DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P. O. Box 12233
Research Triangle Park, NC 27709

October 25, 2007

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner of Food and Drugs
U.S. Food and Drug Administration
Parklawn Building, Room 1471
5600 Fishers Lane
Rockville, Maryland 20892

Dear Dr. von Eschenbach:

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

The test method recommendations are for four *in vitro* test methods proposed for identifying substances that may cause ocular corrosion or severe ocular irritation. The test methods are the: (1) Bovine Corneal Opacity and Permeability (BCOP) assay, (2) the Isolated Chicken Eye (ICE) assay, (3) the Isolated Rabbit Eye (IRE) assay, and (4) the Hen's Egg Test – Chorioallantoic Membrane (HET-CAM) assay. The recommendations are provided in the report, *The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Test Method Evaluation Report: In Vitro Test Methods for Identifying Ocular Corrosives and Severe Irritants* (NIH Publication No. 07-4517, Enclosure 1). The report includes ICCVAM's general recommendations for all of the methods and specific recommendations for each of the four test methods.

ICCVAM recommends that the four alternative test methods should be considered before using animals for ocular safety testing and that the methods should be used when determined appropriate. Two of the methods (BCOP and ICE) are considered to have sufficient performance to substantiate their use for regulatory hazard classification testing of some types of substances. The two other methods (IRE and HET-CAM) are not considered to currently have sufficient performance and/or sufficient data to substantiate their use for regulatory hazard classification purposes but may have applicability for other uses. ICCVAM recommends that the test methods should be used in a tiered-testing strategy, where positive substances can be classified as ocular corrosives or severe irritants without the need for animal testing.

The report also provides ICCVAM recommendations for (1) standardized protocols that should be used when performing the test methods, (2) studies to further optimize and improve the performance of the assays, and (3) reference substances for future validation studies. The report includes technical summaries for the four *in vitro* test methods, applicable U.S. Federal regulations and testing guidelines, relevant *Federal Register* notices, expert panel reports, and discussion of public comments received during the evaluation.

ICCVAM evaluated the scientific validity of these four test methods in response to their nomination by the Environmental Protection Agency. In conjunction with the ICCVAM, the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) prepared comprehensive background review documents containing all available information and data on the proposed methods (Enclosures 2-5). An independent scientific expert panel reviewed this information and the current validation status of the four test methods. Comments were also obtained from the public and the Scientific Advisory Committee on Alternative Toxicological Methods, a federally chartered advisory group for ICCVAM (Enclosure 6). ICCVAM considered all of the reviews and comments and then developed final test method recommendations on the four test methods.

Pursuant to Sections 4(a) and 4(d) of the ICCVAM Authorization Act, agencies are required to review ICCVAM test method recommendations and notify the ICCVAM in writing of their findings, including identification of relevant test methods for which the ICCVAM test recommendations may be added or substituted, no later than 180 days after receipt of the recommendations. Therefore, I would ask that you please send your agency's response by April 28, 2008, to Rear Admiral William S. Stokes, Executive Director, ICCVAM, NIEHS, P.O. Box 12233, Mail Code EC-17, Research Triangle Park, NC 27709, Phone: 919-541-7997, Fax: 919-541-0947, Email: *stokes@niehs.nih.gov*. ICCVAM is required to make 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 posted on the ICCVAM/NICEATM 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/

Samuel H. Wilson
Acting Director

Enclosures

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