DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 08-HFD-45-1004

Kevin W. Klein, M.D.
Department of Anesthesiology and Pain Management
University of Texas Southwestern Medical Center
5323 Harry Hines Boulevard
Dallas, Texas 75390

Dear Dr. Klein:

Between February 6 and 10, 2006, Mr. Joel Martinez, representing the Food and Drug Administration (FDA), conducted an investigation and met with your sub-investigator, [ ]M.D., to review the conduct of two clinical investigations of the investigational drug[ ]performed for [ ]

[ ]- A Randomized, Double-Blinded, Active Controlled, Parallel Study to Evaluate the Comparative Safety and Efficacy of[ ]and[ ]for Induction and Maintenance of[ ]

[ ]- A Randomized, Double-Blinded, Active Controlled, Parallel Study to Evaluate the Short Term Efficacy and Safety of[ ]and[ ]for [ ]

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research; to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected; and to ensure the quality and integrity of data submitted for review.

From our review of the establishment inspection report, documents submitted with that report, and a March 15, 2006, response to the Form FDA 483 from Dr.[ ]sent to Investigator Martinez, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr.

Martinez presented and discussed with Dr.[ ]Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. **You failed to ensure that the investigations were conducted according to the investigation plan [21 CFR 312.60].**

   To evaluate the safety of[ ]the protocols required that[ ]values were to be recorded at 1 through 5 minute intervals during the induction of[ ]and at 10 minute intervals during the maintenance of[ ] In addition,[ ]values were to be recorded before premedication, before induction, and at 1, 2, 3, 5, and 10 minutes after the beginning of the induction injection of[ ]Many of these safety variables were not recorded during the induction and maintenance of[ ]for subjects in both protocol[ ]and protocol[ ]For example, for protocol[ ]for subject[ ]01,[ ]values were not recorded at minutes 1 or 5;[ ]values were not recorded at baseline, at minute 1, 3, or 5 after the induction injection of[ ]and[ ]values were not recorded until 10 minutes after the induction of[ ]For subject[ ]-08,[ ]values were not recorded at baseline, or at minutes 1, 2, 3, or 5; and[ ]values were not recorded before premedication, or at minutes 1, 3, or 5. For protocol[ ]for subjects [ ]-58 and[ ]60,[ ]values were not recorded at baseline, and no values for any of the required variables were recorded at the 2 minute mark.

   We note that in the March 15, 2006, response to the Form FDA 483, Dr.[ ]states that it was not surprising that required values were missed due to the study design. As the clinical investigator of the study, it is your responsibility to assure that the study is conducted according to the investigational plan. If it is apparent that the study cannot be conducted as required, the sponsor should be notified, the protocol amended, and study procedures changed.

2. **You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subject [21 CFR 312.62(a)].**

   a. Operating room pharmacy logs were not kept. There were no records for the preparation and dispensing of[ ]for subjects in protocols[ ]and[ ]

   b. You did not maintain adequate records of partially used and discarded vials of [ ]and[ ]The actual amount of[ ]and[ ]administered to subjects in protocols[ ]and[ ]could not be verified.

   We find the March 15, 2006, response to the Form FDA 483 inadequate in that there was no detailed explanation of how drug accountability procedures would be improved to assure that adequate records of all study drugs used and discarded would

be maintained. To say that it would be helpful to use an Operating Room Pharmacy Log for future trials is not sufficient.

3. **You failed to maintain accurate and adequate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug [21 CFR 312.62(b)].**

Discrepancies were noted among the lists that recorded the initials of subjects who were enrolled in the study using protocol [ ] and received study drug. For example, on the Master Subject List, subject [ ]03 had the initials [ ] however, on the subject list maintained by the study coordinator in the operating room, subject [ ] 03 had the initials [ ] Subject [ ]03 was not listed as a subject that received study medication on the Investigational Product Drug Utilization Form (IPDUF). Subject [ ]27 had the initials [ ] on the Master Subject List and the IPDUF, and [ ] on the study coordinator's list. Also, subject [ ]32 had the initials [ ] on the Master Subject List and the initials [ ] on the study coordinator's list and the IPDUF.

We acknowledge the explanations provided in the response to the Form FDA 483 dated March 15, 2006, for the above discrepancies in subject initials. However, we note that the explanations provided actually indicate that additional inaccurate study information was reported. For example, the response explains that subject [ ] was scheduled to received study drug as subject [ ]-02, however the drug was not prepared in time so [ ] was not randomized. Subject [ ] was randomized and apparently received the study drug as subject [ ]03. While this could explain the discrepancies between the initials on the Master Subject List [ ] and those on the study coordinator's list [ ] it highlights the fact that the IPDUF incorrectly reported [ ] as actually receiving drug. Similarly the response explains that subject [ ] was scheduled for surgery as subject [ ]32; however, [ ] decided not to participate in the study and [ ] was enrolled as subject [ ]32. [ ] was apparently administered the drug originally intended for [ ] but the IPDUF incorrectly indicates that [ ] received study drug. As a result of these discrepancies, it is not possible to determine which patients actually received study drug.

4. **You failed to obtain informed consent in accordance with 21 CFR Part 50 [21 CFR 312.60, 21 CFR 50.20, AND 21 CFR 50.25].**

Specifically, you failed to provide subjects with a description of any reasonable foreseeable risks or discomforts to the subjects as required by 21 CFR 50.25(a)(2).The informed consent forms used for protocols [ ] and [ ] did not explain all the risks associated with the use of [ ] in general. For example, apnea and respiratory depression are known risks associated with [ ] and allergic reactions, bradycardia, hypotension, are additional risks associated with the use of [ ] in general.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address the deficiencies noted above and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Lewin, M.D., M.P.H., at (301) 796-3397; FAX (301) 847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations, Bldg. 51, Rm. 5354
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

{See appended electronic signature page}

Leslie Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

cc: [ ]M.D.
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/s/

Leslie Ball
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