Interagency Coordinating Committee on the Validation of Alternative Methods

Presentation Abstracts and Background Materials

SCIENTIFIC ADVISORY COMMITTEE ON ALTERNATIVE TOXICOLOGICAL METHODS

Session II: Implementing the Strategic Roadmap: Incorporation of Alternatives and Associated Metrics
Wednesday, September 21, 2022

Introduction

Presenter: Dr. Warren Casey, National Institute of Environmental Health Sciences

ICCVAM published "A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States," which described a new approach for promoting the development and use of alternative toxicological methods. The central tenet of this new paradigm was recognizing the importance of agency-specific requirements for toxicity testing and reporting, which vary significantly across the federal government and between international regulatory bodies. One approach will not fit all and attempting to apply one approach to meet the needs of all agencies is the largest factor contributing to failure of alternative methods being adopted both in the U.S. and internationally. ICCVAM also recognized the need to track the progress agency adoption of new methods under this new model and established a resource for stakeholders to track implementation activities.

In early 2020 ICCVAM established its Metrics Workgroup (MWG), comprised of 21 individuals representing nine federal agencies or institutes in response to a recommendation made by the U.S. Government Accountability Office (GAO). The MWG published "Measuring U.S. Federal Agency Progress Toward Implementation of Alternative Methods in Toxicity Testing" in February 2021. As with the Strategic Roadmap, the MWG found that no one set of metrics can be used by all ICCVAM member agencies and recommended that each agency develop its own metrics that are relevant and practical to their unique regulatory domain. The MWG recommended the use of both quantitative and qualitative metrics to assess progress when relevant and practical and provided examples of approaches that could be used for establishing agency-specific metrics (e.g., the U.S. Environmental Protection Agency [EPA] "Strategic Vision for Adopting New Approach Methodologies – Metrics"). Agency progress in this area will be provided in the ICCVAM Biennial Report beginning in 2020-2021.

Major Points:

- ICCVAM Strategic Roadmap identified the need for and commitment to identifying agency-specific uptake of new approach methodologies (NAMs) and associated metrics.
- ICCVAM agency implementation activities can be followed using this web site: https://ntp.niehs.nih.gov/go/838279.
- ICCVAM agency-specific metrics are currently being developed and will be reported in ICCVAM biennial reports.

Background

- A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States
- U.S. Government Accountability Office Report: Animal Use in Research: Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives

- ICCVAM Metrics Workgroup Document: Measuring U.S. Federal Agency Progress Toward Implementation of Alternative Methods in Toxicity Testing
- ICCVAM 2020-2021 Biennial Progress Report [pending]

Metrics Case Studies from ICCVAM Agencies

Communicating Progress in Advancing Alternative Methods for Regulatory Use at the FDA

Presenter: Dr. Paul Brown, U.S. Food and Drug Administration

The U.S. Food and Drug Administration (FDA) is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation. FDA also has responsibility for regulating the manufacturing, marketing, and distribution of tobacco products to protect the public health and to reduce tobacco use by minors. Each product area is regulated under differing authorities. All rely to an extent on nonclinical safety or toxicity data. In some cases, investigational data are submitted to the Agency by the regulated party while in other cases it is not. The Agency has a long-standing commitment to advancing the 3Rs and has participated in a variety of activities related to alternative methods. Recently, the Agency has expanded efforts to implement qualification programs that may facilitate use, acceptance, and submission of alternatives. In addition, the Agency is actively increasing communication on activities related to alternatives to outside stakeholders. This has occurred through website content, presentations, and publications. The Agency is also seeking input from its Science Advisory Board on approaches to facilitate the development and implementation of alternative methods. The Agency has also increased internal educational efforts related to new technologies through, for example, inviting outside experts to present webinars open to all Agency personnel. The Agency is constantly alert to opportunities to expand incorporation of alternative methods in guidance documents when appropriate. FDA thinks documenting and communicating these activities is an effective way to demonstrate progress in the implementation of alternative methods.

