FDA/CDER considerations on NAMs for pharmaceutical development

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April 17, 2020

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Highlights

- Regulations allow alternatives
- Guidance allows alternatives
- Useful assays are those that meet a data need
- Data are needed to show an assay does what is claimed
- Multiple ways to talk to FDA

Regulations allow submission of alternative methods

IND regulations

21 CFR 312.23 (a)(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."

Regulations allow submission of alternative methods

NDA regulations

21 CFR 314.50 (d)(2) *Nonclinical Pharmacology and Toxicology Section*

“A section describing, with the aid of graphs and tables, animal and in vitro studies with drug,…”

Guidances allow submission 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."

Draft Nonclinical Safety Evaluation of the Immunotoxic Potential of Drugs and Biologics

Guidances allow submission of alternative methods

Example ICH guidance wording:

"…consideration should be given to use of new in vitro alternative methods for safety evaluation. These methods, if validated and accepted by all ICH regulatory authorities, can be used to replace current standard methods."

ICH M3(R2)

Some guidances explicitly describe alternative approaches

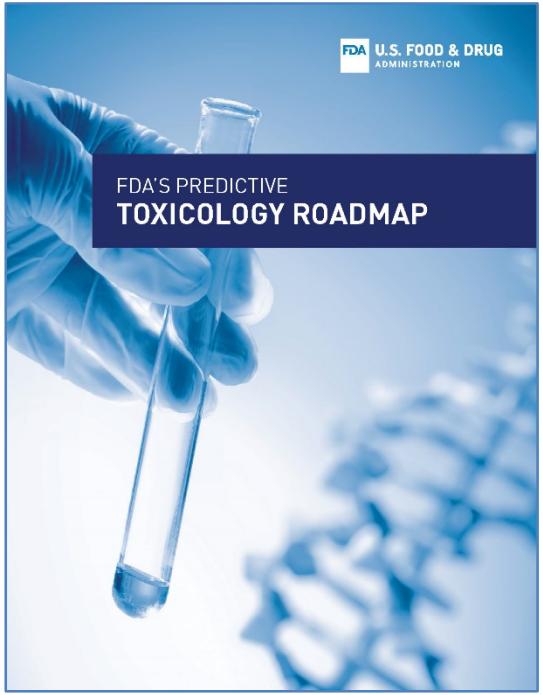
- ICH S3 Q&A - microsampling
- ICH S5(R3) - in vitro, ex vivo and nonmammalian embryofetal toxicity
- ICH S10 - in chemico and in vitro phototoxicity
- Draft Nonclinical Immunotoxicity guidance– in silico, in chemico and in vitro skin sensitization methods

