DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

WARNING LETTER

Food and Drug Administration
Rockville MD 20857

JUL 1 2005

Certified Mail
Return Receipt Requested

Reference No: 05-HFD-45-0701

Carol R. Tometsko
Chief Executive Officer
Litron Laboratories, Ltd.
1351 Mt. Hope Avenue, Suite 207
Rochester, NY 14620

Dear Ms. Tometsko:

Between September 24-28, 2004, Russ E. Davis, representing the Food and Drug Administration (FDA), inspected the following nonclinical laboratory studies conducted by your firm:

1. Protocol #[ ]entitled "Mouse Micronucleus Assay", performed for[ ]
2. Protocol #[ ]Mouse Micronucleus Assay for Medical and Dental Devices," performed for[ ]
3. Protocol #[ ]entitled '[ ]Rat Micronucleus Analysis", performed for [ ]

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 letters dated October 14, 2004, November 19, 2004, January 21, 2005, February 10, 2005, and May 3, 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. You failed to record data generated during the conduct of a nonclinical laboratory study directly and promptly, and to sign and date data entries [21 CFR 58.130(e)].

For studies[ ]and[ ]you failed to record data generated during the conduct of the studies, such as documenting the time and volume of the dose administered. Consequently, the actual dose administered in the studies is unknown. You also failed to record the time of collection and fixation of blood samples. The protocols required

fixation of samples within six hours of blood collection. Without knowledge of the actual dose administered and the integrity of the fixed blood samples, your study director cannot provide a meaningful assessment of the study outcomes.

Also, in several instances, the person that weighed the animals in these studies prior to dosing did not sign and date the data entries as required.

2. **The study director failed to document all changes in or revisions to the approved protocol and the reasons for the change or revisions [21 CFR 58.33(a), 21 CFR 58.120(b)].**

The approved protocol for Study [ ] required a single dose range finding assay with two males and females at each dose level. Following deaths of animals in the high dose levels in the preliminary dose range finding assay, your study director tested additional animals at the lowest and the highest doses without documenting the changes in or revisions to the protocol and the reasons for the additional tests.

3. **The protocol did not contain required information [21 CFR 58.120(a)].**

   Your protocols lacked the following information that is applicable to your studies to assure proper study conduct and accurate results:

   a. The protocol is required to contain the number, body weight range, sex, source of supply, species, strain, substrain, and age of test animals [21 CFR 58.120(a)(4)]. Protocols [ ] and [ ] failed to specify the body weight range, strain, and age of the test animals.

   b. The protocol is required to contain a procedure for identification of the test animals [21 CFR 58.120(a)(5)]. Protocols [ ] and [ ] failed to include a procedure for identification of animals.

   c. The protocol is required to contain the type and frequency of tests, analyses, and measurements to be made [21 CFR 58.120(a)(9)]. Protocols [ ] and [ ] failed to identify the type and frequency of monitoring of test animals.

4. **The quality assurance unit (QAU) failed to fulfill its responsibilities [21 CFR 58.35(b)].**

   a. The QAU failed to inspect each non clinical study at intervals adequate to assure the integrity of the study [21 CFR 58.35(b)(3)].

   QAU records for protocol [ ] document inspection of the study at completion and during the preparation of the study report, but fail to document conduct

of an in-process QAU inspection. Without an inspection during the conduct of the study, you failed to inspect at intervals adequate to assure the integrity of the study.

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

QAU inspection records are required to show, among other things, the phase or segment of the study inspected during a given inspection. For study [ ] QAU inspection records state only that an "in-process" inspection was done and fail to specify the phase (e.g., blood fixation, staining) of the study inspected. The QAU statement in the final report indicates that blood fixation, staining, and analysis were inspected. However, the lack of contemporaneous documentation of these phases of the study in the QAU inspection report makes it impossible to verify the statement in the final report.

c. The QAU failed to periodically submit written status reports on each study to management and the study director [21 CFR 58.35(b)(4)].

In your response to Form FDA 483 dated November 19, 2004, you claim that the QAU communicated its status findings verbally. Verbal communications do not fulfill the requirement for written status reports.

5. You failed to establish procedures for animal care [21 CFR 58.90].

a. You lacked standard operating procedures for the housing, feeding, handling and care of animals [21 CFR 58.90(a)]. Specifically, you lacked procedures for dosing study animals by oral gavage, for monitoring animal care, for sacrificing study animals, and for evaluating the health status of newly acquired animals in accordance with acceptable veterinary medical practice.

b. For warm-blooded animals used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require the animals to be removed from and returned to their home cages for any reason, the regulations require appropriate identification. All information needed to specifically identify each animal within an animal housing unit is required to appear on the outside of that unit [21 CFR 58.90(d)]. Your studies fall within this requirement. You did not have cage tags for animals used in Study [ ] The cage tags used for Study [ ] did not identify the study and animals within the cage.

6. You failed to include required information in the final study report [21 CFR 58.185(a)].

a. The final report is required to describe all circumstances that may have affected the quality or integrity of the data [21 CFR 58.185(a)(9)]. Your study director lacked the results of the analyses of the dose formulations in study [ ] Characteristics of the dose formulation are critical to the study director's assessment of

study outcomes, and the absence of this information may have affected the quality or integrity of the data for study[ ]Thus, the final report should have explained that you lacked information to confirm the actual dose of test article administered to the animals and that the study outcome could not be evaluated without this information.

b. The final report is required to identify any changes in the original protocol [21 CFR 58.185(a)(2)]. The final report for study[ ]failed to note that the route of administration in the original protocol (intraperitoneal injection) was changed to oral gavage.

c. The final report is required to identify the locations where all specimens, raw data, and the final report are to be stored [21 CFR 58.185(a)(13)]. The final report for study[ ]failed to identify the storage location for the raw data.

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. While your responses dated November 19, 2004 and February 10, 2005 addressed some of these deficiencies, your responses 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 include details of the procedures you proposed to ensure that nonclinical studies are inspected at adequate intervals, adequate inspection reports are maintained by your QAU, and animals are properly cared for and handled. The procedures you have proposed to correct these deficiencies must include specific steps to prevent recurrence of violations and to ensure that any on-going or future studies are 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:
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
Telephone: (301) 827-5460

Sincerely,

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