National Institute of Environmental Health Sciences
Division of Translational Toxicology

Peer Review for Validation Studies: Building Confidence and Transparency Into a New Validation Paradigm

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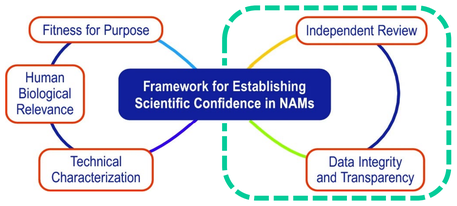
Background

- For a validation study, it is important to demonstrate the integrity and credibility of validation results, from raw data to the final report.
- Peer review of a test method validation study is a key step toward both gaining regulatory acceptance and developing an Organisation for Economic Cooperation and Development (OECD) test guideline (TG).
- Historically, peer review panels have been convened by national validation organizations following a comprehensive, multi-laboratory validation study that is typically managed by the same validation organization.
- OECD has called for external support for validation studies and suggested that validation studies and subsequent peer review be funded by test method developers.
  - This suggestion introduces questions and concerns about how the validation and peer review can be conducted in a sufficiently transparent manner, without concern of conflicts of interest that may bias the outcome.
- As part of establishing scientific confidence in new approach methods (NAMs), as illustrated in the framework graphic below, it is important to demonstrate the integrity and credibility of the validation study by an **independent review process.**
- Here, we consider as a case study a recent peer review of the SENS-IS test method supported by the test method developer.
  - We discuss steps taken by the peer review panel to ensure independence from the test method developer to foster a transparent and unbiased process.
  - We discuss how we confirmed that data and supporting documentation submission packets were complete and correct, and summarize lessons learned throughout the process.



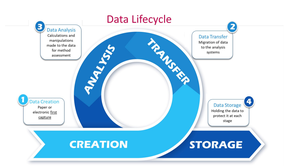
Graphic adapted from: van der Zalm, et al., 2022. https://doi.org/10.1007/s00204-022-03365-4

Current State of Validation and Peer Review

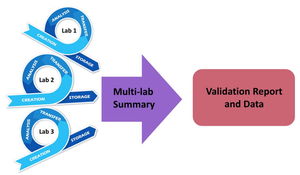
For the last two decades, validation management organizations have evaluated new test methods according to the OECD's Guidance Document 34: Guidance Document On The Validation And International Acceptance Of New Or Updated Test Methods For Hazard Assessment ("GD 34", 2005, https://doi.org/10.1787/20777876; now under revision). GD 34 outlines the following principles for the conduct of validation studies:

- Validation studies should follow the principles of **Good Laboratory Practice.**
- Per OECD policy, information presented to support a test method validation should be **transparent**:
  - Method developers are urged to use other means than confidentiality to protect intellectual property.
  - OECD will host confidential information on a protected webpage only accessible to National Coordinators during TG development. Once a TG is adopted, information will be publicly available.
  - Example of a platform for sharing validation status information: European Union's TSAR - Tracking System for Alternative Methods towards Regulatory Acceptance (https://tsar.jrc.ec.europa.eu/).
- **Independent scientific review** is an important part of the confidence-building process:
  - Appropriate level of external review depends on the NAM and its intended use.
  - External review may include peer-reviewed journal publication or review by an independent scientific advisory panel.
  - International adoption by OECD typically needs formal peer review.
  - Like supporting data, all aspects of peer reviews should be fully transparent.
  - According to GD 34, peer review should be coordinated by an organization established or mandated by law to evaluate test methods, a government agency of a member country, or by OECD itself.
- **Perceived conflicts of interest should be managed appropriately:**
  - Peer review panel (PRP) members' declarations of interests are analyzed before appointment and before peer review to identify potential conflicts of interest.
- **Validation management must demonstrate data integrity** through independent audit and quality assurance before peer review is initiated.
- **NAM developers may fund but should not manage peer review.**

Data Flow for Method Development and Validation



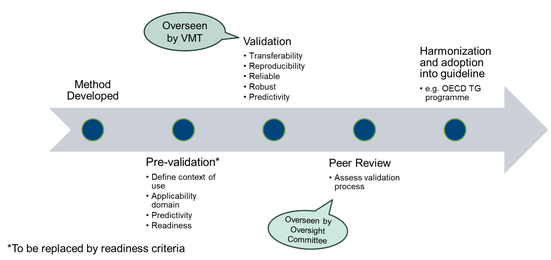
A. Data are produced by a single laboratory according to the illustrated scheme.



