DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

SF

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

DEC 5 2005

Certified Mail
Return Receipt Requested

Reference No: 05-HFD-45-1201

David L. McCormick., Ph.D., D.A.B.T.
Vice-President and Director, Life Sciences Group
IIT Research Institute
10 West 35th Street
Chicago, Illinois 60616

Dear Dr. McCormick:

Between January 3-7, 2005, James W. Plucinski and Charles A. Snipes, Ph.D., representing the Food and Drug Administration (FDA), inspected several nonclinical laboratory studies conducted by your firm including the following:

- Protocol [ ] entitled "Two-Year Carcinogenicity Study of [ ] Administered Subcutaneously in Rats" performed for [ ]
- Protocol [ ] entitled "A Developmental Toxicity Study of Orally Administered [ ] in Rabbits" performed for [ ]
- Protocol # [ ] entitled "A Reproductive Toxicity Study [ ] of Orally Administered [ ] in Rats" performed for [ ]
- Protocol # [ ] entitled "A Reproductive Toxicity Study [ ] of Orally Administered [ ] in Rats" performed for [ ]

These inspections are a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to verify compliance with Title 21 of the Code of Federal Regulations (CFR), Part 58--Good Laboratory Practice (GLP) regulations. The regulation at 21 CFR 58 applies to nonclinical laboratory studies of products regulated by FDA.

At the conclusion of the inspection, our investigators presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. Following our review of the establishment inspection reports and related documents, including your letter dated February 4, 2005, we conclude that you violated FDA regulations governing the conduct of nonclinical laboratory studies. This letter provides you with written notice of the matters under complaint. The applicable provisions of the CFR are cited for each violation.

1. **Failure of testing facility management to assure that test articles or mixtures were appropriately tested for identity, strength, purity, stability, and uniformity, as applicable [21 CFR 58.31(d)].**

Your testing facility management failed to assure that the dose formulations of [ ] prepared by the sponsor and administered in study [ ] were tested for [ ] of the test article in the mixture, uniformity of the mixture, and stability of the test article under the conditions of the study. The protocol stated that the sponsor would test the dose formulations prior to shipment, and samples of the dose formulation would be sent to the sponsor for [ ] analysis during study weeks 5, 13, 26, 52, 78 and 103. You subsequently amended the protocol, approximately one year after dosing ended and two weeks before the final report was signed by the study director, to indicate that the dose formulation results would be submitted separately by the sponsor. Although the sponsor did submit the results to the agency after the inspection, the testing facility failed to assure that the appropriate testing was conducted in order for the study director to include the necessary information in the final report. (See violation #2 below)

2. **Failure to include a description of all circumstances that may have affected the quality or integrity of the data in final study reports [21 CFR 58.185(a)(9)].**

As detailed in item 1 above, the study director lacked critical information regarding the dose formulation administered to animals in study [ ] Characteristics of the dose formulation are essential to the study director's assessment of study outcomes, and the absence of this information limits the quality and the integrity of the data for study [ ] While your final report stated that the sponsor would submit the results separately, it did not describe the impact of the missing information. Specifically, in your summary and conclusion sections of the final report you did not communicate that you lacked the critical data, or that you had reservations about drawing study conclusions without knowing the actual doses of [ ] administered to the animals.

We acknowledge your February 4, 2005 response that the sponsor instructed you to finalize the final report using the data that were available at the time. Since your attempts to obtain required information from the sponsor were unsuccessful, your final report conclusions should have communicated such critical limitations as circumstances that affected the quality and integrity of the data; because you did not know whether the intended doses of [ ] were actually administered to the animals, the study director could not provide a meaningful assessment of study outcome. Thus, your conclusion in the final report summary that there was no evidence of a carcinogenic effect in any organ (except for fibrosarcomas at the injection site) at [ ] dose levels of 10, 20 and 40 mg/kg could not be reached in light of the missing information and should have conveyed that you lacked critical data to draw study conclusions.

3. **Failure to include characteristics of the test article in final study reports [21 CFR 58.185(a)(4)].**

The final reports prepared by your study director for studies [ ] did not include characteristics of the test article such as strength, purity, and composition, or other appropriate characteristics.

4. Not all nonclinical laboratory studies were conducted in accordance with the protocol [21 CFR 58.130(a)].

The protocol for study[ ]required the consent of the study director or study pathologist prior to sacrificing moribund animals (protocol section 12d). Five study animals (146, 405, 263, 268, and 369) were sacrificed without documentation of the required consent.

5. Failure to indicate the reason for change in automated data entries [21 CFR 58.130(e)].

In several instances, entries in the[ ]collection/notes and audit trails failed to provide the reason for changing raw data. For example, audit trail entries for study[ ]demonstrate that observations of "normal" were removed without an explanation. In your response dated February 4, 2005, you agreed that the reasons used by study personnel did not provide sufficient detail regarding the reason for the change. We acknowledge your proposal to provide study personnel additional training in this regard.

6. Failure to have an approved written protocol for each study [21 CFR 58.120(a)].

You conducted study-specific activities for studies[ ]before the protocol was approved. Protocols must contain the date of approval of the protocol by the sponsor and the dated signature of the study director. 21 CFR 58.120(a)(11). Because the study initiation date [21 CFR 58.3(o)] represents the date on which the study director signs the protocol and the study begins, conduct on the study should not commence before that date. In particular, animals were randomized into study specific dosing groups before the study was initiated. In your response dated February 4, 2005, you suggested that animal randomization is considered "pre-start" data collection, similar to the acquisition of a test article's certificate of analysis. Because animal randomization depends upon a protocol-defined group number and size, FDA considers such activities to be part of conducting the study. Thus, you conducted specific study-related activities without an approved protocol.

7. The protocol did not indicate all methods for the conduct of the study [21 CFR 58.120(a)].

In various instances, the protocols for studies[ ]did not identify the automated systems that were used for data collection. In your response dated February 4, 2005, you stated that the raw data and final report documented use of the automated systems. Inclusion of the information in those documents, however, does not meet the GLP requirement that the protocol clearly indicate all methods for the conduct of the study. We acknowledge your proposal to revise the content of active and future protocols to include the required information.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. As described above, your conduct of nonclinical laboratory studies is deficient. Your response dated February 4, 2005 addressed some of these deficiencies; however, your response did not provide adequate assurance that you have established policies and procedures to prevent recurrence of the

violations cited above. For example, you did not adequately address the issue concerning final report content, nor include details of the SOP revision you proposed regarding animal randomization. You must correct the deficiencies noted above and establish procedures to ensure that any on-going or future studies will be conducted in compliance with FDA regulations.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific corrective actions you will take to address all of the deficiencies noted above and to achieve compliance with the FDA regulations. If corrective actions cannot be completed within 15 working days, you may request an extension of time in which to respond by stating the reason for the delay and the time within which the corrections will be completed. We will review your response and determine whether it is adequate. Failure to provide adequate assurances of compliance with FDA regulations may result in further regulatory action without further notice.

Your reply should be sent to:
C.T. Viswanathan, Ph.D.
Associate Director, Bioequivalence
Chief, GLP & Bioequivalence Investigations Branch
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 116
Rockville, MD 20855
(301) 594-0020

Sincerely,

Joanne L Rhoads, M.D.

Joanne L. Rhoads, M.D., M.P.H.
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research