



National Institutes of Health
National Institute of
Environmental Health Sciences
P. O. Box 12233
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MEMORANDUM

DATE: April 17, 2009

TO: The Record

FROM: Director, National Toxicology Program and the
National Institute of Environmental Health Sciences (NIEHS)

SUBJECT: NIEHS Response to ICCVAM Test Recommendations for Five In Vitro Test
Methods for Assessing Pyrogenicity of Pharmaceuticals and Other Products

On October 23, 2008, at the request of the Secretary of the Department of Health and Human Services, Dr. Samuel Wilson, Acting Director, NIEHS, forwarded toxicological test recommendations from the Interagency Coordinating Committee on the Validation of Alternative Methods (ICVAM) to 14 Federal agencies for their consideration. The recommendations were developed and transmitted pursuant to Section 3(e)(4) of the ICCVAM Authorization Act of 2000 (42 U.S.C. 285l-3). Pursuant to Sections 4(a) and 4(d) of the ICCVAM Authorization Act, agencies are required to review ICVAM test 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. This memorandum provides the NIEHS response to the ICCVAM test recommendations.

NIEHS has reviewed the ICCVAM test recommendations provided for the five in vitro test methods proposed for assessing potential pyrogenicity of pharmaceuticals and other products. Detailed recommendations are provided in the Report, *The Interagency 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).

NIEHS agrees with the ICCVAM recommendation 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. NIEHS also agrees that they should 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.

NIEHS has determined that it does not currently use or specify any test methods for which the test recommendations may be added or substituted. Furthermore, NIEHS is not a regulatory agency and therefore does not promulgate regulatory testing requirements for which the recommendations may be applicable. While NIEHS does conduct toxicity testing as part of

its National Toxicology Program activities, pyrogenicity testing is not normally performed. If for some reason, such data are required in the future, NIEHS intends to follow the recommendations of the ICCVAM on this matter and will consider and use the recommended methods where determined scientifically appropriate.

NIEHS scientists and the NIEHS Institutional Animal Care and Use Committee (IACUC) have been informed about the availability of the five alternative test methods and advised that they should be considered when planning and reviewing animal studies involving pyrogen safety testing in order to minimize animal use and to avoid pain and distress. The IACUC has also been asked to ensure that these alternative methods are considered whenever applicable in accordance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals and applicable USDA Animal Welfare Act Regulations, and to ensure that the methods are used when determined appropriate.

NIEHS remains committed to the development, validation, and regulatory acceptance of scientifically sound alternative testing methods that will support improved protection of human and animal health and the environment, and that will provide for improved animal welfare.

/s/

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cc:

Dr. William Stokes

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