



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

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OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

RADM William S. Stokes  
Director, National Toxicology Program Interagency Center for the Evaluation of  
Alternative Toxicological Methods (NICEATM)  
NIEHS  
P.O. Box 12233, EC-17  
Research Triangle Park, NC 27709

Dear Dr. Stokes,

As you may recall in Dr. Samuel H. Wilson's October 23, 2008 letter regarding ICCVAM test method recommendations, he asked that the responses of federal agencies be sent directly to you by April 22, 2009.

The test method recommendations to be considered are for five *in vitro* test methods proposed for assessing potential pyrogenicity of pharmaceuticals and other products. They were 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). The final ICCVAM background review document for these methods, which contains information supporting the recommendations, was also included in the correspondence package.

The U.S. Environmental Protection Agency (EPA) acknowledges the enormous amount of work that went into the evaluation and peer review of the five *in vitro* pyrogenicity assays and the preparation of the test method report and background review document. The recommendations and background materials indicate that the evaluation of these test methods was undertaken by ICCVAM/NICEATM to assess their usefulness for the pyrogenicity testing of pharmaceuticals and other products regulated by the U.S. Food and Drug Administration. When as requested, the ICCVAM recommendations were reviewed for utility in EPA programs, no current applications were found for these particular test methods or for the endpoint evaluated. In addition, at the present time, no relevant test methods were found for which the ICCVAM recommendations might be added or substituted.

EPA is pleased to have had the opportunity to review the test method recommendations and supporting materials for the *in vitro* pyrogenicity tests. We look forward to continuing interactions with ICCVAM as part of the Agency's commitment to advancing the "three Rs" principles of reduction, refinement and replacement of animal use, where possible, in Agency programs.

Sincerely,



**ISI**



Frank Sanders, Director  
Office of Science Coordination and Policy

cc: Jim Jones  
Wendy Cleland-Hamnett  
Debbie Edwards  
Hal Zenick  
Karen Hamernik  
Julian Preston  
Oscar Hernandez  
Tina Levine  
Deborah McCall  
Jerry Smrcek  
Stephanie Padilla