B. Data across multiple independent laboratories are compiled into a multi-lab summary, which is used to produce the validation report and data.

GD 34 Validation and Peer Review

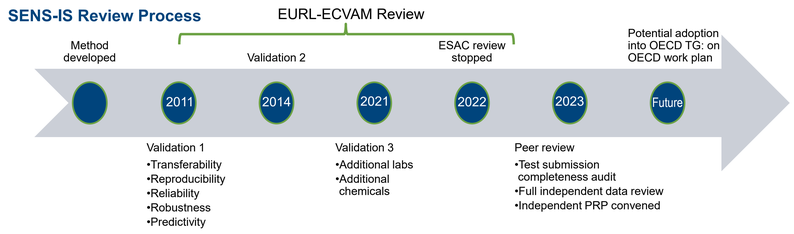
The validation step, overseen by a validation management team (VMT), feeds into the guideline adoption process. It is followed by the peer review step, which is supervised by an oversight committee. After peer review, the test method can proceed to the harmonization step and ultimately, guideline adoption.



*To be replaced by readiness criteria

Peer Review: Case Study of SENS-IS

- ImmunoSearch developed the SENS-IS assay as a reconstructed human epidermis (RhE) gene expression-based alternative to animal tests for identification of skin sensitizers.
- ImmunoSearch has been engaged in validation activities for SENS-IS for over a decade.
  - Early in development, ImmunoSearch began conducting validation studies (2011).
  - The European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) began validation oversight and review in 2011.
  - Additional validation studies were requested by EURL ECVAM and its Scientific Advisory Committee (ESAC) in 2014 and 2021.
  - ESAC suspended its review in 2022 over concerns about data and the validation process.
  - **To move the method forward, ImmunoSearch engaged experts in skin sensitization and NAMs evaluation to discuss conducting an independent peer review (poster authors: SH, DB, FG).**
  - A PRP consisting of independent consultants and representatives of validation of alternative methods organizations (VAMs) was assembled. Independent consultants were **supported** by the test method developer, with **in-kind contributions** (time) by VAMs.
  - Contact was made with the OECD French National Coordinator to share the PRP's plans.
  - To **address ESAC concerns**, these additional steps were taken for the independent peer review:
    - The test method submission report (TST) was evaluated for **completeness** before the review.
    - SENS-IS validation data were independently **audited** with findings shared with the developer for adjudication, and the final report included in the PRP summary.



Avoiding COI and Bias: Case Study of SENS-IS

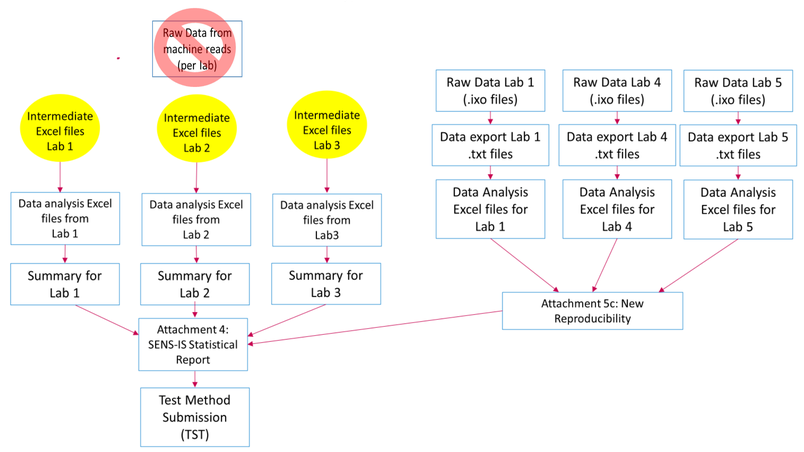
- Transparency requirements were put in place because of the inherent conflict of interest (COI) and to protect against impression of bias.
- PRP members completed Signed Declaration of Interest and Confidential Disclosure agreements, which are available upon request.
- Financially compensated panel members have their Letters of Engagement identified and available.
- PRP limited contact with the test method developer to only formal meetings to answer questions on the test method. Any additional communication on TST updates, results of data audit, etc., were limited to only the co-chairs to limit potential bias or influence from method developer.
- All PRP meetings and calls were recorded with comprehensive meeting minutes.
- Documents for the peer review and from the test method developer were stored independently from the test method developer.
- Updates were provided to the French OECD National Coordinator by co-chairs, who was designated as the recipient of the validation and peer review reports.

