International harmonization of test method validation – the role of readiness criteria to amplify success

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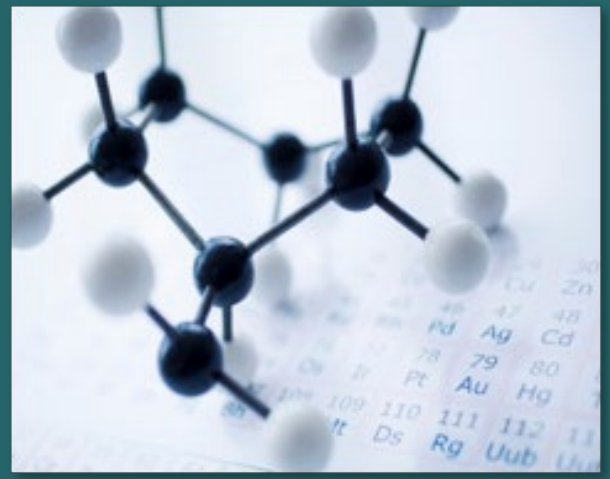

Validation of methods

- Project to modernize guidance on how to validate new or updated test methods for entry into the OECD test guideline program
- GD 34 is 20 years old, and now we have:
  - NAMs
  - Defined Approaches (combinatorial methods)
  - Varied types of in silico tools
  - Experience with using the established guidance to evaluate what works and what doesn't
- Project started in 2023
- Premise: Building confidence in a method that will be used for regulatory decision making

Unclassified ENV/JM/MONO(2005)14

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

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English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

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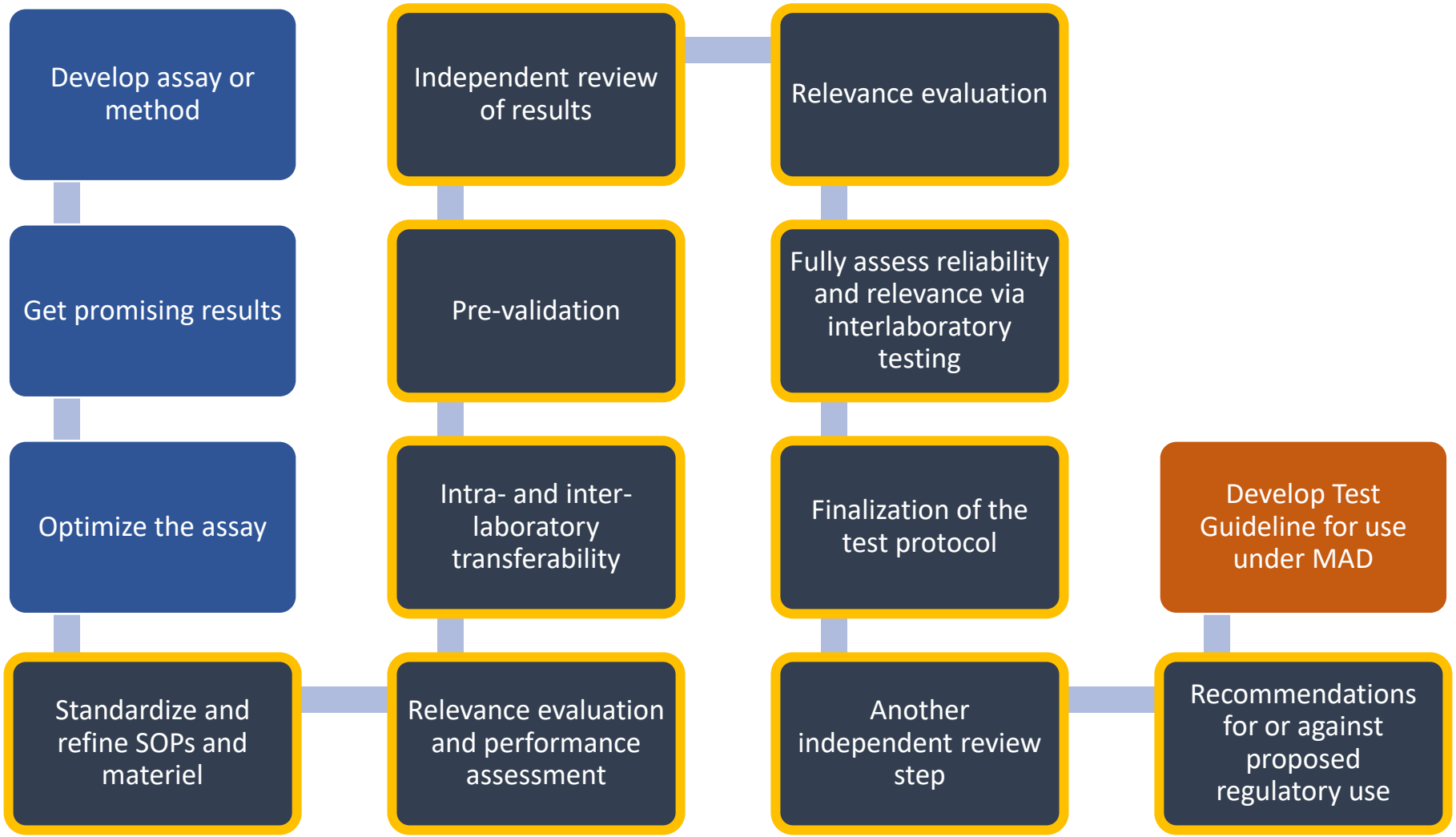
OECD SERIES ON TESTING AND ASSESSMENT
Number 34

