



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

March 18, 2010

RADM William S. Stokes
Director
NICEATM
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Dear Dr. Stokes:

The US Food and Drug Administration (FDA) has reviewed the ICCVAM test method recommendations for (1) the reduced Murine local lymph node assay (rLLNA), (2) an updated LLNA test method protocol, and (3) LLNA test method performance standards. These recommendations are included in the ICCVAM Test Method Evaluation Reports, *The Reduced Murine Local Lymph Node Assay: An Alternative Test Method Using Fewer Animals to Assess the Allergic Contact Dermatitis Potential of Chemicals and Products* (NIH Pub. No. 09-6439) and the *Recommended Performance Standards: Murine Local Lymph Node Assay* (NIH Pub. No. 09-7357). These recommendations from the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) were submitted to the FDA by the National Institute for Environmental Health Sciences for the Agency's consideration on September 18, 2009, pursuant to Section 3(e)(4) of the ICCVAM Authorization Act of 2000 (42 U.S.C. 2851-3).

FDA agrees that for some chemicals for which the traditional LLNA is appropriate, the reduced LLNA as described in NIH Publication No. 09-6439, could also be appropriate and that it could be used as a preliminary screen. However, FDA notes that, based on its experience with dermal formulations in the traditional LLNA, that many dermal formulations and vehicles alone give positive results that are not seen in guinea pigs or humans. This assay would not be appropriate when the pharmacodynamic activity of the drug/ biologic was to release cytokines. Furthermore, known human sensitizers have failed in some dermal formulations. Thus, FDA cannot recommend this assay without reservations. On a case by case basis, this assay could be considered for acceptance for particular products regulated by FDA.

In general, FDA agrees with the essential test method components in recommended performance standards for modifications to the traditional LLNA as described in NIH Publication No. 09-7357. The target audience for this document is test developers. The purpose of the standards is that test method developers can develop modification to the assays and not have to undergo a complete validation study and evaluation. FDA could accept studies from LLNA assays that adhere to the essential test method components as

described in the document on LLNA performance standards, being aware of the limitations of the reference LLNA method

If you need further information, please contact me at 301-796-4880.

/s/

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