The Role of Institutionalized Validation in Integrating Emerging Science into Regulatory Decision-Making

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Presentation Points

1) Alternative toxicity testing approaches as a possible solution to the EHS information gap
2) Overview of validation
3) The need for 21st century validation

Current EHS Information on Chemicals

"the too-many chemicals problem"

Photo: Business Wire

Photo: http://www.all-creatures.org/articles/ar-45.html

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A New Paradigm of Toxicity Testing

A vision that advocates methods and approaches that

(1)decrease the use of traditional *in vivo* methods and use fewer animals,
(2) increase the number of materials that can be tested or screened,
(3)reduce the time and cost of testing and screening, and
(4)maintain predictive capability.

Alternative Testing Technologies as a Possible Solution

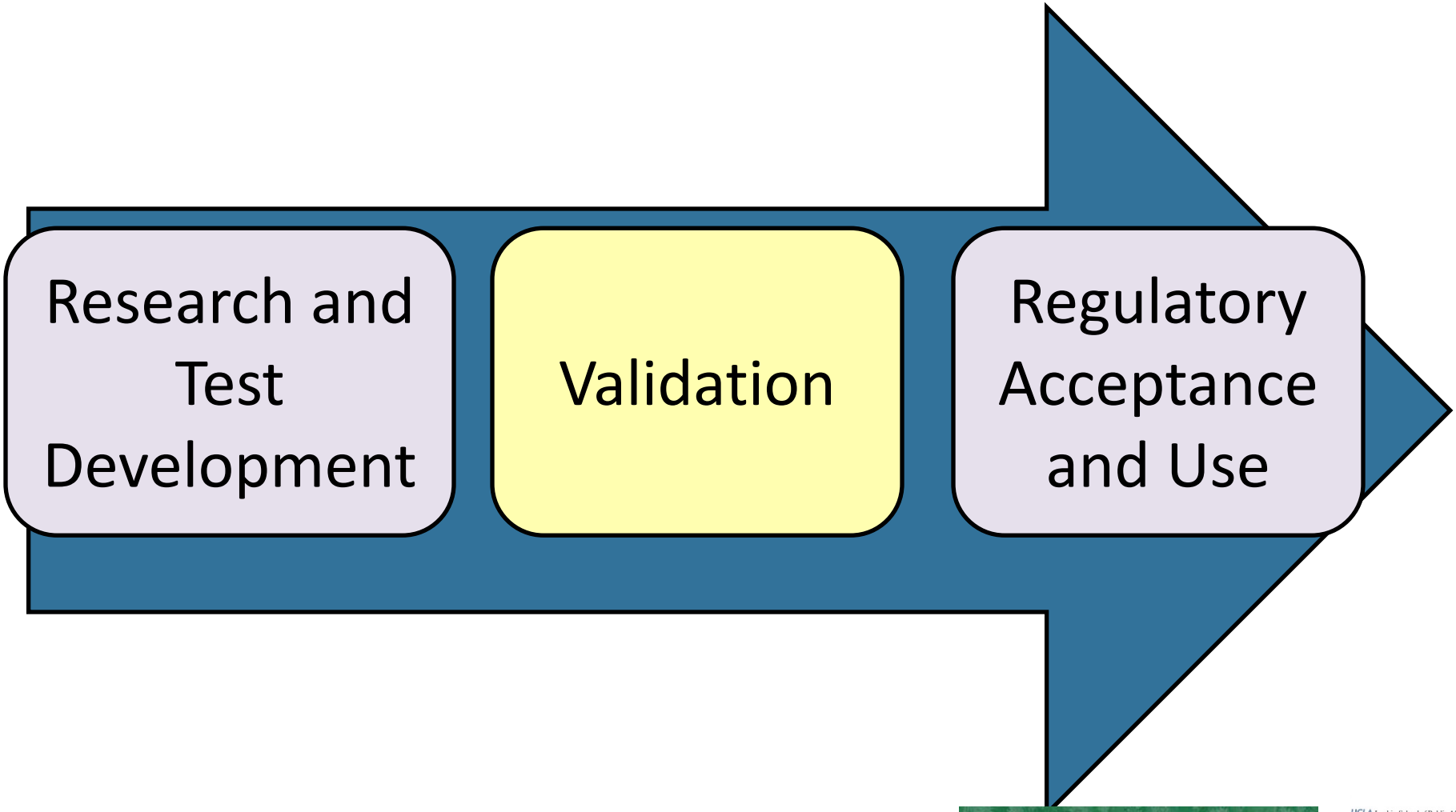
In Vitro

In Silico

Intermediate In Vivo

http://www.cein.ucla.edu/new/p15.php?pageID=186

When is a test method ready for regulatory use?



