Scientific Advisory Committee on Alternative Toxicological Methods Implementation Working Group

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Chair, Working Group

SACATM Meeting
September 5 – 6, 2012

Implementation Working Group

- Members
  - Joy Cavagnaro, Access BIO, Chair
  - Eugene Elmore, University of California - Irvine
  - Steven Hansen, ASPCA
  - Michael Olson, GlaxoSmithKline
  - Daniel Wilson, The Dow Chemical Company
- Designated Federal Officer
  - Lori White, NIEHS/DNTP
- Eight teleconferences: March – August 2012

Charge to the Working Group

Assess implementation of ICCVAM-recommended alternative methods

Scope and Viability of ICCVAM

- ICCVAM cannot do everything
- Interest in alternative testing has grown
  - Society of Toxicology
  - Tox21
  - Small business initiatives
- Great value in ICCVAM-validated methods
- Alignment of priorities
- Global perspective

Current Status of Acceptance

- Adoption ❖ Acceptance
- Responsibility for acceptance
- Perceived lack of:
  - Clarity regarding acceptance
  - Metrics and tracking
  - Champions
  - Oversight and accountability
  - Alignment with risk assessment strategies

Assessment Strategy

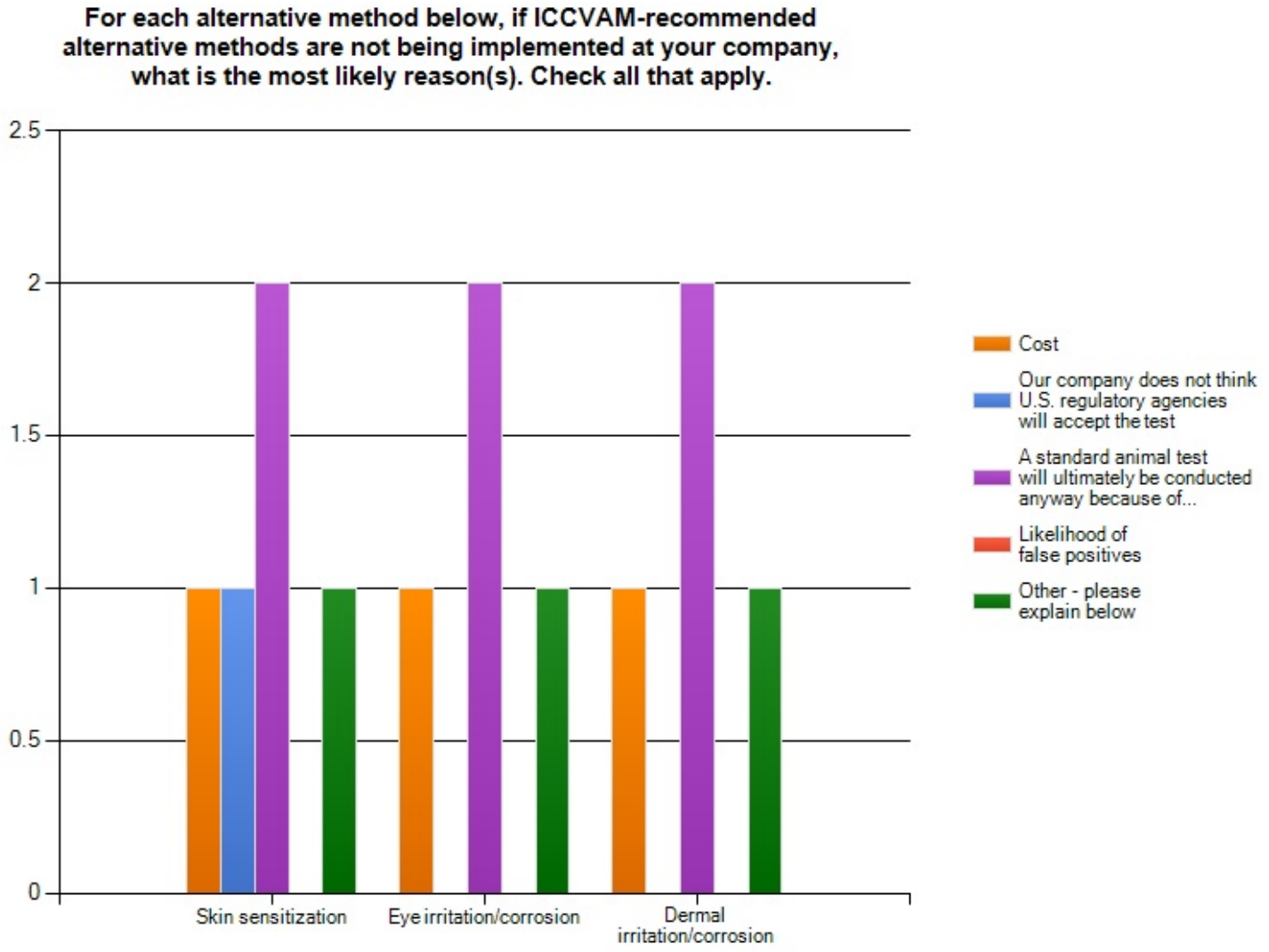
- End-users of alternative methods
  - Regulated industry
    - Life sciences research and services companies
    - Contract research organizations (CROs)
  - U.S. regulatory agencies
- Rationale
  - Confusion within both government and industry
  - Lack of reporting in past

