

May 17, 2015

Dr. Warren S. Casey, Director
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Sent via email to warren.casey@nih.gov

Dear Dr. Casey:

The following comments are submitted on behalf of People for the Ethical Treatment of Animals (PETA) and the Physicians Committee for Responsible Medicine (PCRM) in response to the April 14, 2015 Federal Register Notice by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). Two discussion questions were posted on the ICCVAM public forum website ([here](#)), and our responses below are divided into two sections based on these questions.

Suggestions for tracking progress towards replacement, reduction, and refinement of animal use for safety testing

Quantifying the animals used in testing

The vast majority of animals used in testing are mice and rats yet these animals are not covered under the Animal Welfare Act (AWA) and therefore their numbers are not required to be reported to the U.S. Department of Agriculture (USDA). A recent study, published in the *Journal of Medical Ethics*, documented that an astounding 98.8 percent of animals in leading National Institutes of Health (NIH)-funded laboratories are not covered by the AWA and the numbers of unregulated animals in these laboratories increased by 72.7 percent over the 15-year period from 1997 to 2012.¹ NIH presently collects data on the numbers of all vertebrate animals held and used in NIH-funded institutions in the form of “Facility and Species Inventories” included with the institutions’ Public Health Service Assurance documents. But NIH does not currently compile, analyze, or publish this data.

Thus, we encourage ICCVAM to work with:

- (1) NIH to regularly publish the numbers of all animals, including mice and rats, used in NIH-funded laboratories
- (2) industry to collect and publish the numbers of mice and rats used for both regulatory and non-regulatory purposes
- (3) its member agencies to collect and publish the numbers of mice and rats used in-house

The U.S. lags far behind other countries, such as those in the European Union, that publish the numbers of all animals used as well as the endpoints for which they were used. This information

¹ Goodman, J.R., Chandna, A., & Roe, K. (2015). Trends in animal use at US research facilities. *Journal of Medical Ethics*, 0:1-3.

is critical to help identify areas of priority for ICCVAM and to help understand and quantify the effectiveness of ICCVAM. Without the ability to quantify animal use numbers, congressional appropriators and taxpayers are unable to determine ICCVAM's progress in fulfilling its mandate to coordinate the reduction and replacement of animals in testing throughout the government.

Searching for alternatives to animal tests

The AWA requires that investigators search for and consider alternatives to any procedure that is likely to cause pain or distress (Category D or Category E experiments). Nevertheless, numerous federal reports have indicated that U.S. laboratories fail to conduct a thorough search for alternatives. A September 2005 USDA Office of the Inspector General (OIG) audit report documented that, at almost one-third of all experimentation facilities, investigators failed to consider alternatives to painful procedures. The report cites this failure as being the most frequent AWA violation at animal laboratories.

A December 2014 USDA OIG audit report echoed this concern, reporting that during FYs 2009-2011, USDA inspectors "cited 566 violations related to inadequate protocol review"—including "inadequate searches for alternatives to painful procedures." Furthermore, it is not uncommon for Category E justifications, submitted by USDA-registered facilities in an annual report, to state that alternatives are not available even when alternatives exist, and time constraints make it difficult for inspectors to remain up-to-date on the latest alternative methods and to thoroughly assess whether the information regarding the lack of alternatives is accurate. Due to the number of relevant databases and variety of search terms, it may be challenging for researchers to determine all relevant searches. To address these issues, we would encourage:

- (1) collaboration between ICCVAM and the National Library of Medicine to create a guidance document on search terms and to maintain lists of validated alternatives;
- (2) collaboration between ICCVAM and the NIH to create greater transparency on alternatives searches through the use of a reporting template, which should be made publically available;
- (3) collaboration between ICCVAM and USDA to provide training opportunities to USDA reviewers. Training of USDA reviewers on available non-animal methods would equip reviewers with the ability to determine whether alternatives exist.

Fostering international harmonization of alternative methods

International regulatory requirements are not necessarily standardized, hindering reductions in animal use even when a non-animal test method exists and has been approved for use in one sector. For example, Organisation for Economic Co-operation and Development (OECD) test guidelines developed for Globally Harmonized System of classification may not be applicable to the classification systems of U.S. regulatory agencies. Likewise, alternative methods approved for use by regulatory agencies in the U.S. are not uniformly aligned with similar guidance published by the U.S. Pharmacopeia, the European Pharmacopoeia, the International Standards Organization, and others.

One way to foster global harmonization is through incorporation of additional groups into International Cooperation on Alternative Test Methods (ICATM) meetings. We were happy to

hear that the Brazilian Centre for the Validation of Alternative Methods plans to join ICATM in 2016 and that China is currently an observer. We encourage ICCVAM/ICATM to continue to work to include representation from additional countries at these meetings. Additionally, we ask that ICCVAM work to include representatives from various standards organizations into ICCVAM and Scientific Advisory Committee on Alternative Toxicological Methods meetings, possibly as observers, so that these representatives may be kept aware of changing regulatory requirements that need to be addressed in their own respective guidance documents.

Specific activities or areas on which we would like to see more focus from ICCVAM

Our organizations appreciate the extent to which ICCVAM and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) have now shifted their focus towards areas of need for the member agencies. This close collaboration between staff and scientists at agencies is essential to ICCVAM's success and the ultimate implementation of new test methods in place of *in vivo* methods. Furthermore, NICEATM's creative and capable staff has filled a real need with its emphasis on data gathering and analysis and computational support. Lastly, ICCVAM's priorities seem to include an appropriate mix of short-term (acute and contact toxicology) and long-term (acute, reproductive, and developmental toxicology) endpoints.

