Presentation Abstracts and Background Materials

SCIENTIFIC ADVISORY COMMITTEE ON ALTERNATIVE TOXICOLOGICAL METHODS

Session IIa: Validation Updates
Tuesday, September 17, 2024

Updates to OECD Guidance Document 34 on Validation of New and Updated Test Methods

Presenter: Dr. Charles Kovatch, U.S. Environmental Protection Agency (EPA)

OECD Guidance Document 34 (Guidance Document on the Validation and International Acceptance of new or updated Test Methods for Hazard Assessment) is the foundational document for the OECD Test Guidelines Program (WNT). The document outlines the process by which new or updated methods, guidance documents, or test guidelines are submitted to the WNT and how the WNT reviews those methods/documents to decide whether to approve them.

While the fundamental principles of GD34 (published in 2005) have remained relevant over the past 20 years, the WNT is revising the document to improve the validation process and better receive the increasing number of New Approach Methods (NAMs) and Defined Approaches (DAs) being developed and submitted to the WNT. The WNT will also revisit steps to establish scientific confidence in NAMs and DAs to achieve regulatory acceptance, some of which ICCVAM described in their Validation Report published in 2024. This presentation will discuss some key considerations in updating GD34, including: 1. Terms and definitions for NAMs, DAs, and others to clarify use, validation considerations, and information sources; 2. Readiness criteria for validation/peer-review/regulatory application and self-assessment by method developers; 3. Transferability and reproducibility guidance; and 4. Method relevance for consideration in regulatory decision-making.

Background

- OECD. 2005. Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment. OECD Series on Testing and Assessment Number 34. Paris: Organisation for Economic Co-operation and Development. https://www.oecd-ilibrary.org/environment/guidance-document-on-the-validation-and-international-acceptance-of-new-or-updated-test-methods-for-hazard-assessment_e1f1244b-en.
- ICCVAM. 2024. Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies. Research Triangle Park (NC): National Institute of Environmental Health Sciences. https://doi.org/10.22427/NICEATM-2.

Reviewing the Method Developers Forum – Follow-on Activities from the VWG Report

Presenter: Dr. Emily Reinke, Inotiv

Concurrent to the publication of the ICCVAM Validation Working Group's (VWG) Report on "Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies," NICEATM proposed the organization of a series of Method Developers Forums (MDFs), that provide opportunities for new approach methodologies (NAMs) developers to present their methods and regulatory issues with relevant stakeholders. In this presentation, we will discuss: (1) the impetus behind the development of the MDF; (2) the process by which MDF iterations are conducted; and (3) outcomes of the first MDF.

Each MDF iteration is focused on a specific type of toxicity and is convened as a virtual webinar. In the weeks leading up to the MDF, regulatory and industry stakeholders are invited to record precursory presentations that detail their specific

needs for evaluating the type of toxicity. Interested method developers can then view these recordings and request to participate in the MDF by submitting a proposed presentation that addresses questions predicated on the key concepts for validation described in the VWG report. The MDF steering committee then evaluates each proposed presentation and selects those that best address the key concepts to participate in the MDF. The first MDF took place on August 21-22, 2024, and was focused on NAMs for carcinogenicity testing. Regulatory and industry stakeholder recordings were provided by the Consumer Product Safety Commission, the Environmental Protection Agency (EPA) – Office of Pesticide Programs, EPA – Office of Pollution Prevention and Toxics, Federal Drug Administration (FDA) – Center for Drug Evaluation and Research, FDA – Center for Food Safety and Applied Nutrition, the National Cancer Institute, National Institute for Occupational Safety and Health, Occupational Safety and Health Administration, and Syngenta Crop Protection. Of the method developer presentations received by the steering committee 10 were selected to participate in the MDF.

Background

- ICCVAM. 2024. Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies. Research Triangle Park (NC): National Institute of Environmental Health Sciences. https://doi.org/10.22427/NICEATM-2.

