



INTERNATIONAL CONSORTIUM *for*
INNOVATION & QUALITY
in PHARMACEUTICAL DEVELOPMENT

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Comments from the IQ Consortium on the NICEATM-ICCVAM Five Year Plan (2013-2017)

We are pleased to offer the following comments, prepared by the International Consortium for Innovation and Quality in Pharmaceutical Development (the IQ Consortium). The IQ Consortium is a technically focused organization of pharmaceutical and biotechnology companies, whose mission is to advance science-based and scientifically-driven standards and regulations for pharmaceutical and biotechnology products worldwide. We appreciate this opportunity to provide comments, and would be happy to discuss any portion of them with you as appropriate.

Please contact the IQ Secretariat with any questions:

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The NICEATM-ICCVAM Five-Year Plan (2013-2017)

General Comments:

The IQ Consortium recognizes the considerable effort of ICCVAM to promote the development of alternative test methods and facilitate their acceptance by a very broad regulatory stakeholder population. We also recognize the Committee's interest in developing productive partnerships in and outside the government to facilitate further advances.

ICCVAM's historical focus has been on alternative methods for 'safety' testing of chemicals we are exposed to rather than the deliberate consumption of a chemical (i.e. a medicine), although many of the technologies specifically mentioned have potential utility for pharmacology or efficacy testing as well. Additionally, most of the methods considered specifically address commitments to 2 of the 3Rs (i.e. replace and reduce). This group believes there is significant opportunity to include promotion and validation of platforms that might be applied for either safety or efficacy testing as well as methods that might be 'refinements' to current approaches. The IQ Consortium believes that this will help focus the Five-Year Plan on ICCVAM's objective of applying the 3Rs.

ICCVAM is uniquely positioned to facilitate partnerships across public-private sectors. Positioning this Committee as a platform for partnership to leverage technologic advances would have a significant impact on our ability to protect human, animal, and environmental health.

We have the following specific comments:

Strategic Opportunity #1: Promote the Application and Translation of Innovative Science and Technology

- The description of research interests is encouraging and those interests (*in vitro* and computational methods, Tox21 and high-throughput screening, biomarkers, toxicity databases, use of stem cells) align with our interests and provide opportunities for partnership as outlined in Strategic Opportunity #4.
- This section largely summarizes efforts of "ICCVAM partner agencies". It would be useful to know what role ICCVAM would specifically have with the development of these technologies and how it might facilitate private sector partnerships to contribute.
- The commitment to "swifter progress toward the 3Rs goal of eliminating the use of animals in regulatory testing" is noteworthy but potentially not realistic in the near future (i.e. the scope of this 5 year plan). Additionally, ICCVAM could facilitate conversations between regulators and the pharmaceutical industry.
- It would be useful to have a citation for the "initial projects" funded by the NIH Regulatory Science Initiative for additional information to identify opportunities for contribution.
- Current efforts involving "Stem Cells" seem to offer much opportunity. We suggest that ICCVAM expand this and present specific goals.



- With respect to acceptance of “Biomarkers of Toxicity,” it is important to know how ICCVAM will distinguish its role from the FDA Biomarker Qualification process. It would be also helpful to know how industry and consortia will work with ICCVAM on this.
- ‘Bioimaging’ technologies provide another opportunity for refinements.
- We encourage ICCVAM’s role in facilitating the development of *in silico* modeling tools that might help ‘translate’ *in vitro* data to *in vivo* experiences or clinical outcomes. Increasing predictivity of *in silico* models will reduce the number of animals used.
- We additionally encourage ICCVAM’s role in bringing together collaborations that could develop integrated testing and decision strategies. Vast arrays of non-integrated assay systems would have greater impact assessed in a more holistic and integrated way.

Strategic Opportunity #2: Advance Alternative Test Methods and Testing Strategies

- In the U.S., particular attention is given to USDA ‘reportable’ species that do not include rodents. Also, the historical focus of ICCVAM has been on alternative assays to *in vivo* safety testing. Considerable opportunity exists for advancing 3Rs and improving animal welfare by broadening the Committee’s scope to include efficacy and safety testing as well as all mammalian species.
- The plan appropriately highlights specific regulatory interest in vaccine safety, dermal and ocular irritation, acute systemic toxicity testing, and endocrine disruptors. These areas have broad applicability across private industry sectors, and gaining acceptance by regulatory agencies is a key aspect for industry use of new assays.
- The plan includes an effort to evaluate “two types of cultured liver cells” for acute systemic toxicity testing. Considerable expertise and experience already exist for modeling drug toxicity with *in vitro* hepatocytes. Is there something about this effort that is novel?
- How does ICCVAM consider the influence of individual patient susceptibilities to allergic contact dermatitis as a source for disconnects between results in the mouse LLNA and clinical outcomes?
- Please recognize that the *in vitro* micronucleus test includes an examination for “the presence of chromosome fragments” as well as whole chromosome loss.
- Could it be confirmed that the “genetic toxicity testing” the FDA is testing in “various primary human cells and cell lines” is for consideration as alternatives to carcinogenicity testing rather than replication of current *in vitro* gene tox testing methods?
- ICCVAM could consider assessment of ‘*in vivo*’ alternatives to traditional 2-year bioassays using transgenic animals or “decision strategies” using pre-neoplastic morphologic changes in repeat-dose toxicity studies as a trigger for running the 2 year bioassay/carcinogenicity testing.

Strategic Opportunity #3: Facilitate Regulatory Acceptance and Use of Alternative Methods

- While it is acknowledged that “While NICEATM and ICCVAM promote and employ sound science to determine the validation process of alternative test methods, only Federal agencies can accept these



test methods...”, an annotation of that ‘acceptance’ would strengthen recognition of ICCVAM’s impact on “facilitating regulatory acceptance”. Particular focus should include USDA and FDA as primary stakeholders in animal testing data.

- Lack of the annotation referred to above prevents assessment of the usefulness of methods traditionally used to communicate and facilitate.
- ICCVAM should consider greater engagement in professional societies frequented by animal care stakeholders- e.g. AALAS meetings. The IQ 3Rs Leadership Group can facilitate that engagement.

Strategic Opportunity #4: Develop and Strengthen Partnerships

- We recognize and strongly support the role of ICCVAM to facilitate collaboration between industry, academia, government agencies, and international partners.
- Though workshops have been used to facilitate the exchange of information with respect to alternatives, other methods might be useful as well. For example, symposia to explore opportunities around new technology platforms and from which to form collaborative working groups, informatics platforms as ‘safe harbor’ for shared data, development of data analysis tools to integrate and interrogate that data.
- ICCVAM might consider recognizing specific opportunities for partnership given the breadth of potential activities in Strategic Opportunities 1-3- i.e. where are there priority needs for partnership or cooperation?
- “Working groups” are mentioned that will “continue to identify research needs and promising methods.” Please give examples of previous working groups and ideas for future groups.
- The breadth of federal agency stakeholders and even individual ‘centers’ within those agencies is seen as a significant challenge for communication and influence. Does ICCVAM have any novel strategies for dealing with that complexity?
- We encourage ICCVAM to define goals to increase collaboration that would speed the development and validation of alternatives. Additionally, it would also be helpful if ICCVAM had specific plans for communicating results to encourage quicker acceptance and implementation of validated alternatives.