Assessment Strategy (cont'd)

- Focus on U.S. companies and CROs that use alternatives
- Develop two surveys:
  - 9 or fewer respondents each
  - ICCVAM-recommended alternatives only
  - Anonymity, but use of comments verbatim
  - Focus on use of alternatives, not on quantification of animal usage
  - Not an unbiased industry-wide sample
  - No attempt to be statistically valid

Company Survey

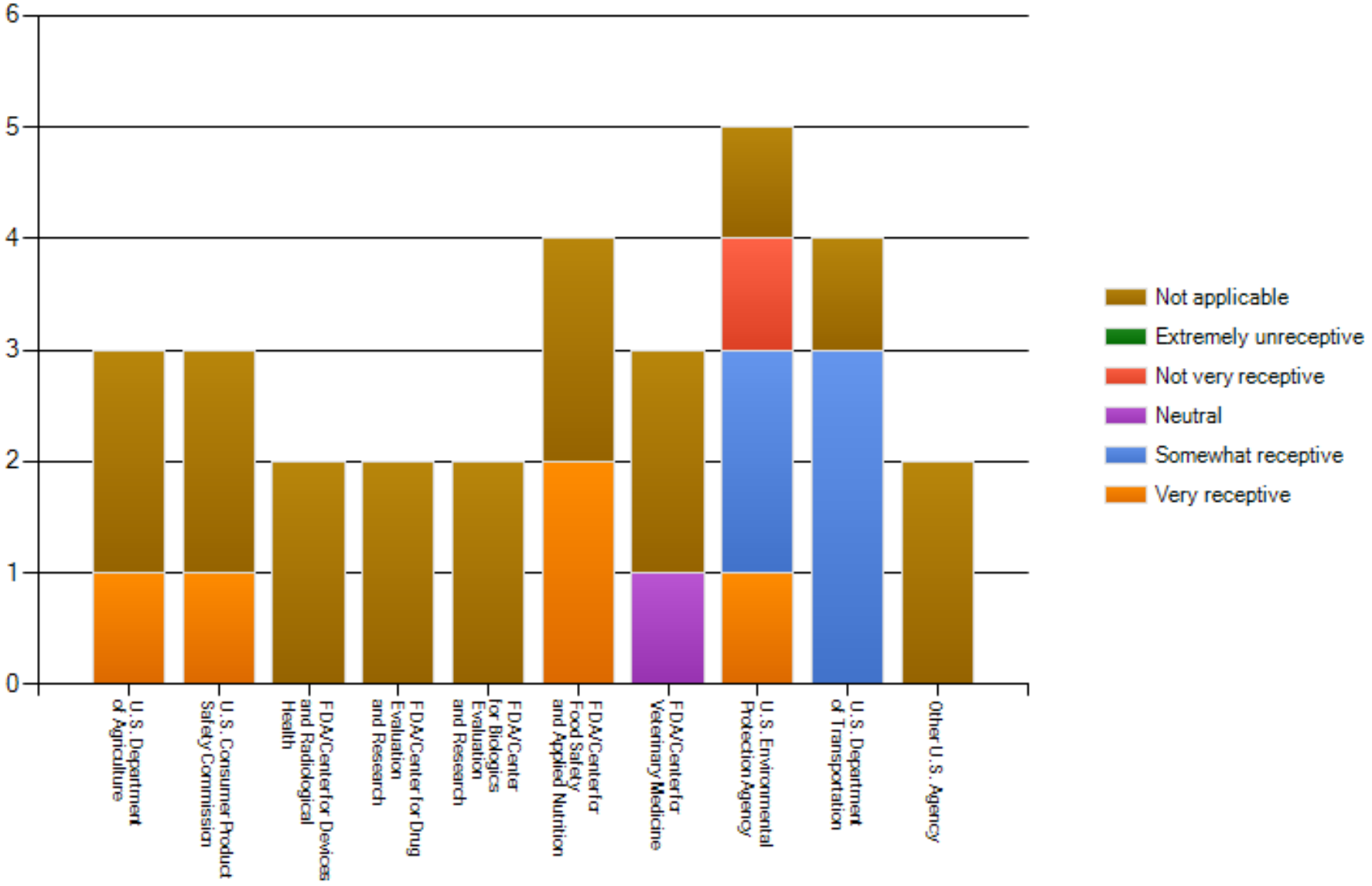
- Submit data?
  - Regularly 14.3%
  - Sometimes 71.4%
  - Never 14.3 %
- Data accepted?
  - Yes 83.8%
  - No 16.7%