Other alternatives routinely accepted

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

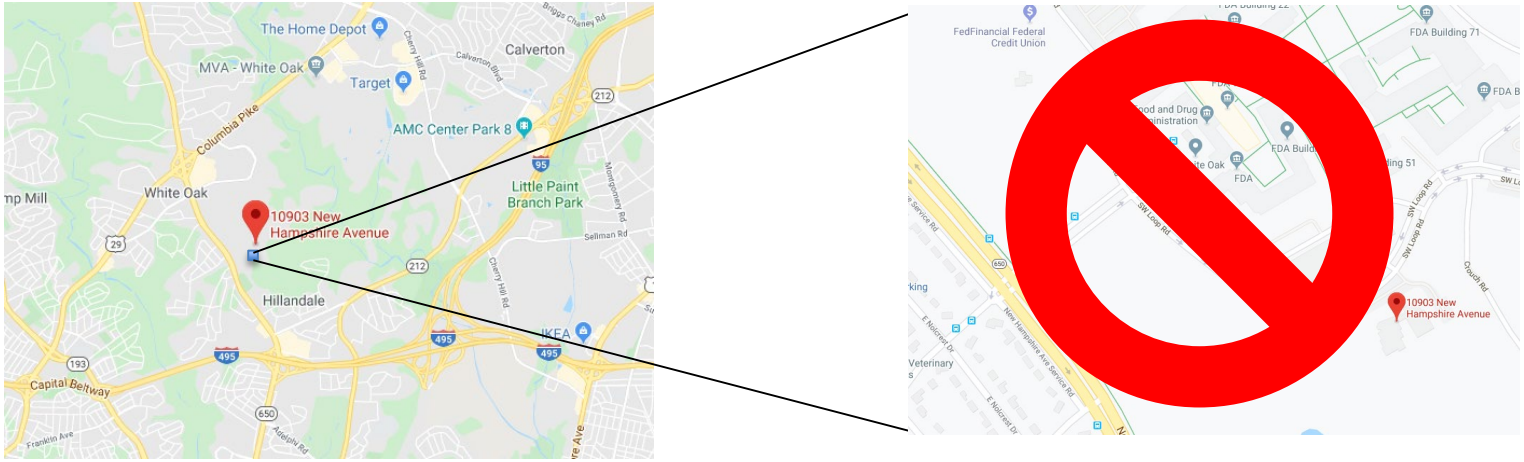
FDA has a Predictive Toxicology Roadmap

- **FDA's Predictive Toxicology Roadmap**
- https://www.fda.gov/science-research/about-science-research-fda/fdas-predictive-toxicology-roadmap



What is the roadmap? What isn't the roadmap?

- Is a high level document – think highways not neighborhood streets
  - Not a check list of things to do to get an assay accepted
  - While many scientific issues are shared across FDA centers, Centers have different regulatory mandates and authorities
  - Because of different Contexts of Use, it is likely that there will be multiple pathways for adoption of new approach methodologies.



Moving toward regulatory use

- Does an assay provide data that can be used to answer fundamental drug development questions?
- Is the assay mature enough?
  - Stable platform, cells
- What endpoints are being measured?
  - Are they predictive of in vivo effects?
  - Translatable to human?
- Has scientific validity been shown?
  - Is it reproducible?
  - What test compounds have been assessed?
    - Need compounds with in vivo data
    - Positives and negatives
- Applicability domain
  - Define compounds the assay can assess and not assess
- Criteria for success
  - What are sensitivity and specificity?

“Pre-regulatory” Opportunities

- No FDA “acceptance” is required in drug discovery
- Increased understanding of disease processes and identifying promising interventions
- Early screening and derisking for toxicity
- Early use of such models can contribute to the 3Rs by reducing iterative cycles of drug candidate selection

Context of use

- What 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

Submitting drug development data to the FDA

- There are no preset requirements for submitting in vitro data to a drug application.
- A method does not have to be formally validated before it is submitted.
- When assessing in vitro data submitted to the agency, reviewers consider how scientifically valid the information is for the particular purpose based on supporting information.

Alternative Methods Working Group (AMWG)

- Under Office of Chief Scientist, Office of Commissioner
  - Chaired by Drs. Fitzpatrick (CFSAN) and Mendrick (NCTR), includes members from each Center and OCS
- Discuss alternative activities across FDA
- Interact with U.S. federal partners and global partners to facilitate discussion, development, and acceptance of regulatory performance criteria for such assays

AMWG Goals

- Key goal is to strengthen FDA's long commitment to promoting the development and use of new technologies to better predict human and animal responses to a wide range of substances relevant to FDA's regulatory mission.
- Discuss new and emerging methods and methodologies across FDA, including research, training, and communication to ensure communication within and between all parts of FDA.
- Interact with U.S. Federal partners and other global stakeholders to facilitate discussion and development of performance criteria for such assays.
- Establish a dialogue and develop partnerships with FDA stakeholders to explore regulatory science applications for such technologies.

Webinar Series on Emerging Predictive Methods

- Opportunity for developers/users to present new methods and methodologies to FDA
- Webinars will be advertised to all FDA scientists exclusively
- If selected as a webinar:
  - participation in FDA's webinar series would not constitute the agency's endorsement of a new method or methodology
  - it would not mean that FDA would assist the developer in qualifying his/her new method for regulatory use

Coming Soon

- FDA will have an Alternative Method Work Group Activities page on the FDA External Site on www.fda.gov
- Comments can be sent to alternatives@fda.hhs.gov

- Sponsors are encouraged to discuss with FDA the potential use of NAMs
  - AMWG webinars
  - Pre-IND meetings/written responses
  - Critical Path Innovation Meetings – outside of a regulatory application
  - CDER is exploring other possible pathways (stay tuned)

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