Background

- FDA Report: Advancing New Alternative Methodologies at FDA

U.S. Consumer Product Safety Commission Metrics on New Approach Methods

Presenter: Dr. John Gordon, U.S. Consumer Product Safety Commission

Dr. Gordon will present progress from the U.S. Consumer Product Safety Commission (CPSC) as it pertains to metrics efforts for new approach methods.

Background

- CPSC Document: Guidance for Industry and Test Method Developers: CPSC Staff Evaluation of Alternative Test Methods and Integrated Testing Approaches and Data Generated from Such Methods to Support FHSA Labeling Requirements

Animal Reduction Metrics Used by U.S. Environmental Protection Agency Office of Pesticide Programs

Presenter: Dr. Monique Perron, U.S. Environmental Protection Agency

The EPA Office of Pesticide Programs (OPP) requires substantial toxicology testing to support pesticide registration. Toxicological studies in vertebrate animals are generally used to provide information on a wide range of adverse health outcomes, routes of exposure, exposure durations, species, and life stages. The number of vertebrate animals used

varies widely depending on the pesticide type and use pattern. EPA has flexibility in implementing 40 CFR Part 158 data requirements, with the Federal Insecticide, Fungicide, and Rodenticide Act allowing for waivers to be granted and alternative methods to be accepted on a case-by-case basis. By using waivers, EPA can avoid the generation of data that does not influence the scientific certainty of a regulatory decision. The number of waivers granted and animals saved from not needing to perform repeated-dose toxicity studies have been tracked by the OPP's Hazard and Science Policy Council since 2012 and constitutes an important metric for vertebrate animal use reduction for EPA. Similarly, OPP has started tracking the use of waivers for acute toxicity studies.

Background

- EPA Document: New Approach Methods Work Plan
- Reducing the Need for Animal Testing While Increasing Efficiency in a Pesticide Regulatory Setting: Lessons from the EPA Office of Pesticide Programs' Hazard and Science Policy Council

U.S. Department of the Interior: Potential Metrics to Track and Encourage Use of Alternative Methods in Ecotoxicological Research and Testing

Presenter: Dr. Barnett Rattner, U.S. Department of the Interior

The mission of the Department of the Interior (DOI) is broad and includes the generation of scientific information to assist in the conservation and management of the nation's natural resources. Part of the stewardship responsibilities of DOI include management of fish, wildlife, and threatened and endangered species, in response to no fewer than 20 environmental statutes and regulations. DOI conducts a wide array of ecotoxicological research and testing, contaminant biomonitoring, natural resource damage assessment, diagnostic and forensic activities, and registration of toxicants for invasive species control. At least two of its bureaus (U.S. Geological Survey, U.S. Fish and Wildlife Service) conduct ecotoxicological research and testing, and others (*e.g.*, Bureau of Land Management, Bureau of Reclamation, National Park Service) use these data for management activities. Studies are designed to minimize the number of animal subjects, collect sublethal or even noninvasive samples, and in some instances use in vitro or in silico methods in place of animals. Efforts to foster the use of alternative methods are ongoing through training, scientific information exchange, and detailed review of research activities and ecotoxicity test designs. Metrics to track progress toward use of alternative methods and new approach methodologies (NAMs) are being developed. These may include staff compliance with 3Rs training, evidence of application of NAMs in ecotoxicological activities, and long-term tracking of animal versus alternative method use in toxicity testing through review of Institution Animal Care and Use documents, scientific publications, and associated data releases.

