Date: Thu, 7 Jun 2007 09:00:44 -0400
Subject: NTP NICEATM Nomination of experts and response to call for data - LLNA
Ref.: Federal Register vol. 72 no. 95, p. 27815, 17 May 2007

Dr. Stokes -
Responding to the request for comment on the US CPSC proposal to ICCVAM-NICEATM for evaluation of the validation status of the murine local lymph node assay, I am pleased to submit the following information for consideration. (The views expressed in item 1.) below are solely my own and do not necessarily reflect the corporate position of GSK.)

1.) Appropriateness and relative priority of items comprising the proposed review of the status of the LLNA: It seems entirely justified that the proposed review should be undertaken based on the large volume of high quality peer-reviewed information published on performance, data evaluation and proposed protocol modifications of the LLNA in the period since the original ICCVAM-sponsored LLNA validation exercise. As proposed by US CPSC, ICCVAM-NICEATM preparation of a comprehensive background review should precede activation of a study panel. Regarding the priority of items for the background review as presented in the Federal Register notice, I suggest that the priority sequence should be slightly rearranged to highlight items 1, 5, 4, 2 and 3 (as identified in the Fed. Reg. notice) in priority sequence. Thus, from most to least pressing: 1. development of data to allow the LLNA to be used as a stand-alone tool in determining potency / severity of sensitising potential of chemicals; 2. evaluation and extension of the domain of applicability of the LLNA; 3. use of the LLNA for testing mixtures, aqueous solutions, and metals; 4. development of an animal-sparing cut-down approach to the LLNA focused on use of untreated vs. single high-concentration test group; and 5. assessment of the status of LLNA methods using non-radiolabeled tracer for end-point analysis.

2.) Nomination of expert scientists to serve on a possible LLNA review panel: I am pleased to offer the name of my GSK colleague Frederick J. Guerriero as a possible panel member. Mr Guerriero is a key member of the GSK Occupational Toxicology working group and in this capacity has had the responsibility of protocol development, study contracting and evaluation of a large number of LLN assays over the past 7-8 years. In addition, Mr Guerriero has previously served on the NICEATM study panel which evaluated *in vitro* alternatives for evaluation of ocular irritant/corrosion effects of chemicals. As a secondary potential candidate for the study panel, I would also be pleased to volunteer my service which is based in similar experience to that of Mr. Guerriero.

3.) Submission of LLNA data: Over the past 5 years GSK has transitioned to sole use of the LLNA as a means for evaluating the sensitising potential of a wide variety of chemical materials used in the synthesis of pharmaceuticals. The spectrum of substances which have been evaluated includes commodity chemicals used as starting materials, proprietary synthetic intermediates of varying structural complexity, and active pharmaceutical entities. All of these

assessments have been conducted by the "traditional" control + 3 concentration protocol using 3H-thymidine label. A small proportion of materials also have companion data evolved with the M&K or Beuhler dermal sensitisation protocol. Although the composite data are not presently in a readily transmitted form, I believe that we could be in position to share results of assessment of *ca.*190 chemicals if materials from the pharmaceutical sector would be of interest in the assessment which NICEATM is planning.

I will send this letter in print form with mailing today. I look forward to your reply in due course.

Sincerely yours -
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