Validation Powerlifting: Strengthening Confidence in NAMs with Flexibility and Fitness (for Purpose)

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New approach methodologies (NAMs) are increasingly being used to assess potential toxic effects of chemicals and products on human health. However, as modern approaches to toxicity testing have evolved (e.g., from replacing in vivo tests with a single alternative assay to the more contemporary practice of integrating results from multiple alternative approaches), so has the need to adapt the assessments of a NAM's scientific validity. This presentation will summarize how this need is being addressed by recent activities of the U.S. federal Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).

As described in the ICCVAM 2024 report, "Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies," confidence in a NAM should not be based entirely on historical approaches such as the outcome of a ring-trial study or exclusive comparison to reference animal data. Instead, confidence should be strengthened through flexible, fit-for-purpose validation strategies that consider a NAM's intended application. Key concepts include consideration of the NAM's context of use, biological relevance to the species of interest, technical characterization, data integrity, information transparency, and independent review.

The report emphasizes that establishing confidence in NAMs is an iterative process that requires communication among method developers, regulators, and validation bodies. NAMs developers need to understand end-user needs to assure that the method is fit-for-purpose (i.e., provides information that is scientifically sound and meets requirements for the intended regulatory decision or use case). When appropriate and feasible, stakeholders should communicate if or when a NAM is acceptable for their needs.

To implement the report's concepts, ICCVAM is organizing Method Developers Forums (MDFs), each iteration focused on a specific toxicity/endpoint. To prepare for the MDF main event, NAMs developers review materials summarizing stakeholder information requirements and/or decision frameworks relevant to the topic. Each proposal submission describes their method and how the key concepts have been addressed in validation efforts. Developers are then invited to present their method and how it may be useful for stakeholders at the MDF main event. A panel of stakeholders provides feedback on the featured NAMs' readiness, confidence, and other aspects that should be addressed to strengthen the validation efforts. Thus, the MDF provides an opportunity for reciprocal communication among NAMs developers and intended end-users that can help advance NAMs toward implementation and regulatory acceptance. This project was funded in whole or in part with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C. The views expressed above do not necessarily represent the official positions of any federal agency.