DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

August 27, 2008

Rear Admiral William S. Stokes
Executive Director, NICEATM
NIEHS
P.O. Box 12233,
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Dear Dr. Stokes:

FDA has reviewed the ICCVAM test method recommendations for two *in vitro* alternative test methods that are recommended for estimating starting doses for acute oral systemic toxicity tests. The test methods are (1) the BALB/c 3T3 mouse fibroblast (3T3) test method and; 2) the normal human epidermal keratinocytes (NHK) test method. There recommendations were provided to the FDA in the report, *The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Test Method Evaluation report: In Vitro Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Test).*

ICCVAM recommends that these two methods be considered before using animals for acute oral toxicity testing, and that, where appropriate, should be used in a weight-of-evidence approach for determining starting doses for *in vivo* studies. ICCVAM has concluded that these two *in vitro* test methods are not sufficiently accurate to replace animals for regulatory purposes.

FDA does not have any relevant test methods requirements for which these two test methods could be added or substituted. FDA does not ordinarily require acute oral lethal toxicity studies for the products that it regulates.

FDA will encourage manufacturers to use the 3T3 or NHK test methods when appropriate to determine starting doses if they believe that acute oral systemic toxicity testing using the UDP or ATC methods is necessary. FDA will also make its pharmacology/toxicology reviewers aware of these assays and the ICCVAM recommendations.

Although FDA does not envision a lot of regulatory utility for these *in vitro* cytotoxicity test methods in its present testing requirements, it applauds all attempts at reducing numbers of test animals used in regulatory testing.

If you need any further information, please do not hesitate to contact me.

Norris E. Alderson, PhD
FDA Associate Commissioner for Science