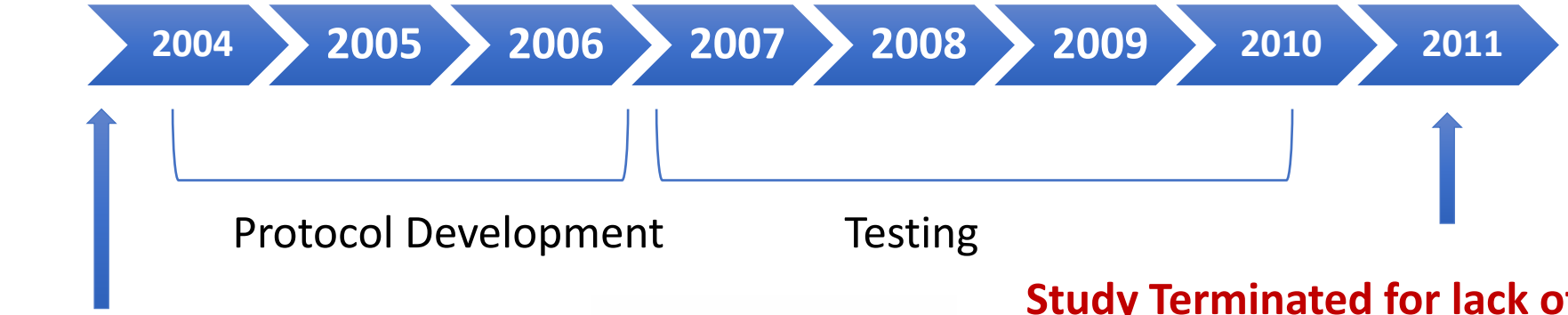
GUIDANCE DOCUMENT ON THE VALIDATION AND INTERNATIONAL ACCEPTANCE OF NEW OR UPDATED TEST METHODS FOR HAZARD ASSESSMENT

How validation is described in current GD 34



Why are readiness criteria beneficial?

ICCVAM Validation of an MCF-7 Estrogen Receptor Cell Proliferation Assay



Study Terminated for lack of between-lab reproducibility (transferability)

> $4 Million

Relatively “minor” procedure difference led to lack of reproducibility

VS

OECD 2022-23: 2-Day Workshop

- OECD Stakeholders workshop on operational and financial aspects of test method validation & what improvements could be made
- After almost 2 decades of experience engaged in method validation – how are processes evolving & where are the continued pain points?

- OECD released a statement calling on member countries to “urgent mobilisation of national and regional resources for the demonstration of reproducibility and reliability of methods developed in single laboratories.”