Background

- Current Ecotoxicity Testing Needs Among Selected U.S. Federal Agencies

Industry Approaches

Animal Metrics: Tracking New Approach Methods (NAMs) Impacts on Animal Use

Presenter: Dr. Sue Marty, Dow/Corteva

New approach methods (NAMs) offer industry an opportunity to screen chemicals more quickly, generate mechanistic and/or human relevant data, reduce animal use, and align with trends in global regulatory practices. Dow has developed a strategy to monitor our progress adopting NAMs and reducing animal use in product safety assessments. To do this, baseline animal use was established by defining the scope of the program (e.g., definition of animals and study types to include) and establishing protocols for consistent "animal use" tracking from year to year. For NAM-based animal savings,

metrics were developed for computational modeling/read across, in chemico/in vitro assays, study waivers, and intelligent designs. The central theme is that all NAM data have value if useful for internal decision-making, but the value varies based on how the information is used and the level of certainty (e.g., early screening versus fulfilling a regulatory requirement). Animal savings is allocated based on the NAM endpoint assessed, the corresponding in vivo study (including breadth of hazard information obtained and number of animals used), animal savings number assigned to the NAM, and rationale for the assigned value. Generally, NAM equivalents should be conservative, reflecting the degree of certainty in the results. NAM-based animal savings may be reported as absolute number of animals saved or percentage reduction in animal use due to NAMs. Tracking NAM impact on animal use allows companies to show progress in adopting NAMs in product safety, supports resource investment in NAM programs, and identifies priority areas for future NAM development.

Background

- Tracking Contributions of New Approach Methods to Reduce Animal Use

A Data-Driven Decision Making Framework for the Selection, Application, and Development of Advanced In-Vitro Models for Preclinical Drug Development

Presenter: Dr. Daniela Ortiz Franyuti, Roche

With a low rate of successful translation from animal model to clinical trials (potentially as low as less than 8% for cancer indications), we have an increasing and urgent need, as drug developers, for the development, refinement, and validation of human in vitro models to be used for decision making in preclinical safety assessment. Such need is exacerbated by the increasing biological complexity of novel therapeutic molecular entities, for which it becomes more challenging to find relevant animal models to evaluate safety and efficacy. Even with a rich and fast developing palette of advanced in vitro models that can potentially be used to fill such gaps, we continue to face challenges in terms of model characterization and validation both from the biological and the technical perspective. We present here how our team is tackling the challenge of preparing in vitro, human-only safety regulatory packages using multi-model, multi-readout studies requiring data-rich, complex interpretation. To do this, we are applying a biology-centric data integrity and management strategy and data interoperability framework to enable data-driven decision making on the short term, and back and forward translatability with the clinical setting on the long term.

Background

- Opportunities and Challenges with Microphysiological Systems: a Pharma End-user Perspective
- Transforming Preclinical Assessment to Meet Clinical Relevance with Advanced Models
- Investigating the Replicability of Preclinical Cancer Biology
- The FAIR Guiding Principles for Scientific Data Management and Stewardship

Consideration of Alternative Methods Workgroup

Presenter: Dr. Jessie Carder, United States Department of Agriculture

Despite regulatory requirements, in practice, there is little incentive for investigators that have long used specific in vivo models and well-established protocols to work toward validating or even adopting validated alternative approaches. Traditional toxicology testing and research may have been built on the cumulative historical data, or entire businesses founded upon the application of in vivo test methods, so moving to NAMs could alter such establishments, and without

incentives they are less likely to actively seek out, validate, or research NAMs. Therefore, the ICCVAM Consideration for Alternative Methods Working Group (CAMWG) was formed to provide solutions to some of these challenges.

The presentation will discuss the CAMWG scope and charges, such as working with stakeholders to identify potential incentives that could be used to encourage the use of NAMs in conjunction with existing in vivo test methods. It will also include an overview of current requirements for the consideration of NAMs, and how those might be modified/expanded upon to foster more serious consideration by stakeholders. Lastly, an update on the status of the working group will be provided such as a general summary of the discussions with stakeholders so far, and what's to come.

Background

- ICCVAM Metrics Workgroup Document: Measuring U.S. Federal Agency Progress Toward Implementation of Alternative Methods in Toxicity Testing