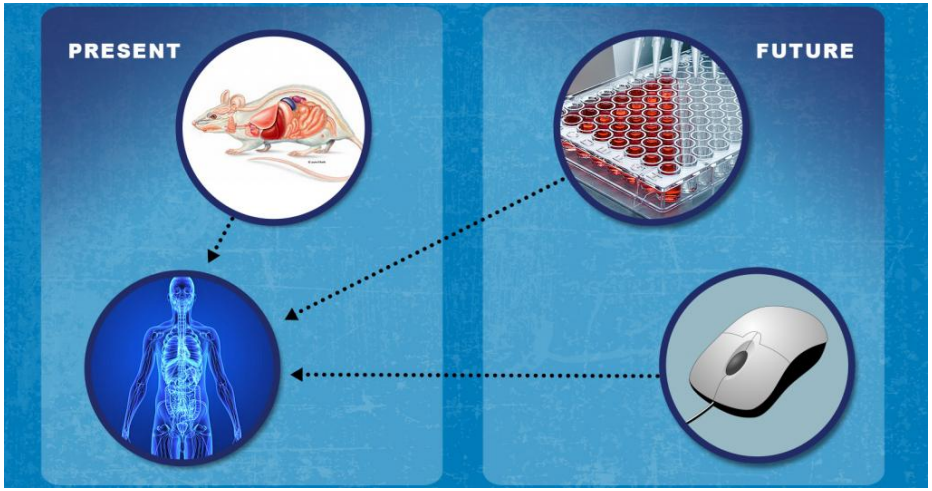
- Giving presentations as well as attending
- Both internal and external (this talk!)

Collaborations with FDA Laboratories/Stakeholders

- Division of Applied Regulatory Science (DARS/CDER) technology evaluations
- NCTR evaluations
- Alternative Methods Working Group (AMWG)

Alternative Methods Working Group (AMWG)

- Under Office of Chief Scientist, Office of Commissioner, FDA
  - Contact: Alternatives@fda.hhs.gov



- Strengthen FDA's commitment to promote/use of new technologies to better predict efficacy and safety
- Coordinate research, training, and discuss around new, emerging methodologies across FDA
- Interact with partners/stakeholders to facilitate discussion and development of performance criteria for assays
- Explore use of such technology for regulatory science applications

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

- Pilot creates a pathway for developers to submit proposals for novel approaches that don't have an existing regulatory path.
- The pilot provides:
  - Early engagement with developers and early FDA input – before the novel approach is tried in an IND development program or submitted within an NDA
  - New mechanisms to efficiently collaborate and share knowledge of new tools throughout divisions, offices, and centers, creating more consistency on FDA's advice to external parties
- Potential outcomes:
  - Qualification of novel drug development tools (DDT)
  - If not optimal for DDT qualification: Public meeting, White Paper, Guidance
- ISTAND Web page

NAMs in CDER

Goals

- Improve predictivity while not compromising current safety evaluations
- Contribute to the 3Rs

Future Plans

- Participation in the development and regulatory use of NAMs
- Determine metrics that can be used to measure the success of NAMs and how they should be evaluated for utility in drug development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