Comments:

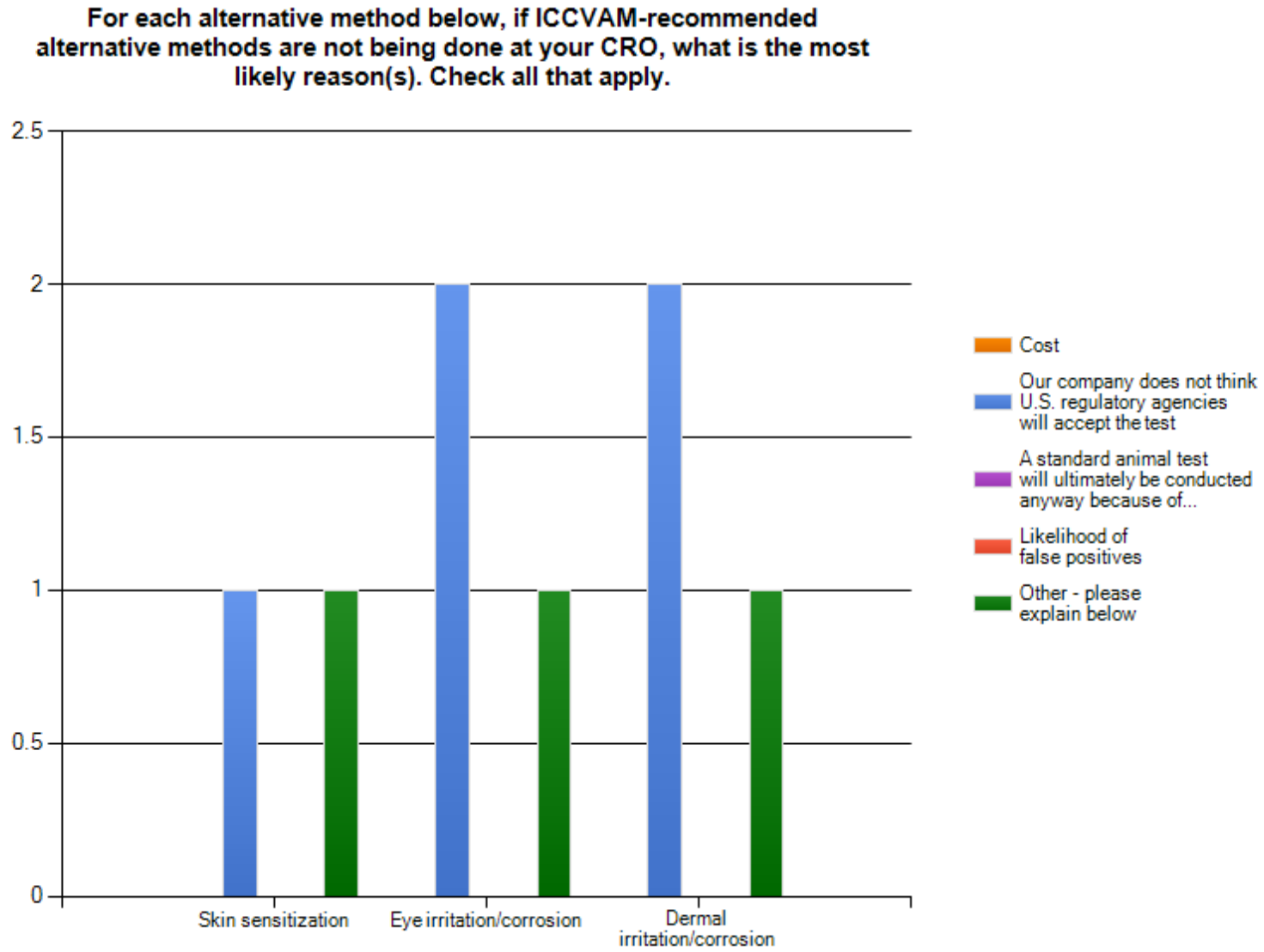
- "Likelihood of false negatives; cost increases since *in vitro* often must be followed by *in vivo* testing in any case."
- "We are using all of these an[d] other alternative methods not yet reviewed or approved by ICCVAM."

Based on your company's past experience in submitting data from ICCVAM-recommended alternative methods to U.S. regulatory agencies, please rank the receptivity of the agencies to these data.



