UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
BETHESDA, MD 20814

BALLOT VOTE SHEET

Date: DEC 24 2008

TO : The Commission
Todd A. Stevenson, Secretary

THROUGH: Patricia Semple, Executive Director PS

FROM : Cheryl A. Falvey, General Counsel CAF

SUBJECT : Staff Response to ICCVAM Recommendations for Five *In Vitro* Methods for Assessing Pyrogenicity of Pharmaceuticals and Other Products.

BALLOT VOTE due: JAN - 5 2009

The attached memorandum from the Health Sciences Directorate discusses the recommendations of ICCVAM for the use of five *in vitro* tests to assess pyrogenicity in pharmaceuticals and other products. The staff recommends that the Commission not recommend the use of these alternative tests for consumer products. Staff further recommends that the Commission instruct the staff to draft a letter to be sent to RADM Stokes indicating that the five test methods are not tests that are relevant to CPSC testing requirements or needs and, therefore, CPSC will not be recommending their use.

Please indicate your vote.

I. Accept the staff recommendations and instruct the staff to draft a letter to be sent to RADM Stokes indicating that the five test methods are not tests that are relevant to CPSC testing requirements or needs and, therefore, CPSC will not be recommending their use.

Signature _____ Date _____

II. Reject the staff recommendations and instruct the staff to draft a letter to be sent to RADM Stokes indicating that CPSC will accept the five test methods and will be recommending their use.

Signature _____ Date _____

Attachment – *Staff Response to ICCVAM Recommendations for Five In Vitro Methods for Assessing Pyrogenicity of Pharmaceuticals and Other Products*, memorandum from Marilyn Wind, P.h.D., Directorate for Health Sciences, to the Commission, December 2008.

Note: This document has not been reviewed or accepted by the Commission.
Initials ___ Date 12-24-08

CPSA 6(b)(1) CLEARED for PUBLIC 12/24/08
NO MFRS/PRVTLBLRS OR PRODUCTS IDENTIFIED
EXCEPTED BY: PETITION

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

Memorandum

Date: DEC 2 4 2008

TO : The Commission

THROUGH: Todd A. Stevenson, Secretary
Cheryl A. Falvey, General Counsel CAF
Patricia M. Semple, Executive Director

FROM : Robert J. Howell
Acting Assistant Executive Director
Office of Hazard Identification and Reduction
Marilyn L. Wind, Ph.D. MLW
Deputy Associate Executive Director for Health Sciences

SUBJECT : Staff Response to the ICCVAM Recommendations for Five *In Vitro* Methods for Assessing Pyrogenicity of Pharmaceuticals and Other Products

This briefing memo discusses the recommendations of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) for the use of five *in vitro* tests to assess pyrogenicity in pharmaceuticals and other products.

Introduction

Internationally, for over a decade, there has been a movement to refine, reduce, or replace the use of animals in toxicological testing. The National Institutes of Health Revitalization Act of 1993 (Public Law No. 103-43, Section 1301) directed the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH) to establish a program dealing with alternative test methods, those methods that refine, reduce, or replace the use of animals. The Act further directed NIEHS to establish criteria for the validation[1] and regulatory acceptance[2] of alternative testing methods and to recommend a process by which validated methods could be accepted for regulatory use. In 1994 NIEHS established ICCVAM as an *ad hoc* interagency committee to accomplish these goals. The ICCVAM Authorization Act of 2000 (Public Law No. 106-545) established ICCVAM as a permanent committee of the NIEHS/NIH.

ICCVAM coordinates issues of interest relating to the development, validation, acceptance, and national/international harmonization of toxicological test methods that are alternatives to animal

[1] Validation is the determination that a method is reliable (measure of the degree to which a test can be performed reproducibly within and among laboratories over time), repeatable (closeness of agreement of results within a laboratory when the same procedure is performed on the same substance within a given time period), and relevant (the extent to which a test method will correctly predict or measure the biological effect of interest in humans).

[2] Regulatory acceptance is how a particular test method fits into the regulatory structure at a given agency, whether it will provide the type of data mandated under that particular agency's rules.

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tests. The ICCVAM Authorization Act of 2000 mandates that when ICCVAM has validated a test method, it must send a report detailing its review and recommendations to the appropriate Federal agencies. The Federal agencies then have 180 days to respond to ICCVAM, describing test methods for which the recommended test could be added or substituted.