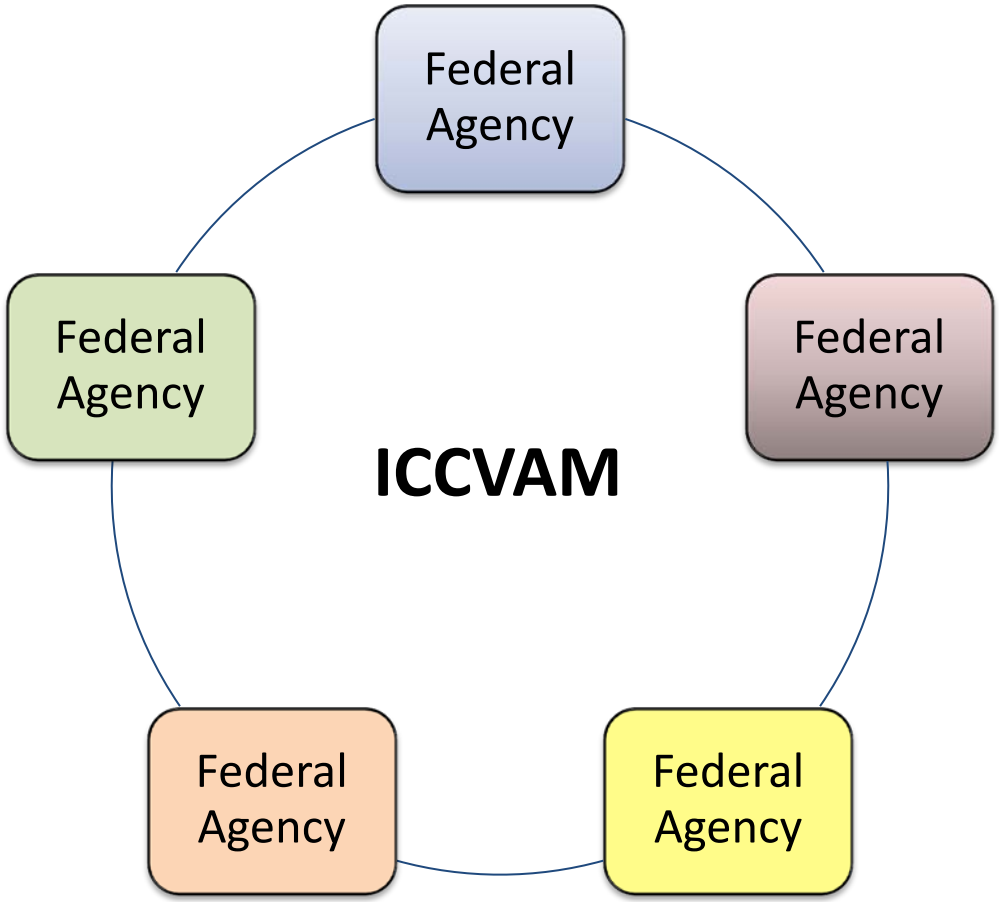
Definition of Validation

The OECD Definition of Validation:

"the process based on scientifically sound principles by which the reliability and relevance of a particular test, approach, method, or process are established for a specific purpose."

OECD SERIES ON TESTING AND ASSESSMENT No 34, Development, Validation and Regulatory Acceptance of New and Updated Internationally Acceptable Test Methods in Hazard Assessment, ENV/JM/MONO(2005)14

