DEPARTMENT OF HEALTH & HUMAN SERVICES

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RADM William S. Stokes, Director, National Toxicology Program
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National Institute of Environmental Health Sciences
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Dear Dr. Stokes: Bill

This letter is in response to Dr. Linda S. Birnbaum's, Director, National Institute of Environmental Health Sciences June 30, 2011 request that the US Food and Drug Administration review NIH Publication Number 11-7709 entitled: **ICCVAM Test Method Evaluation Report: Use of the Murine Local Lymph Node Assay for Potency Categorization of Chemicals Causing Allergic Contact Dermatitis in** . The recommendations are for a specific criterion for the murine local lymph node assay (LLNA) to be used in potency categorization of chemicals that cause allergic contact dermatitis in humans.

FDA agrees that the ICCVAM LLNA protocol is a validated sensitization assay that could be used as part of a weight-of-evidence evaluation to discriminate between strong and weak sensitizers and that the LLNA should not be considered as a stand-alone test method for predicting sensitization potency.

However, FDA notes the following with respect to use of the LLNA and FDA-regulated products. Based upon FDA's experience with dermal pharmaceutical formulations in the traditional LLNA, many dermal formulations and vehicles alone, and some dermal irritants, give positive results that are not seen in guinea pigs or humans. This assay would also not be appropriate when the pharmacodynamic activity of a drug/ biologic was to release cytokines. Furthermore, known human sensitizers have failed in some dermal formulations.

Additionally, the use of LLNA to correctly categorize strong and weak sensitizers will have a limited role with medical devices because FDA does not generally categorize device materials (substances) as strong, moderate or weak sensitizers. FDA generally warns device users of any sensitization potential.

FDA also notes that LLNA potency characterization of chemicals does/would not stand alone when reviewing cosmetic ingredient safety. FDA would need peptide reactivity, in vitro testing data, human data, and/or existing data from similar chemicals before being convinced about an LLNA categorization result.

With respect to the discussion of the use of the LLNA test in the context of the Globally Harmonized System of Classification and Labeling of Chemicals (GHS), the FDA considers that it is beyond the purview of ICCVAM to develop recommendations for changes in this international agreement or in its interpretation.

In accordance with Sections 4 (a)-(e) of the ICCVAM Authorization Act, FDA has addressed each of the requirements as follows:

1. Identification of Tests: FDA agrees that the ICCVAM LLNA protocol is a validated sensitization assay that could be used as part of a weight-of-evidence evaluation to discriminate between strong and weak sensitizers and that the LLNA should not be considered as a stand-alone test method for predicting sensitization potency. However, use of this assay may not be appropriate for FDA-regulated products, as discussed above.

2. Alternatives: FDA is committed to promoting and encouraging the use of alternatives when appropriate. FDA's guidance can be found on our website at www.fda.gov. FDA has no specific plans for modifying any guidance as a result of these recommendations.

3. Recommendation Adoption: The FDA concurs with the technical aspects of the recommendations. However, the ICCVAM test recommendations are not acceptable for satisfactorily fulfilling the test needs for FDA regulated products.. Rather, FDA would like to see a screening battery of in vitro assays.

The FDA appreciates the opportunity to review these materials, and it acknowledges the enormous amount of work that went into the evaluation and peer review. FDA acknowledges the time and energy ICCVAM devotes to advancing the "three Rs" principles of reduction, refinement and replacement of animal use and looks forward to continuing interactions with ICCVAM as part of the FDA's commitment to applying the 3 R's, where possible, in FDA programs.

Sincerely,

/s/

Jesse Goodman, MD, MPH
FDA Chief Scientist & Deputy Commissioner for
Science & Public Health