Participant perspectives at the workshop

Manager

- Either an Agency, Center for validation, or independent body manages the study
- Coordinates conduct of studies and evaluates the resulting data
- Often blinds samples or reagents and manages analysis of blinded data

Participating Labs

- Heterogenous mix of industry, CRO, academics ; as few as two labs used up to several labs
- Mix of self-funded/in-kind, fully or partially grant-funded
- Mixed experience with validation studies (ranges from newcomer to veteran)

Regulatory And Agencies

- Benefits to frequent contact and/or participation of the regulators in the management process and/or final review of the data and protocols
- Whether Agencies are directly involved, helpful when the method developer works with regulators to understand application of the method

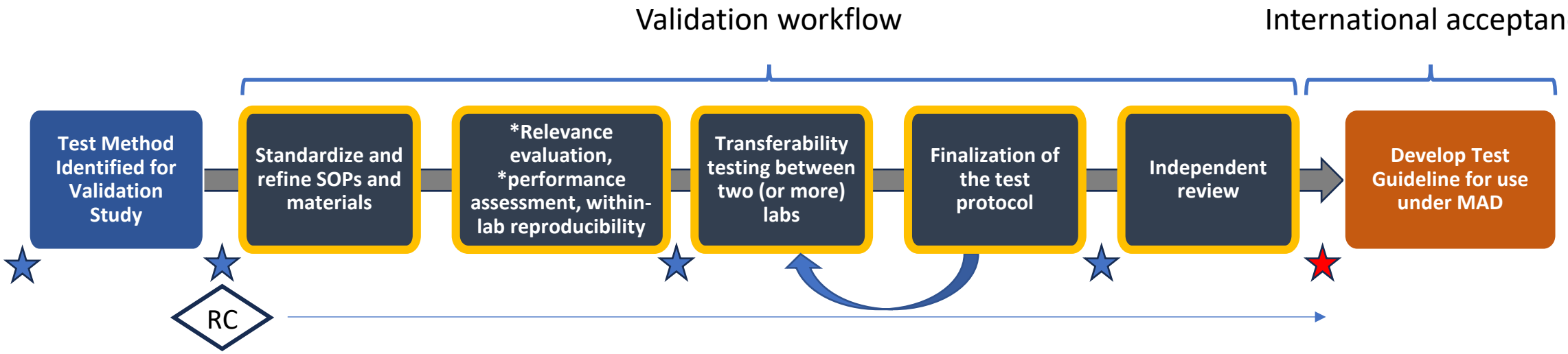
What is going well in validation studies worldwide

- Partnering with a “CVAM” is helpful to guide development and completion of a validation project
- Institution of a project management team (ideally with an experienced and attentive manager) is a key to success; it’s been especially helpful when the management team coordinates shipping and coding of chemicals and the review of coded data
- Despite a lack of funding validation studies, public-private partnerships and access to competitive grants has enabled labs to handle the average $300-500k cost
- Regulatory bodies and OECD have taken an active role in participating in and guiding validation programs
- Flexibility has allowed between-lab transferability studies to be designed down to using 2-3 labs in some cases

What hurdles remain for validation studies

- Funding for validation studies is challenging to obtain, properly budget for, and maintain on changing timelines
- Changes in staffing, loss of key personnel or instrumentation are frequently cited reasons for long delays in validation programs
- Shipping assay or reference chemicals and samples across borders remains difficult and some regions are keeping participation “local” for this reason
- How to facilitate ***knowledge sharing*** on approaches to validation studies for interested labs, nonprofit centers, and Agencies remains a gap; ***training*** is an important component of participation in a validation study

Incorporating readiness criteria in method validation



*Relevance includes biological/mechanistic relevance, applicability domain, regulatory relevance and regulatory application (incl. e.g., predictive capacity)
In the case of non-standalone methods, regulatory application should be assessed at the level of a DA (Defined approach)

*Performance assessment includes control measurements, mechanistic reference chemicals or reference data, technical variability source analyses, etc.

