DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Toxicology Program (NTP), NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Announcement of an Independent Scientific Peer Review Meeting on the Use of In Vitro Pyrogenicity Testing Methods; Request for Comments

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

ACTION: Meeting announcement and request for comments.

SUMMARY: NICEATM in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) announces an independent scientific peer review meeting to evaluate the validation status of five in vitro pyrogenicity test methods: (1) Human PBMC/IL–6 *in vitro* pyrogen test (PBMC/IL–6), (2) human whole blood/IL–1 *in vitro* pyrogen test (WB/IL–1), (3) human whole blood/IL–1 *in vitro* pyrogen test: application of cryopreserved human whole blood (cryo WB/IL–1), (4) the human whole blood/IL–6 *in vitro* pyrogen test (WB/IL–6), and (5) an alternative *in vitro* pyrogen test using the human monocytoid cell line MONO MAC–6 (MM6/IL6). These five *in vitro* test methods are proposed as replacements for the in vivo rabbit pyrogen test (RPT). At this meeting, a scientific panel will peer review the draft background review document (BRD) on each test method, evaluate the extent that the BRD addresses established validation and acceptance criteria for each test method, and provide comment on draft ICCVAM recommendations on the proposed use of these test methods, draft test method protocols, and draft performance standards. NICEATM invites public comments on the draft BRDs, draft ICCVAM test method recommendations, draft test method protocols, and draft performance standards.

DATES: The meeting will be held on February 6, 2007, from 8:30 a.m. to 5 p.m. The meeting is open to the public with attendance limited only by the space available. In order to facilitate planning for this meeting, persons wishing to attend are asked to register by January 23, 2007, via the ICCVAM/NICEATM Web site (*http://iccvam.niehs.nih.gov*). Comments should be sent by mail, fax, or email to the address given below by January 26, 2007.

ADDRESSES: The meeting will be held at the National Institutes of Health (NIH), Natcher Conference Center, 45 Center Drive, Bethesda, MD 20892.

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

SUPPLEMENTARY INFORMATION:

Background

The European Centre for the Validation of Alternative Methods (ECVAM) conducted a validation study to independently evaluate the usefulness and limitations of five *in vitro* pyrogenicity test methods (PBMC/IL–6, WB/IL–1, cryo WB/IL–1, WB/IL–6, and MM6/IL6). In June 2005, ECVAM submitted BRDs for these five methods to NICEATM for consideration as replacements for the currently required test, the RPT. ICCVAM and NICEATM reviewed the BRDs for completeness and concluded that these five *in vitro* test methods appear to have considerable potential for pyrogenicity testing, but that the sponsor needed to provide additional information prior to a formal scientific review by an expert panel. In anticipation of proceeding with an evaluation of these test methods, ICCVAM and NICEATM requested public comments as to the appropriateness and relative priority of a panel review activity and the nomination of scientists with relevant knowledge and experience to potentially serve on the panel (**Federal Register** Vol. 70, No. 241, pp. 74833–4, December 16, 2005). NICEATM also requested submission of data using the standard in vivo rabbit pyrogen test, the bacterial endotoxin test (BET), and *in vitro* pyrogenicity tests. These requests were sent directly to over 100 interested stakeholders; no additional data were received.

In March 2006, ECVAM responded to the ICCVAM/NICEATM request for information by providing a revised BRD for each test method. ICCVAM and NICEATM drafted a BRD that combines all of the available information on the five *in vitro* pyrogenicity test methods into a single document and includes each of the ECVAM BRDs as an appendix. Based on this information, ICCVAM developed draft test method recommendations regarding the proposed usefulness, limitations, and validation status of these test methods. ICCVAM subsequently recommended that an independent scientific panel be convened to (1) peer review the draft BRD for the test methods and (2) determine whether the data and analyses in the draft BRDs support the draft ICCVAM test method recommendations. The panel will also be asked to comment on the adequacy of the draft recommended performance standards, proposed future validation studies, draft standardized test method protocols, and recommended reference substances. In making their conclusions and recommendations, NICEATM will ask the panel to consider all available information including the scientific studies cited in the draft BRD, public comments, and any new information identified during the peer review.