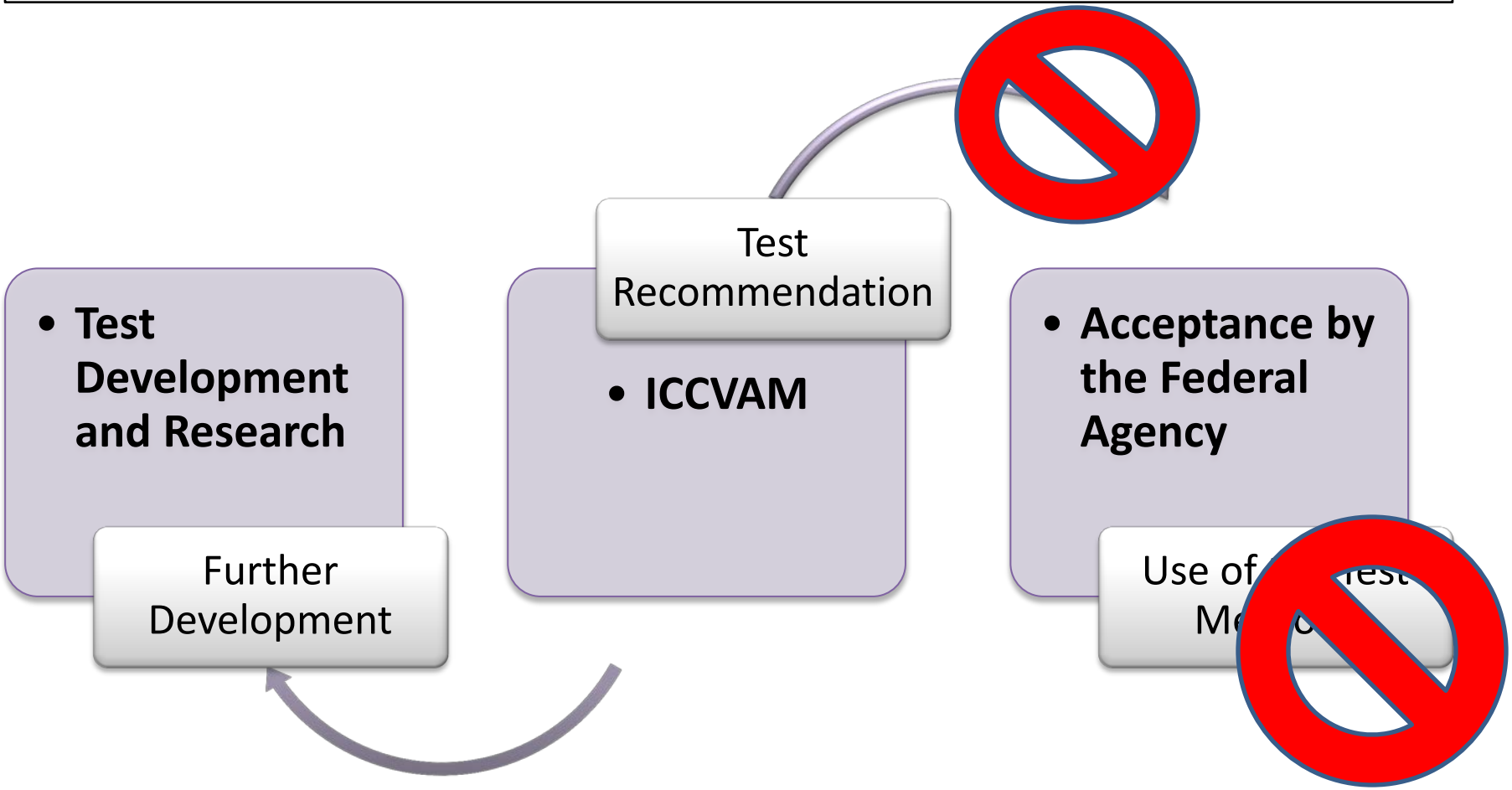
US Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)



Composed of the heads of **15 federal agencies [** § 285*l*-3 (c)]

ICCVAM Authorization Act of 2000, Pub. L. No. 106-545, § 4(e), 114 Stat. 2721 (2000) (codified at 42 U.S.C. §§ 201, 285l-4(e) (2006))

What is the impact of ICCVAM's test recommendations?



Criticisms of Institutionalized Validation

- "time consuming, low throughput, and expensive."
- Rigidity: Anchors the test and discourages further developments
- Using animal studies as the "gold standard"
- Does not address the needs of federal agencies

Richard Judson et al., (2013) Perspectives on Validation of High-Throughput Assays Supporting 21st Century Toxicity Testing. ALTEX 30, 51-66, p.52

Thomas Hartung, (2010) Lessons Learned from Alternative Methods and Their Validation for a new toxicology in the 21st Century, Journal of Toxicology & Environmental Health, Part B, 13:277-290, p.284

Thomas Hartung et al., (2013) Food for Thought—Mechanistic Validation, ALTEX 30, 119-130, p.127

Marcel Leist, Validation and quality control of replacement alternatives – current status and future challenges, Toxicol. Res., 2012, 8-12, fig.3

The Need for 21st Century Validation

Innovation.luskin.ucla.edu/nano

The type and purpose of a Test method

Types of Test Methods

- Screening test method
- Definitive test method
- Adjunct test methods
- Replacement test method
- Test battery

Purposes of test methods

- Prioritization
- Comparison
- Hazard Assessment
- Risk Assessment

A New Vision and Direction for ICCVAM

NTP, Draft, "A New Vision and Direction for ICCVAM" (2013)

- Main change is to have member agencies take a more active role
- This will be achieved through changes in the submission/nomination process. An assay would now have to be supported by one federal agency who takes on the role of 'sponsor' for the proposed project.
- Focus on projects with expectation of short term success (1-5 years)
- Acknowledgement that validation needs to be re-considered for integrated testing strategies, in silico and in vitro approach for screening and prioritization- however, the role that ICCVAM will play in these paradigm shifts is unclear.

Moving Forward

- Test methods are not one size fits all
- Type of testing that is appropriate depends on the regulatory decision
  - Is the goal to screen chemicals? To prioritize? Conduct a comprehensive risk assessment?
- Is a "full" validation necessary for every test method?
- How think about re-review, re-iteration (for new purposes, new scientific information etc.)?

Considerations

- What is quality science?
- When is the science “good enough” to be used in regulatory decision making?
- Who gets to decide?

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Thank You!

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