★ There are multiple points in the process where an understanding of suitability to move to the next phase is desirable

Background documents informing approach

- Bal-Price et al., 2018 (for DNT NAMs)
- JRC-EURION template, 2022 (for EDs, *in vitro*)
- OECD GD GIVIMP, 2018
- ToxTemp
- PEPPER's ReadEDTest
- EURL ECVAM Test submission template
- Holzer et al., 2023
- Petersen et al., 2023
- Van der Zalm et al., 2022
- ICCVAM Validation Paper, 2024

Readiness criteria

- Provides a means to evaluate regulatory relevance, maturity of the assay, and reproducibility of the method at various points of the validation process – *i.e.,* **is this a method worth prioritizing for expensive and lengthy validation studies?**
- Who can use it?
  - Method developers (what should I consider in my development program to position the method well?)
  - Validation bodies (how do we triage and prioritize methods to move into various phases of expensive validation programs?)
  - Regulators (what's the status of this method to enable decision making and does it provide key information I need to make decisions?)
- May require different criteria for different method types (*i.e.,* in vitro vs. in silico)
- Doesn't have to be scored, but provides an information set that enables a clear picture of where the method falls in a validation continuum

Progress on readiness criteria for GD 34

- Draft templates have been prepared for –
  - In vitro test methods
  - In silico / computational test methods

- These are in draft as document annexes and being used to inform development of the revised guidance document

Key components of readiness assessment

- ***Method Relevance*** – Regulatory use/application, regulatory relevance, mechanistic and biological relevance, predictive capacity for endpoint of interest
- ***Test Method Characterization*** – Basic information and quality control, metabolic competence, control and reference items/data, assessment of interference, identification of critical steps and assay tolerances, key sources of variability or sensitivity analysis, detailed protocol, domain of applicability is defined
- ***Data management, evaluation, and interpretation –*** Processes for data management -> collection, analysis, storage, and reporting. Describe guidelines followed (FAIR, OORF, etc). Also includes QA processes, as applicable, and independent audit.
- ***Within-lab reproducibility; WLR –*** Describe training of method implementers, criteria for selecting chemicals or data to evaluate the method, reproducibility of results within the developer's lab and across time

Key components of readiness assessment

- ***Between-lab reproducibility (BLR)***
  - Describe results of transfer of the protocol to at least one other lab (and explain how COI was managed with the method developer)
  - Were deviations or needed revisions to the protocol identified during BLR studies? How were these addressed?
  - If there was variability in results among labs, how was it assessed or dealt with?

- ***Independent audit -*** Were data audited and analyzed and/or reviewed by an independent party to verify results?

Key components of readiness assessment

- ***Computational Models –***
  - Detailed description of algorithm and processes allowing for independent evaluation, including model calibration and code verification results
  - Well-defined and quality-controlled inputs and outputs (including training data), with documented metadata and description of controlled vocabularies used
  - Documented software version and dependencies, with model accessible for independent review and implementation
  - Model risk assessment – Evaluate the model for incorrect predictions

How will readiness assessment be incorporated into GD34?

- Expert Group has developed templates for in vitro, Defined Approaches, and computational methods that will be included as annexes to the guidance document
- Templates are meant to be a starting point for validation managers and may be modified to suit the needs of a particular program or method
- Lessons learned from developing readiness criteria are being shared with the NIH COMPLEMENT-Arie VQN for consideration on optimizing their method review processes
  - Cross-membership between the GD34 EG leads (Warren Casey NIH & Alison Harrill EPA) and COMPLEMENT-Arie

Summary

- An up-front assessment of readiness, including both technical elements and regulatory relevance, may aid in selection of promising methods for validation programs, thereby streamlining the process.
- As a method moves through a validation program, more of the ‘criteria’ will become available for review.
- Programs may opt to refine or prune methods from programs based on elements of the readiness checklist.
- Sharing of best practices from international validation bodies is cross-pollinating related efforts, including COMPLEMENT-Arie.

Reference Documents

- ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods
- OECD Series on Testing and Assessment No. 34: Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment
- Recommended Procedures Regarding the CPSC's Policy on Animal Testing
- FDA Predictive Toxicology Roadmap
- Qualification of Medical Device Development Tools: Guidance for Industry, Tool Developers, and Food and Drug Administration Staff
- EPA Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program
- ICCVAM Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States
- Guidance Document on Good In Vitro Method Practices (GIVIMP)
- 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
- Qualification Process for Drug Development Tools Guidance for Industry and FDA Staff
- EPA New Approach Methods Work Plan
- EPA Strategic Plan to Reduce the Use of Vertebrate Animals in Chemical Testing
- Advancing New Alternative Methodologies at FDA

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