

Inspections, Compliance, Enforcement, and Criminal Investigations

Sitek Research Laboratories 5/21/09



Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Rockville, MD 20857

WARNING LETTER

Certified Mail
Return Receipt Requested

Reference No: 09-HFD-45-05-02

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 November 18-24, 2008, Cynthia A. Harris, M.S., R.N., Gopa Biswas, Ph.D., and Jacqueline A. O'Shaughnessy, Ph.D., representing the Food and Drug Administration (FDA), inspected the following nonclinical laboratory studies conducted by your firm:

1. Study **(b) (4)**, *In Vivo* Test for Chemical Induction of Micronucleated Polychromatic Erythrocytes in Mouse Bone Marrow Cells, Test Article **(b) (4)**, sponsored by **(b) (4)**
2. Study **(b) (4)**, Salmonella typhimurium/Escherichia coli Plate Incorporation Mutation Assay in the Presence and Absence of Induced Rat Liver S-9, Test Article **(b) (4)**, sponsored by **(b) (4)**

3. Study **(b) (4)**, Test for Chemical Induction of Chromosome Aberrations in Cultured Chinese Hamster Ovary (CHO) Cells With and Without Metabolic Activation, Test Article **(b) (4)**, sponsored by **(b) (4)**

4. Study **(b) (4)**, *In Vivo* Test for Chemical Induction of Micronucleated Polychromatic Erythrocytes in Mouse Bone Marrow Cells, Test Article **(b) (4)**, sponsored by **(b) (4)**

5. Study **(b) (4)**, Evaluation of a Test Article in the L5178Y TK +/- Mouse Lymphoma Mutagenesis Assay with Colony Size Evaluation the Presence and Absence of Induced Rat Liver S-9 with a Confirmatory Study, Test Article **(b) (4)**, sponsored by **(b) (4)**

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) regulation. The regulation at 21 CFR 58 applies to nonclinical laboratory studies of products regulated by FDA. Prior inspection of your facility between December 6-22, 2006 found significant noncompliance with the GLP regulations and the Agency issued a Warning Letter to you on June 25, 2007. The Warning Letter cited the following violations of the regulation at 21 CFR Part 58:

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 [21 CFR 58.130(e)].

2. Failure of Quality Assurance Unit (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 [21 CFR 58.35(b)(6)].

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)].

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

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

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

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

You proposed corrective action for these deficiencies in your response to the Warning Letter dated July 18, 2007. The current inspection found that you have not corrected all of the deficiencies from the December 2006 inspection, as cited in the June 25, 2007 Warning Letter.

At the conclusion of the current inspection, our investigators 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, 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. The study director failed to assure that all experimental data, including observations of unanticipated responses of the test system, were accurately recorded and verified [21 CFR 58.33(b)].

The study director failed to assure accurate record keeping and document in the raw data that discrepancies in study conduct were verified. For example:

- For Study (b)(4), your paper records document that slides for scoring chromosomal aberrations in trial (confirmatory assay without S9 activation) were prepared on July 22, 2007. In contrast, the slides in the archive were labeled July 13, 2007, nine days earlier.
- The following deficiencies were found for Study **(b)(4)**:
 - The final report presented definitive trial **(b)(4)** (4 hour test article exposure with S9 activation) as a "valid assay" although it failed to meet the protocol and SOP criteria for a valid assay. The study director failed to document in the source data or discuss in the final report that the experiment was not valid.
 - Raw data for definitive trial **(b)(4)** (4 hour test article exposure without S9 activation) were changed by the study director without explanation.
 - Test article maximum tolerated doses identified through the range finding assay and documented in the study file were not used for the definitive assay. Instead, the study director changed the doses for subsequent experiments and failed to retain source data to document that he initiated the change and the reason for the change.
 - Triplicate raw data counts observed for each culture plate were not transcribed into the spreadsheet used to determine mutant frequency. Instead, the median of the displayed count from the **(b)(4)** counter was recorded without documenting the individual raw data counts. Thus, the accuracy of the median count cannot be verified.

Your failure to accurately document experimental data and study conduct is a repeat violation from the December 2006 inspection of your firm, as cited in the June 25, 2007 Warning Letter. Please note Studies **(b) (4)** and **(b) (4)** were initiated after the December 2006 inspection, on June 25, 2007 and February 6, 2007, respectively.

2. The final report failed to include a description of all circumstances that may have affected the quality or integrity of the data [21 CFR 58.185 (a) (9)].

The study director failed to describe in the final report the impact of not obtaining necessary characteristics of the dosing formulations used in several studies. For example:

- For Study **(b) (4)**, the strength and stability of the test article and dosing solutions and controls under the experimental conditions were not determined.
- For Study **(b) (4)**, you collected and submitted samples of the dosing solutions for analysis, but at the sponsor's request, the study director signed the final report without the test results.
- For Study **(b) (4)**, although the test article mixture was a **(b) (4)**, the sponsor performed and provided the study director the results of concentration analyses only. Uniformity testing to verify accurate dosing was not done. Furthermore, there was no documentation in the study record regarding the handling of the **(b) (4)** at the time of dosing.

In all three studies, the study directors failed to discuss in the final report the consequence of missing critical information and the subsequent impact on study outcome. Because the results of dose formulation analyses are essential to the study director's assessment of study outcome, the absence of this information limits the quality and integrity of the data. Without these analyses, the study director cannot be certain of the doses administered and, therefore, cannot meaningfully assess the study outcome. Although the final report compliance statements for Studies **(b) (4)** and **(b) (4)** described that the testing was not done, the study directors should have addressed how the lack of information impacted the ability to assure the actual dose of test article administered to the test system.

3. The quality assurance unit (QAU) failed to inspect each nonclinical laboratory study at intervals adequate to assure integrity of the study [21 CFR 58.35(b) (3)].

The QAU did not conduct any in-process inspection of Studies **(b) (4)** and **(b) (4)**. Contrary to your claim during the inspection that this only reflects a deviation from your standard operating procedure, the lack of in-process QAU inspections is a

significant departure from the GLP regulations as each study must be inspected at least once during the study conduct.

Failure of your firm's OAU to fulfill its responsibilities is a repeat violation from the December 2006 inspection and cited in the June 25, 2007 Warning Letter. Please note Studies **(b) (4)** and **(b) (4)** were initiated after the December 2006 inspection, on May 2, 2008 and June 25, 2007, respectively.

4. Nonclinical laboratory studies were not conducted in accordance with the protocol [21CFR 58.130(a)].

For Study **(b) (4)**, protocol section 17.6 required blinded slide scoring to avoid bias on the part of the scorers. However, the paper records used by the slide scorers to record chromosomal aberrations included the test article doses.

For Study **(b) (4)**, protocol section 15.1 stated that **(b) (4)** would be used as the positive control for experiments without metabolic activation and that other controls could be used with sponsor approval. You used **(b) (4)** for definitive trial **(b) (4)** (4 hour test article exposure without S9 activation) in August 2007 without obtaining sponsor approval.

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 ongoing 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 respond satisfactorily to this letter and take appropriate corrective action could result in FDA taking regulatory action including disqualification in accordance with 21 CFR 58.204.

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 Compliance
Center for Drug Evaluation and Research

Food and Drug Administration
10903 New Hampshire Avenue, WO51 Room 5346
Silver Spring, MD 20993

Sincerely,

{See appended electronic signature page}

Leslie K. Ball, M.D.

Director

Division of Scientific Investigations

Office of Compliance

Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed
electronically and this page is the manifestation of the electronic
signature.

/s/

LESLIE K BALL

05/21/2009