Packet Completeness: Case Study of SENS-IS

- The OECD GD 34 chapters on reporting and record-keeping are short and generalized, so previously completed validation studies were referenced to confirm TST packet completeness.
- GD 34 requires that the TST be a complete and comprehensive report of the study and include assessments of both the level of adherence to validation and acceptance criteria and of the appropriateness of the test method for its proposed use.
  - The TST should document and justify all decisions for study amendments and deviations, as well as comprehensively reporting data and results.
- Test developer's TST was deemed acceptable for review by an independent consultant.

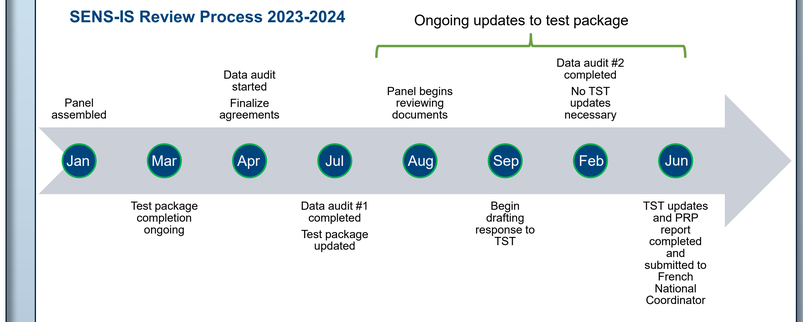
Quality Assurance Data Audit: Case Study of SENS-IS

- ImmunoSearch contracted with the Institute for In Vitro Sciences (IIVS) to perform a complete data audit of the TST and raw data. The data audit provided information on the integrity of the data presented and provided context to the information in the TST report that will be useful to peer reviewers as they assess the method and data.
- The data were audited according to the flow chart below. Chart indicates the types of files available for review by IIVS and how the data were interrelated across the different file types.



Peer Review Timeline: Case Study of SENS-IS

- The SENS-IS peer review did not proceed under the "traditional" GD 34 approach. Multiple processes in the peer review were ongoing simultaneously:
  - Data audit
  - Test packet updates
  - Packet completeness
- This resulted in delays and repeated reviews with each subsequent update.
- The actual SENS-IS peer review process is detailed in the timeline below and highlights the overlapping nature of all the efforts in the process.



Lessons Learned: Peer Review Panels Outside a Validation Oversight Committee

What we did right (we hope)…

- Put appropriate guardrails in place between panel and method developer.
- Third-party data storage for working documents and long-term maintenance of the final package, signed agreements, data audit reports, and minutes/recordings.
- Transparency about the process throughout.
- Quality assurance of the data.
- **Coordination with French National Coordinator.**

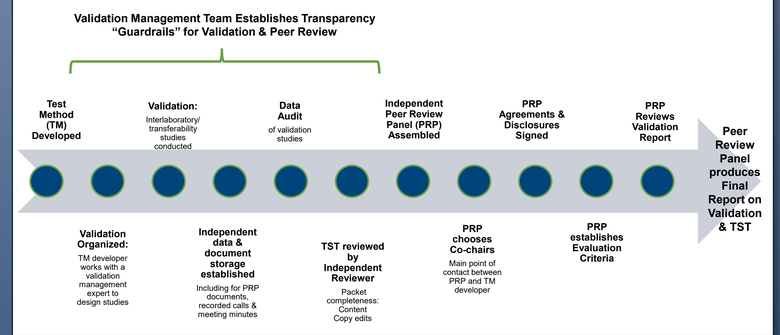
How the process should have gone…*

- Test method developer could engage a validation management expert to organize interlaboratory studies.
- Audit of validation data.
- Package completeness review.
- Content and copy edit of TST.
- Determine participants and the participation agreements for peer review panel.
- Peer review panel begins review.
- Peer review report completed.

*These steps were all completed, but the process was not as streamlined as it could have been.

Proposed Steps for Peer Review in the Future

From our lessons learned, we suggest the following flow for a comprehensive independent peer review in the future.



Acknowledgments

This project was funded with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C. The authors would like to thank Elizabeth Farley-Dawson for her detailed review and development of this poster.

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IIVS Institute for In Vitro Sciences