On October 23, 2008, recommendations for five *in vitro* pyrogenicity tests were transmitted to Nancy A. Nord, Acting Chairman of the U.S. Consumer Product Safety Commission (CPSC, the Commission) (TAB A). The Commission is, therefore, required to send a response to Rear Admiral (RADM) William S. Stokes, Director of the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, by April 22, 2009.

ICCVAM Recommendations and Applicability to Consumer Products

ICCVAM evaluated the five test methods for assessing the potential pyrogenicity of pharmaceuticals and other products and concluded that none of them could be considered complete replacements for the rabbit pyrogen test (RPT) for all testing situations for the detection of Gram-negative endotoxin. However, ICCVAM did recommend "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."

Since parenteral drugs are not within the jurisdiction of the Commission and since there are no requirements in any of the CPSC Acts or regulations requiring detection of Gram-negative endotoxins, these recommendations are not relevant to CPSC testing requirements or needs.

Recommendation

Staff recommends that the Commission not recommend the use of these alternative tests for testing consumer products. Staff further recommends that the Commission instruct the staff to draft a letter to be sent to RADM Stokes indicating that the five test methods are not tests that are relevant to CPSC testing requirements or needs and, therefore, CPSC will not be recommending their use.

TAB A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P. O. Box 12233
Research Triangle Park, NC 27709

October 23, 2008

The Honorable Nancy A. Nord, Ph.D.
Acting Chairwoman
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, Maryland 20814-4408

Dear Madam Chairwoman:

I am pleased to forward toxicological test method recommendations from the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) for your consideration. These test method recommendations are being sent to you for action pursuant to Section 3(e)(4) of the ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*-3).

The test method recommendations are for five *in vitro* test methods proposed for assessing potential pyrogenicity of pharmaceuticals and other products. Detailed recommendations are 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, Enclosure 1).

ICCVAM evaluated these test methods following their submission by 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. The evaluation process included review by an independent scientific peer review panel (Panel) and comments from the public and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), a federally chartered advisory group for ICCVAM. ICCVAM considered the Panel report, all public comments, and the comments of SACATM in preparing the ICCVAM final test method recommendations.

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.

U.S. Federal animal welfare regulations and policies require consideration of alternative methods whenever animals are proposed for studies that may involve more than slight or

momentary pain and distress. Since pyrogenicity testing may involve more than slight or momentary pain and distress, these and other *in vitro* alternative test methods should be considered prior to *in vivo* pyrogenicity testing and should be used where determined appropriate. Use of these methods, following appropriate product-specific validation, will support improved animal welfare while ensuring the continued protection of human health.

The TMER describes the validation status of the *in vitro* pyrogen test methods and discusses ICCVAM consideration of the peer review panel, public and SACATM comments. The TMER provides a recommended standardized protocol for each test method that is based primarily on ECVAM standard operating procedures. Recommendations are provided for research, development, optimization, and validation studies that may further improve the usefulness and applicability of these methods. The Peer Review Panel Report, relevant Federal pyrogenicity regulations and testing guidelines, applicable *Federal Register* notices, public comments, and SACATM meeting minutes are included as appendices to the TMER. The final ICCVAM background review document (BRD) is also enclosed, which provides data and information supporting the validity of the five test methods (Enclosure 2). The ICCVAM Test Method Evaluation Report and BRD should assist stakeholders (e.g., applicable U.S. Federal regulatory agencies, the international regulatory community, and the pharmaceutical industry) with determining when these test methods are appropriate for use.

Pursuant to Sections 4(a) and 4(d) of the ICCVAM Authorization Act, agencies are required to review ICCVAM test method 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, no later than 180 days after receipt of the recommendations. Therefore, I would ask that you please send your agency's response by April 22, 2009, to RADM William S. Stokes, Director, National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (contact information, NIEHS, P.O. Box 12233, EC-17, Research Triangle Park, NC 27709, telephone: 919-541-2384, facsimile: 919-541-0947, email: *stokes@niehs.nih.gov*. ICCVAM is required to make the ICCVAM final test method recommendations and the responses from agencies regarding such recommendations available to the public per Section 3(e)(6) of the Act. Accordingly, your response will be made available on the NICEATM-ICCVAM website at *http://iccvam.niehs.nih.gov*.

I appreciate your agency's participation on ICCVAM. The committee serves an important role in facilitating the scientific evaluation and adoption of test methods that will help protect human health and the environment while providing for improved animal welfare whenever possible.

Sincerely,

Samuel H. Wilson
Acting Director

Enclosures

cc:
Marilyn L. Wind, Ph.D., CPSC ICCVAM Principal Agency Representative