In Vitro Inhalation Toxicity: A Case Study in Building Confidence in New Methods

Presenter: Dr. Amy Clippinger, People for the Ethical Treatment of Animals (PETA)

Differences in the respiratory tracts of humans and rats have called into question the ability of rats to reliably predict human effects. These scientific limitations, as well as ethical concerns, have led to the development of in vitro approaches for evaluating inhalation toxicity that are grounded in human biology and mechanisms of toxicity. This talk will discuss a case study of developing and gaining scientific confidence in a harmonized in vitro approach for assessing portal of entry effects on the respiratory tract. First, a systematic review was used to identify publicly available in vitro inhalation toxicity data and study designs and to inform a list of reference chemicals. Reference chemical selection included consideration of ease of procurement, mechanisms of action, and breadth of severity of toxicity of the chemicals, as well as feedback from experts in the field. The study designs identified in the systematic review were analyzed for differences and the potential implication of those differences and will incorporate input from leaders in the field to inform the development of a harmonized testing protocol. To build confidence in the testing approach, the in vitro system and existing data will be analyzed in the context of an established scientific confidence framework that includes human relevance, technical characterization, fitness for purpose, data integrity and transparency, and independent review. The described process is collaborative and iterative, with expert feedback, lessons learned, and new data informing the development of an approach that is as good as or better than the currently used rat test and that can continue to improve as the science advances.

Background

- Stucki AO, Sauer UG, Allen DG, Kleinstreuer NC, Perron MM, Yozzo KL, Lowit AB, Clippinger AJ. 2024. Differences in the anatomy and physiology of the human and rat respiratory tracts and impact on toxicological assessments. Regul Toxicol Pharmacol 150:105648. https://doi.org/10.1016/j.yrtph.2024.105648.
- Van der Zalm A, Barroso J, Browne P, Casey W, Gordon J, Henry TR, Kleinstreuer NC, Lowit AB, Perron M, Clippinger AJ. 2022. A framework for establishing scientific confidence in new approach methodologies. Arch Toxicol 96(11):2865–2879. https://doi.org/10.1007/s00204-022-03365-4.

Session IIa: NAMs Pipeline – Future Directions
Tuesday, September 17, 2024

Catalyzing the Development and Use of New Approach Methods (NAMs) to Advance Biomedical Research: Implementation of Recommendations from the NIH Advisory Committee to the Director Working Group

Presenter: Dr. Ellen Gadbois, National Institutes of Health (NIH), Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)

In December 2023, the NIH Advisory Committee to the Director Working Group on Catalyzing the Development and Use of Novel Alternative Methods (NAMs) to Advance Biomedical Research issued a report and seven recommendations setting forth a vision for an integrated ecosystem to catalyze scientific discovery. Per the report, successful integration across approaches in combinatorial NAMs requires multidisciplinary teams with access to interoperable, reliable data sets. Part of integration is effective technology dissemination and engagement with end users to make sure the approach is socially responsible and fit for purpose. Recommendations included creating avenues for comprehensive training about how to use these different technologies, including workshops and coordinated infrastructure people can use to learn. This synthesis across models and fields can enable a virtuous cycle where NAMs research informs work done in other models, which informs human health, from which we can use biomedical data to further improve models.

The NIH Director accepted the recommendations in February 2024, and the Division of Program Coordination, Planning, and Strategic Initiatives is leading NIH-wide implementation planning. NIH has assessed the recommendations for prioritization, feasibility, and which Institutes, Centers, and Offices (ICOs) are most appropriate for involvement and is engaging through NIH-wide data calls and strategic conversations with ICOs expected to have the most significant involvement based on their portfolio and mission. This presentation will discuss progress on implementation planning across NIH, including achievements so far and metrics and processes to track progress.

