Pathways to regulatory acceptance – looking beyond validation

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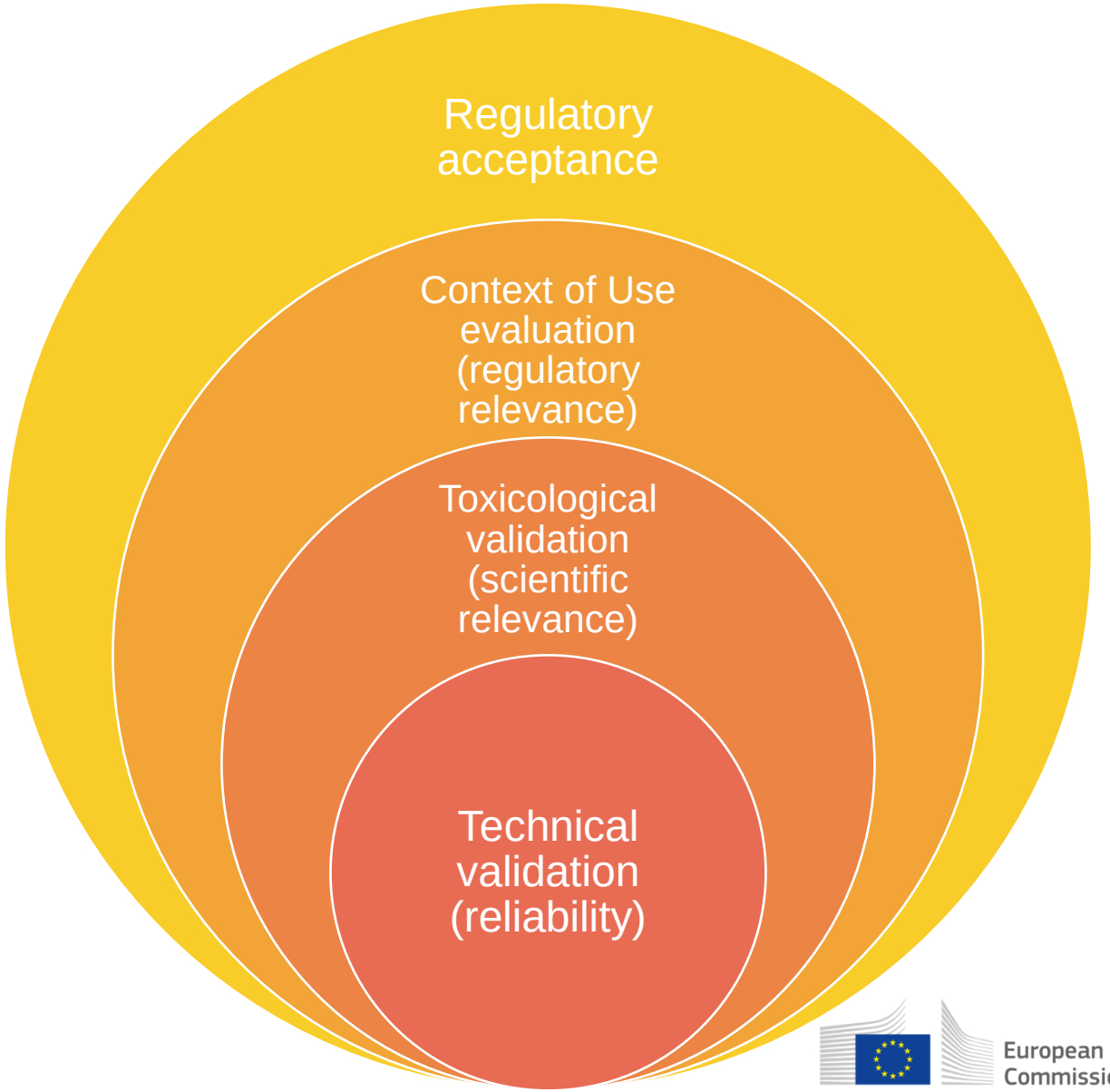
From validation to acceptance

- **Validation** is a scientific exercise
- Necessary, but not sufficient for acceptance and use

Acceptability depends on:

- **Credibility**: willingness to base decisions on information from the NAM (Schruben, 1980)
- **Feasibility**: regulatory and practical barriers



Beyond scientific validity – what's at stake?

