



September 2, 2010

The Honorable Margaret Hamburg, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue, Room 2217
Silver Spring, Maryland 20993

Dear Dr. Hamburg:

I am pleased to provide toxicological test method recommendations from the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) for your consideration. These recommendations are being sent to you for action pursuant to Sections 3(e)(4) and 4(a)-(e) of the ICCVAM Authorization Act of 2000 (42 U.S.C. 285f-3).

The recommendations are for alternative testing methods and strategies proposed to further reduce and refine the use of animals for assessing the ocular hazard potential of chemicals and products. Detailed recommendations are provided in four reports (Enclosures 1-4). The ICCVAM evaluation process included scientific peer review by an international independent panel, review by the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), and multiple public commenting opportunities. ICCVAM considered the peer review report, public comments, and SACATM comments in preparing the ICCVAM final test method recommendations.

In the first report, ICCVAM recommends pain management procedures that should always be used to avoid or minimize pain and distress when it is necessary to conduct the rabbit eye test for regulatory safety purposes (see Enclosure 1). These procedures include the routine use of topical anesthetics, systemic analgesics, and humane endpoints.

In the second report, ICCVAM recommends that the Cytosensor Microphysiometer (CM) test method can be used as a screening test to identify some types of substances that may cause permanent or severe eye injuries (see Enclosure 2). ICCVAM also recommends that the CM can be used to determine if some types of substances will not cause sufficient injury to require hazard labeling for eye irritation. ICCVAM evaluated four other *in vitro* test methods for their validity for identifying reversible and nonsevere ocular injuries, but concluded that these need improved predictivity before they can be used for regulatory safety testing. The report includes ICCVAM recommendations for future studies that could potentially improve these test methods.

In the third report, ICCVAM recommends further studies to characterize the usefulness and limitations of a non-animal *in vitro* testing strategy that uses three *in vitro* test methods (see Enclosure 3). In the fourth report, ICCVAM recommends that a proposed low volume rabbit eye test should not be used for regulatory testing due to performance issues when compared to the current standard rabbit eye test (see Enclosure 4).

ICCVAM also discovered during these evaluations that an estimated 30% of chemicals identified as eye hazards by current U.S. regulations will not be labeled as eye hazards by the United Nations Globally Harmonized System for Classification and Labelling of Chemicals (GHS), which some Federal agencies are or will be considering for implementation. The reduced hazard labeling that will result from

implementing the GHS was based on analyzing actual testing data for over 250 chemicals. Of concern is that over 50% of the chemicals that will no longer be labeled using GHS criteria produced eye injuries expected to interfere with normal vision. Accordingly, the report includes an optional GHS hazard category that could be used to provide at least equivalent hazard labeling as current U.S. regulations in order to support continued protection of consumers and workers.

Pursuant to Sections 4(a-e), of the ICCVAM Authorization Act, Federal agencies are required to:

- 1) No later than 180 days after receipt of ICCVAM test recommendations, identify and forward to the ICCVAM any relevant test method specified in a regulation or industry-wide guideline which specifically, or in practice requires, recommends, or encourages the use of an animal toxicological test method for which the ICCVAM test recommendation may be added or substituted;
- 2) Promote and encourage the use of alternative test methods for the purpose of complying with Federal statutes, regulations, guidelines, or recommendations, if such alternative test methods are found to be effective for generating data in an amount and of a scientific value at least equivalent to the data generated from existing tests for hazard identification, dose-response assessment, or risk assessment purposes;
- 3) Ensure that any new or revised acute or chronic toxicity test method is determined to be valid for its proposed use prior to requiring, recommending, or encouraging the application of such test method;
- 4) Not later than 180 days after receiving an ICCVAM test recommendation, review such recommendation and notify ICCVAM in writing of its findings; and
- 5) Adopt the ICCVAM test recommendation unless the agency determines that one or more of the criteria in Section 4(e)(1) to (4) are met.

Please send your agency's response regarding each of these requirements to RADM William S. Stokes, Director, National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, National Institute of Environmental Health Sciences (contact information, NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709, telephone: 919-541-2384, facsimile: 919-541-0947, email: stokes@niehs.nih.gov). ICCVAM is required to make the final ICCVAM test method recommendations and the responses from agencies regarding such recommendations available to the public per Section 3(e)(6) of the Act. Accordingly, your response will be made available on the NICEATM-ICCVAM website at <http://iccvam.niehs.nih.gov>.

I appreciate your agency's participation on ICCVAM. The committee serves an important role in facilitating the scientific evaluation and adoption of test methods that will help protect human health and the environment while providing for improved animal welfare whenever possible.

Sincerely,

/s/

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.

Enclosures (4)

cc:

Suzanne Fitzpatrick, Ph.D., FDA ICCVAM Principal Agency Representative