Reviewer Training

In vitro and *in chemico* methods are increasingly being included in test guidelines, and *in silico* methods are continuously being developed and updated. Furthermore, the ways in which these methods can be used in integrated approaches to testing and assessment are constantly being developed and updated. As a result of this very dynamic situation, it is difficult for reviewers to keep up-to-date and, as a result, industry finds that there is a high degree of variability in the acceptance of non-animal methods due to differences in reviewer familiarity with the methods.

In order to see a reduction in the use of animals, it is critical that industry to use non-animal methods and that these methods be accepted by regulatory agencies. Therefore the appropriate training of reviewers is an absolute necessity. We urge ICCVAM to partner with its member agencies to organize training on non-animal methods. This could include training sessions on *in vitro* and *in chemico* methods applicable to a certain agency and how to use them in an integrated approach, or on the use of the OECD Toolbox, among others. These trainings could be in the form of presentations given by speakers from NICEATM, industry, or non-profit groups such as the Institute for In Vitro Sciences which has a focus on both conducting testing as a contract research organization and on outreach and education.

Biologics

In 2010, vaccine testing accounted for approximately two-thirds of the animals used in regulatory tests in the European Union (EU). In the same year, vaccine testing accounted for at least 59 percent of the animals reported to USDA as experiencing pain without relief (Category E). The magnitude of these figures shows that U.S. regulatory agencies must focus more efforts on opportunities to replace and reduce the use of animals during the development and testing of biologics. We urge ICCVAM to ensure that the following issues are formally addressed:

- *Updates on progress toward the recommendations and goals of ICCVAM workshops:* ICCVAM and NICEATM have co-organized several international [workshops](#) on the use of alternative methods in the development and testing of biologics. Recommendations put forth during these workshops have great potential to reduce animal use, but little has been published on the progress of agencies toward achieving many of these goals. For example, at the 2012 “International Workshop on Alternative Methods for *Leptospira* Vaccine Potency Testing: State of the Science and the Way Forward,” the Center for Veterinary Biologics (CVB) announced ongoing projects intended to evaluate the possibility of combining bacterial back-titrations with challenge controls, standardizing procedures for use of cryopreserved *Leptospira*, and reviewing issues regarding the parallelism requirements for using ELISA in place of the *in vivo* batch potency test—each of which is important to reducing animal use. We encourage ICCVAM to partner with the U.S. Food and Drug Administration (FDA) and USDA to provide an update on the progress in these areas, in the form of follow-up workshops or reports.

- *Report on the implementation of currently available vaccine challenge replacement assays:* A number of *in vitro* and serological replacements for *in vivo* challenge assays have been developed and made publicly available for industry use:
 - *In vitro* leptospira potency assay (USDA SAM 624—627)
 - *In vitro* erysipelas potency assay (USDA SAM 612 and 613)
 - *In vitro* clostridial potency assay (USDA Draft SAM 220)
 - *In vitro* tetanus toxoid potency assay (USDA SAM 217)
 - *In vitro* rabies vaccine potency assay(s)

Nevertheless, little information is available in the public domain suggesting that these alternatives have been implemented, even when the replacement methods have been validated for regulatory use. We urge ICCVAM to work with FDA and USDA to organize an assessment of the degree to which the methods listed below have been routinely used in place of *in vivo* standard requirements, and in cases where there has not been uptake of a method, to work with member agencies to overcome obstacles to their use. We would like to see ICCVAM aid in developing a procedure by which manufacturers and federal agency representatives are directly engaged with one another regarding each available biologic alternatives, including opportunities for agencies to provide training and guidance on the use, optimization and troubleshooting of alternative methods.

- *Integrating the consistency approach in U.S. regulatory policy:* Production consistency is an issue relevant to FDA and USDA and a key area in which standardization of procedures can reduce animal use. With specific reference to the reduction of animal use in batch testing for biologics, an international push to standardize production consistency has had much success in the EU but only limited success in the U.S. The International Alliance for Biological Standardization (IABS) is hosting a conference on September 16-18th on “3Rs alternatives and consistency testing in vaccine lot release testing.” As the general consistency approach has far-reaching applications—including many of the items below—we encourage ICCVAM to participate in this conference and to open discussion with its member agencies on adopting consistency-based policies and guidance.

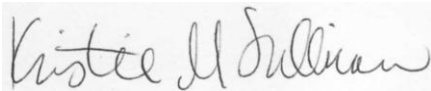
- *Assessment of the use of humane endpoints, analgesia and anesthesia for intracerebral challenge and other challenge procedures:* Among the recommendations of the 2011 “International Workshop On Alternative Methods for Human and Veterinary Rabies Vaccine Testing: State of the Science and Planning the Way Forward,” participants agreed on the necessity of providing anesthesia, analgesia, and humane endpoints for animals required for rabies vaccine testing. The following year, USDA codified this policy in CVB Notice 12-12. We encourage ICCVAM to collect information on the implementation of this guidance, its impact on Category E animal use numbers, and to help the FDA develop a similar FDA policy.
- *Progress toward waiving target animal batch safety testing (TABST):* In 2013, USDA CVB Memorandum 800.116 introduced a process through which manufacturers could apply for exemptions from TABST based on historical data. Although some companies have applied for these waivers or are preparing to do so, it is unclear whether any companies have been successful in this process. Also, Memorandum 800.116 restricts companies to a single waiver application at a time before USDA will consider additional applications. We encourage ICCVAM to seek an update on the number of successful and pending TABST waivers and information on USDA’s timeline for expanding this waiver program.

Thank you for the opportunity to comment. We have been happy to see many projects begin and flourish under NICEATM’s new leadership and we look forward to the reductions in animal use that will result.

Sincerely,



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