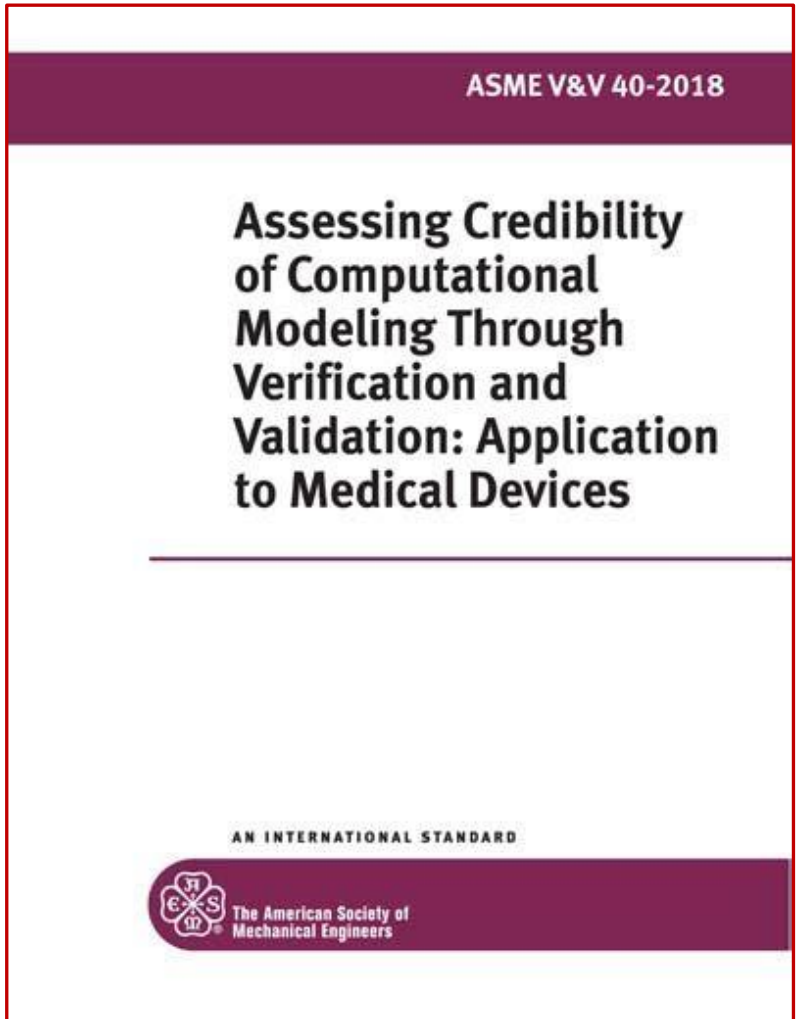
Concepts from *in silico* medicine (ASME V&V 40)

Influence: contribution of the NAM to the decision relative to other available evidence

