



April 22, 2009

RADM William S. Stokes
Director
NICEATM
National Toxicology Program
PO Box 12233, EC-17
Research Triangle Park, NC 27709

Dear Dr. Stokes:

The US Food and Drug Administration (FDA) has reviewed the toxicological test recommendations for five *in vitro* test methods proposed for assessing potential pyrogenicity of pharmaceuticals and other products. These recommendations from the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) were submitted by the National Institute for Environmental Health Sciences for the Agency's consideration on October, 23, 2008, pursuant to Section 3(e)(4) of the ICCVAM Authorization Act of 2000 (42 U.S.C. 2851-3).

FDA has considered the detailed recommendations 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) in the context of the products that FDA regulates.

FDA concurs with the ICCVAM recommendations that none of the *in vitro* pyrogen test methods can be considered as a complete replacement for the rabbit pyrogen test (RPT) without additional product-specific information. FDA also endorses the recommendation that these *in vitro* pyrogen test methods may be considered on a case by case basis for the detection of Gram negative endotoxin in parenteral drugs, subject to product-specific validation.

FDA supports the use of scientifically validated alternatives to the RPT for products that it regulates, and encourages sponsors of investigational products to propose one of the alternative pyrogenicity assays for consideration along with supporting data to demonstrate that the assay can detect pyrogenicity for their particular product. Clearly these assays are not appropriate replacements for the RPT for those drugs or biologics whose pharmacodynamic activity is to release cytokines.

If you need further information, please contact me at 301-827-3303.

Norris E. Alderson, PhD
FDA Associate Commissioner for Science