DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

WARNING LETTER

Food and Drug Administration
Rockville MD 20857

Certified Mail
Return Receipt Requested

JUN 25 2007

Reference No: 07-HFD-45-0603

Paul E. Kirby, Ph.D.
President and Director of Operations
Sitek Research Laboratories.
15235 Shady Grove Road, Suite 303
Rockville, MD 20850

Dear Dr. Kirby:

Between December 6-22, 2006, Stephanie Shapley, representing the Food and Drug Administration (FDA), inspected the following nonclinical laboratory studies conducted by your firm:

1. Study #[ ]"Test for Chemical Induction of Unscheduled DNA Synthesis in Rat Primary Hepatocytes Obtained from Rats Treated Orally with [ ]

2. Study #[ ]"Evaluation of [ ]in [ ]Assay in the Presence and Absence of Induced Rat Liver[ ]

3. Study[ ]; "In Vivo Test for Chemical Induction of[ ]in Mouse Bone Marrow Cells"

This inspection is 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 investigator presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. Following our review of the establishment inspection report and related documents, including your response dated February 19, 2007, we conclude that you violated FDA regulations governing the conduct of nonclinical laboratory studies. This letter provides you with written notice of the violations. The applicable provisions of the CFR are cited for each violation.

1. **Failure of the study director to assure that all experimental data were accurately recorded and verified [21 CFR 58.33(b)] and document the reason for any change in the entries [21CFR 58.130(e)].**

For Study[ ]your study director failed to assure that dosing data were accurately recorded to confirm that study animals received protocol-specified doses of the vehicle, test and positive control articles. For example, the protocol required that animals in the high dose group receive 2000 mg/kg[ ]We found that the source records for the 2000 mg/kg group fail to demonstrate that this dose was achieved. Specifically, the documented dosing solution concentration and volumes administered resulted in a dose that was one-half the protocol-required dose. Thus, because there is no assurance that animals were dosed accurately in the 2000 mg/kg[ ]group, your study director could not meaningfully conclude that there was a lack of chemical induction on unscheduled DNA synthesis (UDS) in the high dose group. Similarly, source records for the vehicle control group document that the dosing volume was one-half the volume required by the protocol. In your response dated February 19, 2007, you claimed that the vehicle control group was dosed twice to achieve the required volume. However, you lack source records to support your claim in that you did not document that the animals were dosed twice or the volume administered for the second dose.

Furthermore, dosing records indicate that animals in the two positive control groups received double the protocol-specified dose, based on the volumes documented at the time of dosing. Approximately seven weeks after dosing, the study director altered the source records to reduce the dosing volumes to one-half the volume originally documented. The study director failed to document the reason for the changes. Consequently, the actual dose administered to the animals in both positive control groups is questionable. Your study director's conclusion in the final report that the criteria for a valid assay were met based on the response from the positive controls is invalid because the dose that elicited the response cannot be assured. Contrary to your response dated February 19, 2007, while the dose volume corrections for the test and vehicle control groups were related to rounding up the decimal values of the calculated dose volumes, the corrections for the positive control groups were not.

2. **Failure of QAU to fulfill its responsibilities [21CFR 58.35(b)].**

a. Failure of QAU to assure that the reported results in the final study report accurately reflected the raw data [21CFR 58.35(b)(6)].

For Study[ ]the net nuclear grain count per cell was the critical measurement used to conclude the study outcome. However, we found discrepancies in the data reported for this measurement. For example,

- data from animal B4995 with the highest number of affected nuclei (i.e. five or more net nuclear grain counts) was excluded from the final report and the data from animal B4999 with a smaller number of affected nuclei was included in its place
- for animal B4998, only one affected nuclei was reported although the raw data documented six
- for animal B5019, data from only 150 nuclei was reported although the transcribed data documented that 200 nuclei were counted

In light of these discrepancies, we have no assurance of the quality and integrity of the final report you prepared for Study[ ]As described in your response dated February 19, 2007, we acknowledge your proposal to correct these discrepancies and submit a revised final report to the sponsor.

b. Failure of QAU to maintain a copy of the master schedule of all nonclinical laboratory studies indexed by nature of the study [21 CFR 58.35(b)(1)].

Specifically, the master schedule did not list terminated GLP study[ ] Additionally, you failed to maintain a key to decode the nature of studies with code[ ]

c. Failure of QAU to maintain written and properly signed records of each periodic inspection [21CFR 58.35(b)(3)].

For Study[ ] your QAU documented inspection of colony counting on October 26, 2005. However, according to your source records, no colony counting occurred on that day; instead, the counting actually occurred on October 24, 2005.

In your response dated February 19, 2007, you attributed the observations under item 2 above, to inadvertent errors on the part of the QAU. As described in your response dated February 19, 2007, we acknowledge your proposal to revise your QAU procedures for future studies.

3. Failure to identify the test and control articles with appropriate characteristics in the final report [21 CFR 58.185(a)(4)]

The final reports prepared by your study directors for Studies[ ] did not include required information on test and control article characterization. For example, the purity and specific lot numbers of the test article and the vehicle control for Study[ ]and the purity and stability of the test article for Study[ ]were not included. The statement in the final report that purity and composition of the test article were determined by the sponsor is not adequate to satisfy the requirement that the final report contain the actual characteristics of the test article.

4. Failure to adequately test, calibrate, and /or standardize all equipment used for the generation, measurement, or assessment of data [21CFR 58.63(a)].

You failed to assure that the[ ]used to count the colonies in Studies[ ]was adequately calibrated to assure an accurate measure of cell and/or colony counts. Although your SOP[ ]required instrument calibration prior to use, your records indicate that you used this instrument without calibrating it for 15 of 20 days for Study[ ]and 1 of 3 days for Study [ ]

The failure to test, calibrate and /or standardize all equipment used in nonclinical studies is a repeat violation. This deficiency was cited on Form FDA 483 during FDA's March 2001 inspection of your nonclinical laboratory studies and was again discussed with you during FDA's April 2003 inspection of your nonclinical laboratory studies. In your response dated February 19, 2007, we acknowledge your proposal for frequent monitoring of equipment calibration by the QAU and additional training of study personnel in this regard.

5. **Failure to prepare a final report for each nonclinical laboratory study [21CFR 58.185 (a)].**

Your study director failed to prepare final reports for Studies[ ] terminated after administration of the first dose of test article. Also, we found at least six GLP studies[ ] with draft reports pending since May 2004.

The failure to prepare final reports for each nonclinical laboratory study is a repeat violation. Following the inspection of your facility in April 2003, FDA's letter to you dated August 25, 2003 expressed our concerns about this deficiency. In your December 3, 2003 response you proposed to correct this deficiency by preparing memoranda for terminated studies that would include an overview of the study history. The current inspection found that the memorandums prepared for terminated studies[ ] was inadequate to facilitate reconstruction of the study conduct and stated that "no draft and final reports were issued". In light of this finding, we conclude that you failed to implement corrective actions to ensure the preparation of a final report for each nonclinical laboratory study.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. Your violation of the FDA regulations outlined above resulted in the submission of unreliable data to the sponsor. You must address these deficiencies and establish procedures to ensure that any on-going or future studies be conducted in compliance with FDA regulations.

Within fifteen (15) working days of receipt of this letter, you must 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:

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Chief, GLP & Bioequivalence Investigations Branch
Division of Scientific Investigations
Office of Medical Policy
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Sincerely,

6/25/07

Gary J Della Zanna D.O. M.Sc.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research