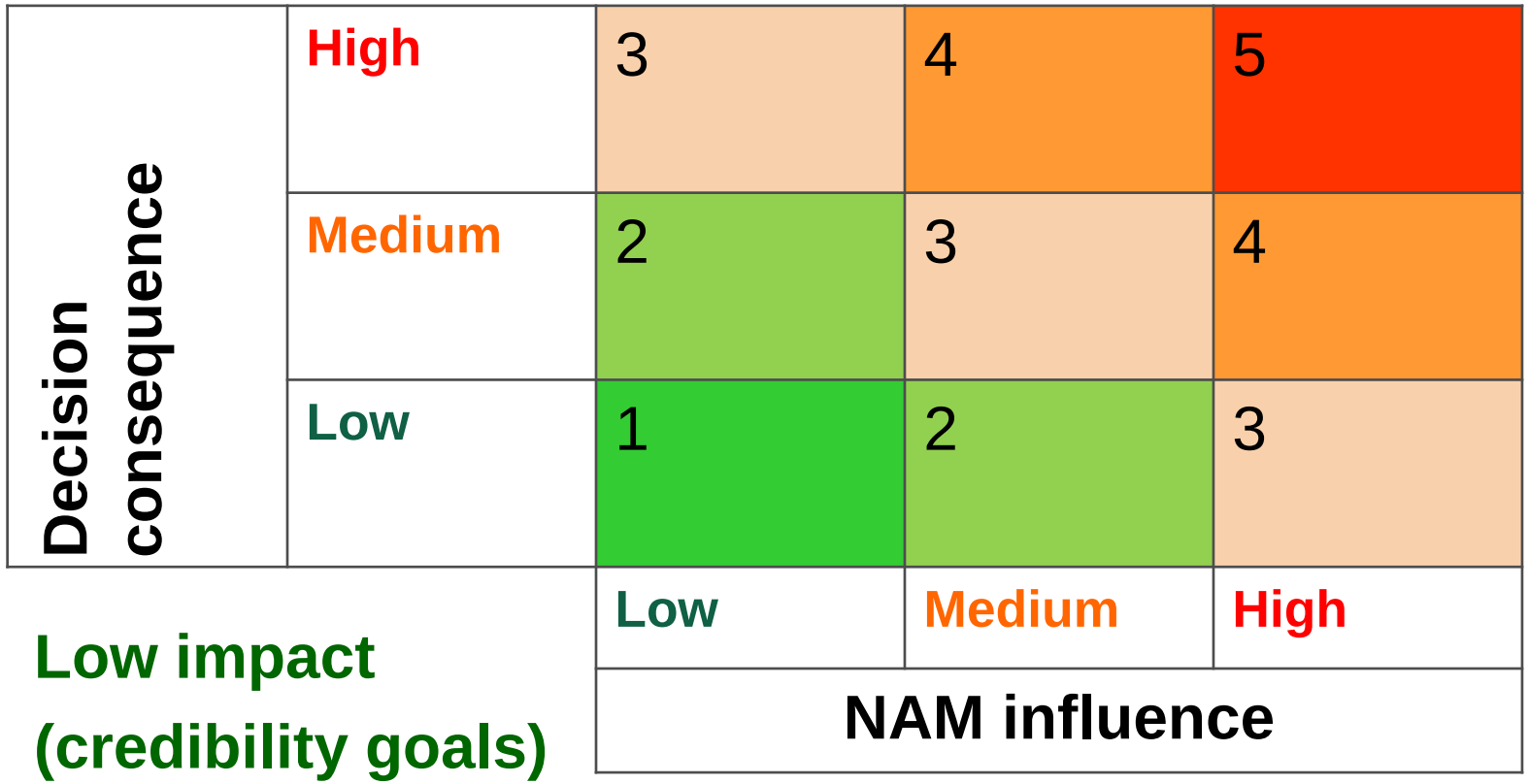
- NAM drives the decision
- NAM used as part of Weight of Evidence
- NAM provides supporting evidence

Decision Consequence: significance of an adverse outcome resulting from an incorrect decision

- False positive leading to an unnecessary restriction
- False negative resulting in harm to health or environment



Beyond scientific validity - setting credibility goals for NAMs



High impact (credibility goals)

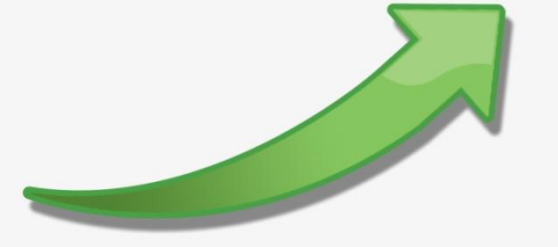
Low impact (credibility goals)

NAM Impact Matrix (risk of being wrong)
Based on ASME VV-40 and FDA guidance
(credibility of computational models used in medical device submissions)

Multiple pathways to acceptance

Rebuild: design a new regulatory framework with NAM-based criteria

Co-evolution of NAMs and new criteria (e.g. EPAA Designathon)



Replace: the NAM replaces an animal test in current regulatory framework

Standalone method or component of testing strategy

Repurpose: adapt an established NAM for a different application

Different endpoint or context of use

Augment: introduce a NAM to address a concern (otherwise neglected)

No animal method or no explicit information requirement

Concluding remarks

- The journey from validation to acceptance crosses multiple levels of assessment:
  - **technical** validation (reproducibility, reliability)
  - **toxicological** validation (scientific relevance)
  - **context-of-use** evaluation (regulatory relevance, decidability)

- Beyond validation, we need:
  - impact-based credibility assessment
  - multiple pathways to acceptance
  - clarity on who accepts for a given context of use

- Prior agreement on credibility goals could avoid long and winding roads