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 23, 2008

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner for 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 five *in vitro* test methods proposed for assessing potential pyrogenicity of pharmaceuticals and other products. Detailed recommendations are provided in the report, *The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Test Method Evaluation Report (TMER): Validation Status of Five In Vitro Test Methods Proposed for Assessing Potential Pyrogenicity of Pharmaceuticals and Other Products* (NIH Publication No. 08-6392, Enclosure 1).

ICCVAM evaluated these test methods following their submission by the European Centre for the Validation of Alternative Methods (ECVAM), a unit of the Institute for Health and Consumer Protection at the European Commission's Joint Research Centre. The evaluation process included review by an independent scientific peer review panel (Panel) and comments from the public and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), a federally chartered advisory group for ICCVAM. ICCVAM considered the Panel report, all public comments, and the comments of SACATM in preparing the ICCVAM final test method recommendations.

ICCVAM concludes that none of these test methods can be considered as a complete replacement for the rabbit pyrogen test (RPT) for all testing situations for the detection of Gram-negative endotoxin. However, ICCVAM recommends that they can be considered for use on a case-by-case basis to detect Gram-negative endotoxin in human parenteral drugs, subject to product-specific validation to demonstrate equivalence to the RPT, in accordance with applicable U.S. Food and Drug Administration regulations. When used in this manner, these methods can reduce the number of animals needed for pyrogenicity testing.

U.S. Federal animal welfare regulations and policies require consideration of alternative methods whenever animals are proposed for studies that may involve more than slight or momentary pain and distress. Since pyrogenicity testing may involve more than slight or momentary pain and distress, these and other *in vitro* alternative test methods should be considered prior to *in vivo* pyrogenicity testing and should be used where determined appropriate. Use of these methods, following appropriate product-specific validation, will support improved animal welfare while ensuring the continued protection of human health.

The TMER describes the validation status of the *in vitro* pyrogen test methods and discusses ICCVAM consideration of the peer review panel, public and SACATM comments. The TMER provides a recommended standardized protocol for each test method that is based primarily on ECVAM standard operating procedures. Recommendations are provided for research, development, optimization, and validation studies that may further improve the usefulness and applicability of these methods. The Peer Review Panel Report, relevant Federal pyrogenicity regulations and testing guidelines, applicable *Federal Register* notices, public comments, and SACATM meeting minutes are included as appendices to the TMER. The final ICCVAM background review document (BRD) is also enclosed, which provides data and information supporting the validity of the five test methods (Enclosure 2). The ICCVAM Test Method Evaluation Report and BRD should assist stakeholders (e.g., applicable U.S. Federal regulatory agencies, the international regulatory community, and the pharmaceutical industry) with determining when these test methods are appropriate for use.

Pursuant to Sections 4(a) and 4(d) of the ICCVAM Authorization Act, agencies are required to review ICCVAM test method recommendations and notify 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 22, 2009, to RADM William S. Stokes, Director, National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (contact information, NIEHS, P.O. Box 12233, EC-17, Research Triangle Park, NC 27709, telephone: 919-541-2384, facsimile: 919-541-0947, email: stokes@niehs.nih.gov. ICCVAM is required to make the ICCVAM final 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/
Samuel H. Wilson
Acting Director

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