

**DEPARTMENT OF HEALTH AND
HUMAN SERVICES****National Toxicology Program (NTP);
NTP Interagency Center for the
Evaluation of Alternative Toxicological
Methods (NICEATM); Availability of the
Interagency Coordinating Committee
on the Validation of Alternative
Methods (ICCVAM) Test Method
Evaluation Report: Validation Status of
Five *In Vitro* Test Methods Proposed
for Assessing Potential Pyrogenicity of
Pharmaceuticals and Other Products
and Final Background Review
Document: Validation Status of Five *In
Vitro* Test Methods Proposed for
Assessing Potential Pyrogenicity of
Pharmaceuticals and Other Products;
Notice of Transmittal of ICCVAM Test
Method Recommendations to Federal
Agencies**

AGENCY: National Institute of
Environmental Health Sciences
(NIEHS), National Institutes of Health
(NIH)

ACTION: Availability of the ICCVAM Test
Method Evaluation Report and Final
Background Review Document.

SUMMARY: NICEATM announces
availability of the *ICCVAM Test Method
Evaluation Report: Validation Status of
Five In Vitro Test Methods Proposed for
Assessing Potential Pyrogenicity of
Pharmaceuticals and Other Products*
(NIH Publication 08–6392). The test
method evaluation report (TMER)
describes five *in vitro* pyrogen test
methods that can be used for detecting
Gram-negative endotoxin in human
parenteral pharmaceuticals. The report
includes ICCVAM's (a)
Recommendations on uses and
limitations for each test method, (b)
recommendations for standardized
protocols, (c) recommendations for
future studies, and (d) recommendations
for the development of performance
standards.

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.
The report also recommends that these

and other *in vitro* alternative test methods be considered prior to *in vivo* pyrogenicity testing, where determined appropriate for a specific testing situation.

NICEATM also announces availability of the final *ICCVAM Background Review Document: Validation Status of Five In Vitro Test Methods Proposed for Assessing Potential Pyrogenicity of Pharmaceuticals and Other Products* (NIH Publication 08–6391). The final background review document (BRD) provides the data and analyses used to assess the current validation status of these five *in vitro* test methods.

The ICCVAM TMER and supporting BRDs have been forwarded to U.S. Federal agencies for regulatory and other acceptance consideration, where applicable. Responses received will be posted on the NICEATM–ICCVAM Web site.

ADDRESSES: Electronic copies of the ICCVAM TMER and final BRD are available from the NICEATM–ICCVAM Web site at <http://iccvam.niehs.nih.gov> or by contacting NICEATM (see **FOR FURTHER INFORMATION CONTACT**).

FOR FURTHER INFORMATION CONTACT: Dr. William S. Stokes, Director, NICEATM, NIEHS, P.O. Box 12233, MD EC–17, Research Triangle Park, NC 27709, (telephone) 919–541–2384, (fax) 919–541–0947, (e-mail) niceatm@niehs.nih.gov Courier address: NICEATM, NIEHS, 79 T.W. Alexander Drive, Building 4401, Room 3128, Research Triangle Park, NC 27709.

SUPPLEMENTARY INFORMATION:

Background

In 2005, 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, submitted BRDs for five *in vitro* pyrogen test methods proposed as replacements for the RPT to ICCVAM for formal evaluation of their scientific validity for regulatory testing purposes. ICCVAM unanimously agreed that the five submitted *in vitro* pyrogen test methods should have high priority for evaluation. On December 16, 2005, NICEATM published a **Federal Register** notice (Vol. 70, No. 241, pages 74833–74834), requesting public comments on the appropriateness and relative priority of convening an independent peer review panel (Panel) to evaluate the validation status of the five *in vitro* pyrogen test methods, the nomination of scientists to serve on the Panel, and the submission of data from *in vivo* and *in vitro* pyrogenicity testing. Based on the ECVAM BRDs as well as data and

information submitted in response to the aforementioned **Federal Register** notice, NICEATM subsequently compiled a comprehensive draft BRD on the five *in vitro* pyrogen test methods and released it for public comment on December 12, 2006 (Vol. 71, No. 238, pages 74533–74534).

On February 6, 2007, NICEATM and ICCVAM convened a Panel to review the ICCVAM draft BRD for errors and omissions and to evaluate the validation status of the five *in vitro* pyrogen test methods. The Panel also reviewed the extent that the information contained in the ICCVAM draft BRD supported the ICCVAM draft test method recommendations for proposed test method uses, standardized protocols, test method performance standards, and additional studies. The Panel considered public comments made at the Panel meeting, as well as public comments submitted in advance of the meeting, before concluding their deliberations. NICEATM made the Panel's report available in May 2007 (Vol. 72, No. 89, pages 26395–26396). The ICCVAM draft BRD and draft recommendations, the Panel's report, and all public comments were made available to the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) for review and comment at their meeting on June 12, 2007 (Vol. 72, No. 83, pages 23831–23832).

ICCVAM considered the Panel's report, all public comments, and the comments of SACATM in finalizing its recommendations on the use of these five *in vitro* test methods proposed for assessing potential pyrogenicity of pharmaceuticals and other products. The ICCVAM TMER includes the ICCVAM recommendations on uses and limitations for each test method, standardized protocols, future studies, and the development of performance standards, as well as the Panel's report and **Federal Register** notices. The final BRD, which provides the supporting documentation for this report, is available as a separate document. ICCVAM forwarded the ICCVAM TMER and the supporting final BRD to U.S. Federal agencies for consideration, in accordance with the ICCVAM Authorization Act of 2000 (42 U.S.C. 285l–3). Agency responses to the ICCVAM test method recommendations will be made available on the NICEATM–ICCVAM Web site as they are received.

Background Information on ICCVAM, NICEATM, and SACATM

ICCVAM is an interagency committee composed of representatives from 15

Federal regulatory and research agencies that use, generate, or disseminate toxicological information. ICCVAM conducts technical evaluations of new, revised, and alternative methods with regulatory applicability and promotes the scientific validation and regulatory acceptance of toxicological test methods that more accurately assess the safety and hazards of chemicals and products and that refine, reduce, and replace animal use. The ICCVAM Authorization Act of 2000 established ICCVAM as a permanent interagency committee of the NIEHS under NICEATM. NICEATM administers ICCVAM and provides scientific and operational support for ICCVAM-related activities. NICEATM and ICCVAM work collaboratively to evaluate new and improved test methods applicable to the needs of U.S. Federal agencies. Additional information about ICCVAM and NICEATM can be found at <http://www.iccvam.niehs.nih.gov>.

SACATM was established January 9, 2002 (Vol. 67, No. 49, page 11358), and is composed of scientists from the public and private sectors. SACATM provides advice to the Director of the NIEHS, to ICCVAM, and to NICEATM regarding the statutorily mandated duties of ICCVAM and activities of NICEATM. Additional information about SACATM, including the charter, roster, and records of past meetings, can be found at <http://ntp.niehs.nih.gov/go/167>.

Dated: November 7, 2008.

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Acting Director, National Institute of Environmental Health Sciences and National Toxicology Program.

[FR Doc. E8–27790 Filed 11–21–08; 8:45 am]

BILLING CODE 4140–01–P