Peer Review Panel Meeting

The purpose of this meeting is the scientific peer review evaluation of the validation status of five *in vitro* pyrogenicity test methods as replacements for the RPT. First, the panel will review the draft BRD on the current status of five in vitro test methods for the detection of pyrogenicity and evaluate the extent that established validation and acceptance criteria are addressed for each test method (Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods, NIH Publication No. 97–981, *http://iccvam.niehs.nih.gov*). Next, the panel will comment on the extent to which the ICCVAM recommendations are supported by the information provided in the BRD and on the proposed use of these test methods, draft test method protocols, draft performance standards, and any proposed validation studies.

Information about the panel meeting, including a roster of the panel members and the draft agenda, will be made available two weeks prior to the meeting on the ICCVAM/NICEATM Web site (*http://iccvam.niehs.nih.gov*) or can be

obtained after that date by contacting NICEATM (see **FOR FURTHER INFORMATION CONTACT** above).

Attendance and Registration

This public meeting will take place February 6, 2007, at the NIH Campus, Natcher Conference Center, Bethesda, MD (a map of the NIH campus and other visitor information are available at *http://www.nih.gov/about/visitor/index.htm*). The meeting begins at 8:30 a.m. and will conclude at approximately 5 p.m. Persons needing special assistance, such as sign language interpretation or other reasonable accommodation in order to attend, should contact 919–541–2475 (voice), 919–541–4644 TTY (text telephone), through the Federal TTY Relay System at 800–877–8339, or by e-mail to *niehsoeeo@niehs.nih.gov*. Requests should be made at least seven business days in advance of the event.

Availability of the BRD and Draft ICCVAM Recommendations

NICEATM prepared a BRD on five *in vitro* pyrogenicity test methods that describes the current validation status of the in vitro test methods and contains all of the data and analyses supporting this validation status. The draft BRDs, draft ICCVAM test method recommendations, draft test method protocols, and draft test method performance standards are available from the ICCVAM/NICETAM Web site (*http://iccvam.niehs.nih.gov*) or by contacting NICEATM (see **FOR FURTHER INFORMATION CONTACT** above).

Request for Comments

NICEATM invites the submission of written comments on the BRDs, draft ICCVAM test method recommendations, draft test method protocols, and draft test method performance standards. When submitting written comments, it is important to refer to this **Federal Register** notice and include appropriate contact information (name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization, if applicable). Written comments should be sent by mail, fax, or e-mail to Dr. William Stokes, Director of NICEATM, at the address listed above, not later than January 26, 2007. All comments received will be placed on the ICCVAM/NICEATM Web site (*http://iccvam.niehs.nih.gov*), sent to the panel and ICCVAM agency representatives, and made available at the meeting.

This meeting is open to the public and time will be provided for the presentation of public oral comments at designated times during the peer review. Members of the public who wish to present oral statements at the meeting (one speaker per organization) should contact NICEATM (see **FOR FURTHER INFORMATION CONTACT** above) no later than January 26, 2007. Speakers will be assigned on a consecutive basis and up to seven minutes will be allotted per speaker. Persons registering to make comments are asked to provide NICEATM a written copy of their statement by January 26, 2007, so that copies can be distributed to the panel prior to the meeting or if this is not possible to bring 40 copies to the meeting. Written statements can supplement and expand the oral presentation. Each speaker is asked to provide contact information (name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization, if applicable) when registering to make oral comments.

Summary minutes and the panel's final report will be available following the meeting on the ICCVAM/NICEATM Web site (*http://iccvam.niehs.nih.gov*). ICCVAM will consider the panel's conclusions and recommendations and any public comments received in finalizing their test method recommendations and performance standards for these methods.

Background Information on ICCVAM and NICEATM

ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that use or generate 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 (42 U.S.C. 285l–3, available at *http://iccvam.niehs.nih.gov/about/PL106545.htm*) establishes ICCVAM as a permanent interagency committee of the NIEHS under the 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 federal agencies. Additional information about ICCVAM and NICEATM can be found at the following Web site: *http://iccvam.niehs.nih.gov*.

Dated: November 27, 2006.

Samuel H. Wilson,

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

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