Background

- Chang H, Jorgenson L. 2023. Catalyzing the development and use of novel alternative methods (NAMs). Presentation to the June 2023 meeting of the NIH Advisory Committee to the Director. https://acd.od.nih.gov/documents/presentations/06092023_Chang_NAMS.pdf.

Catalyzing the Development and Use of Novel Alternative Methods (NAMs) to Advance Biomedical Research

Presenter: Dr. Margaret Ochocinska, NIH Office of the Director (OD)

The NIH Common Fund's Complement Animal Research In Experimentation (Complement-ARIE) Program aims to catalyze the development, standardization, validation, and use of human-based New Approach Methodologies (NAMs) that will transform the way we do basic, translational, and clinical sciences. NAMs, which broadly span in chemico, in vitro, and in silico approaches intended to more accurately model human biology, and complement, or in some cases, replace traditional research models. The Complement-ARIE program will build upon ongoing efforts related to NAMs, while identifying opportunities for innovation and coordination. Complement-ARIE will significantly advance understanding of human health and disease by providing a range of ready and standardized biomedical research models. Developing these models will require expertise in disease research, personalized medicine, and in screening therapeutics for safety and effectiveness. This presentation will provide an overview of the background and goals of this new program.

Complement-ARIE will bring together a consortium of researchers participating in the following efforts: 1) Technology development projects/centers that will develop NAMs to fill in areas of greatest need. Projects will emphasize biological complexity, high throughput techniques, combining approaches, and data sharing; 2) A NAMs Data Hub and Coordinating Center that will create integrated data structures and a searchable NAMs repository; 3) A Validation and Qualification Network that will accelerate deployment and regulatory approval of NAMs for biomedical research; 4) Community engagement and training that will promote the development of an inclusive, diverse, biomedical research workforce with the skills to build and use new NAMs; and 5) Strategic engagement with key partners that will advance emerging opportunities in development and use of NAMs in basic, translational, and clinical research. Complement-ARIE will significantly advance understanding of human health and etiology of human disease, have near-term application in fields such as mechanism elucidation, personalized precision medicine, safety pharmacology, predictive toxicology, and efficacy evaluation of candidate therapeutics, and provide a range of ready and standardized models for health and disease biology.

Background

- NIH. 2024. Complement-ARIE Landscape Analysis. https://commonfund.nih.gov/complementarie/strategicplanning/landscape-analysis.
- NIH. 2024. Executive Summary of the NIH Listening Sessions on the Complement-ARIE Program Concept. https://commonfund.nih.gov/complementarie/strategicplanning/listeningsessions.
- NIH. 2024. Complement-ARIE Interagency Retreat Summary. https://commonfund.nih.gov/complementarie/strategicplanning/interagencyretreat.

FNIH Status Update: Public Private Partnership for NAMs and an Update on the Design Phase and Implementation of a Validation and Qualification Network (VQN) for NAMs Adoption and Implementation

Presenter: Dr. Stacey Adam, Foundation for the National Institutes of Health (FNIH)

This session will provide a brief introduction to the Foundation for the National Institutes of Health (FNIH) and its role in developing and executing public-private partnerships (PPP) to support public health and the mission of the NIH. Information will be provided to describe the selection process and design of a PPP through the FNIH, and the stakeholders who have been engaged in this process to build a Validation and Qualification Network (VQN) for NAMs. Progress on the development timeline of the VQN, objectives and partners engaged will be provided, and opportunities for input and engagement will be shared.

Background

- Menetski JP, Hoffman SC, Cush SS, Kamphaus TN, Austin CP, Herrling PL, Wagner JA. 2019. The Foundation for the National Institutes of Health Biomarkers Consortium: past accomplishments and new strategic direction. Clin Pharm Ther 105(4):829-843. https://doi.org/10.1002/cpt.1362.
- Dolgin E. 2019. Massive NIH–industry project opens portals to target validation. Nature Reviews Drug Discovery 18:240-242. https://www.nature.com/articles/d41573-019-00033-8.