CRO Survey

- CRO testing capabilities?
  - *In vitro* primarily 16.7%
  - *In vivo* primarily 16.7%
  - Both *in vitro* and *in vivo* 66.7%
  - *In vivo*, but only after tests have been conducted *in vitro* 0%



“We do not believe that there is a fully accepted regulatory replacement for this test. Currently, these are screens.”
“We have been providing alternatives to *in vivo* irritation studies since 1990.
“We do not do environmental chemical testing, only pharmaceutical products.
“We believe this to be true under most circumstances.”

Reason(s) *in vitro* cytotoxicity methods are not being implemented at your CRO for picking starting doses for acute oral toxicity testing?

- Cost 25%
- Timing 25%
- Just not practical – we can do a better job using experience 25%
- Other 75%
- Comments
  - "We have not investigated this test."
  - "Most sponsors rely on knowledge of the chemistry of their products to estimate the starting levels for any of the acute oral toxicity testing. In the 2010 - 2011 time frame we performed 67 up and down and 38 acute toxic class oral studies. None were performed using cytotoxicity to estimate the starting points and in virtually all studies the estimated starting dose was correct."
  - "*In vitro* tests are not remotely predictive of animal responses, especially for the types of pharmaceutical products we evaluate. The idea that an *in vitro* test is going to accurately predict the complex drug metabolism that goes on in an animal that impacts toxicity is amusing."
  - "The majority of the studies we conduct are limit tests and most of these pass."

At your CRO, are most alternative methods that are being implemented:

- ICCVAM-recommended for regulatory use 25%
- Screening methods for non-regulatory use 75%
- Comments:
  - "We have a very wide selection of *in vitro* tests, primarily offered at our [redacted] facility. Most of the tests are OECD test guideline driven or have been through ECVAM (some ICCVAM) validation."
  - "Although some alternatives are being used as screening methods, most are being used to provide estimates of irritancy/nonirritancy for cosmetic and personal care products and ingredients not subject to regulatory review."
  - "We use a significant number of *in vitro* ADMET tests to support early drug discovery, not to replace FDA mandated animal tests."
  - "We have and will continue to adopt alternative methods once they become uniformly acceptable to the global regulatory agencies"

IWG Recommendations

- ICCVAM should regularly collect data regarding implementation of their recommended alternative testing methods from both regulated industry and U.S. regulatory agencies. A survey instrument and the intention to collect information should become part of ICCVAM efforts in the future.

- ICCVAM should generate a concise plan and timeline of implementation of methods and the resulting reduction in volume of animals used. There should be clear articulation of goals and anticipated milestones.

- The preliminary data from this survey should be shared with U.S. regulatory agencies and ICCVAM agencies should formally respond to this report.

IWG Recommendations (cont'd)

- The current survey can be used as a starting point for assessment of implementation of ICCVAM-recommended methods.

- When requesting data on implementation, specify numeric data regarding the kinds and numbers of assays submitted and accepted. Further, ask how many assays were submitted resulting in requests to go back and do follow-up *in vivo* testing.

- Provide advance notice for the request for data; data have been requested only informally in the past. Encourage industry and regulatory agencies to collect data on implementation on a continual basis.

IWG Recommendations (cont'd)

- Use initial industry-wide and agency-wide surveys to establish a benchmark for the current levels of implementation. This will be important for obtaining the trajectory of change in implementation.
- Each regulatory agency will require a unique survey tailored to its mission.
- Determine a regular interval period for the surveys to be repeated.
- Targeting the right people to receive the surveys in industry and U.S. agencies will be critical.
- Work closely with EPA to assure that ICCVAM-recommended methods are adopted and accepted in a timely way.

IWG Recommendations (cont'd)

- Open a dialogue with FDA regarding the relevance of ICCVAM-recommended methods to FDA's mission.

- Make a goal of surveying agencies to determine how they accept data; what is the signal to move on to an *in vivo* test; are the *in vitro* tests just considered:
  - screening tests
  - supplementary/refinement tests, or
  - definitive/replacement tests

- Encourage U.S. regulatory agencies to be more proactive in supporting alternatives and becoming involved in ICCVAM activities.

- At future SACATM meetings, provide input on alternatives used for device testing,

- The next generation of alternative test needs to be treated more thoughtfully.

- ICCVAM should work with ICATM to advocate for worldwide acceptance of alternative methods.

Discussion Questions

1. Please comment on the Working Group's report

2. Regarding the recommendations in the report, do you have further recommendations for advancing implementation of ICCVAM-recommended alternative test methods?

3. Do you have suggestions for additional assessment of implementation of ICCVAM-recommended alternative test methods?

SACATM will be asked to vote on acceptance of the Working Group report.