

From: Khurana, Taruna
Sent: Monday, October 31, 2016 12:10 PM
To: nadine_margaretten@merck.com
Cc: Sweeney, Colleen; Steele, Matthew (Matthew.Steele@fda.hhs.gov)
Subject: STN125592/0 HDM SLIT Genotox Information Request

Hi Nadine,

We have the following request for additional information regarding the genotox study. A quick response will be helpful in the review process.

1. Final Study Report TT#12-7810 entitled, "Induction of chromosome aberrations in cultured human peripheral blood lymphocytes," reports the (b) (4) of the drug substance, *Dermatophagoides pteronyssinus* (*Der p*) allergen (b) (4), and the drug substance *Dermatophagoides farinae* (*Der f*) allergen (b) (4). In the report, the (b) (4) of the *Der p* test article is stated as (b) (4).
The (b) (4) of the *Der f* test article is (b) (4). Please clarify the (b) (4) portion of the test articles used in this test. Also, please clarify if (b) (4) for *Der f* at (b) (4) is within the expected range.
2. You have provided negative evidence of genotoxicity using a combined Comet and micronucleus assay as an *in vivo* assay as well as complementary bacterial mutagenicity assays; however, the utility of *in vivo* assays presumes exposure to the target tissue to be valid and this not been demonstrated. Based on the available information, it is unlikely that exposure did take place, particularly for the micronucleus aspect of the assay and this essentially invalidates the negative results. We recommend that you perform an *in vitro* mouse lymphoma assay since it is not dependent on biodistribution and utilizes a similar target tissue to the human lymphocyte assay that yielded positive results. This would assist in developing a weight of evidence approach to an assessment of genotoxicity.

Please let me know if you have any question.

Thank you

Taruna Khurana, PhD

Biologist (Regulatory)

Center for Biologics Evaluation and Research
Office of Vaccines Research and Review
U.S. Food and Drug Administration
Tel: 301-796-2640
Taruna.khurana@fda.hhs.gov



THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify the sender immediately by e-mail or phone.