Measurement science in ICCVAM

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Technical Framework Manuscript

Bench Marks!

Technical Framework for Enabling High-Quality Measurements in New Approach Methodologies (NAMs)

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Technical Framework for High Quality NAMs

Collaborative project with CPSC, NICEATM, DOD, EMPA, NIST

- To yield reproducible NAM results across time and among laboratories, the framework includes a series of inter-related steps that describe
  - How to apply basic quality tools (cause-and-effect analysis, flow charts, control charts, etc) to improve confidence in NAMs
  - Approaches for adding statistical confidence to decisions based on NAM results
  - There may be tradeoffs though with more controls potentially leading to higher costs

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Case Study with Oral Mucosal Tissue

Human Oral Epithelium

- TR146 cells (derived from a **squamous cell carcinoma** of the buccal mucosa) **EpiOral** & EpiGingival or SkinEthic
- 8-11 layers of cells per construct
- Mattek EpiOral chosen as a case study

Test

- Material Irritants in polar or nonpolar solvents
- Described in ISO 10993:23 for skin irritation using human epidermal tissue

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Biological relevance and measurement quality influence predictive power of a new approach method (NAM)
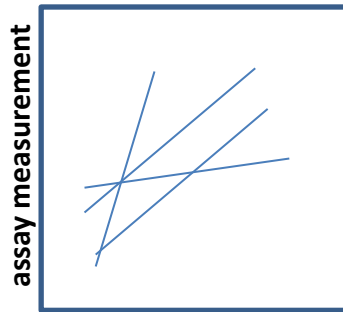

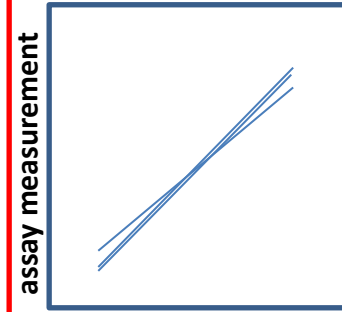Quality: YES/NO, Biological relevance: NO
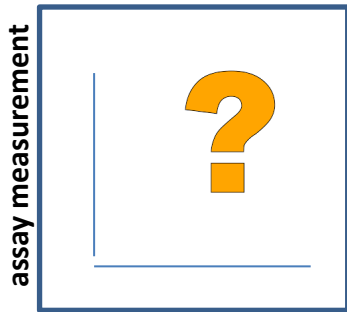
assay measurement

Clinical measurement

Unlikely predictive

Quality: NO, Biological relevance: YES

assay measurement

Clinical measurement

Poorly predictive

Quality: YES, Biological relevance: YES

assay measurement

Clinical measurement

Highly predictive

decisions

Results

- Assay has unique design considerations in that each experiment uses tissues that cost ~2k per set and are only available every two weeks
- Conceptual tools have been applied to the assay such as cause-and-effect analysis, flow charts, and plate design
- Robustness testing has been applied to evaluate key sources of variability such as the MTT reagent, storage conditions, pipetting approach, etc.
- Control charts have been made for the positive control, negative control, and solvent controls
- Multiple relevant test compounds have been evaluated
- A statistical model has been developed to provide positive/negative calls with an associated statistical probability
  - This may help making links to the traditional animal approach, which has its own uncertainties