DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 27 2005

WARNING LETTER

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RETURN RECEIPT REQUESTED

Spencer B. Jones, M.D.
Radiant Research
1002 East South Temple, Suite 510
Salt Lake City, Utah 84102

Ref. No.: 05-HFD-45-1001

Dear Dr. Jones:

Between August 11 and 26, 2004, Ms. Ginger M. Sykes, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of the following clinical investigation:

Protocol #[ ]entitled: "A Randomized, Double-Blind, Placebo Controlled Study Evaluating the[ ]for Induction of Local Anesthesia for Vascular Access Procedures in Pediatric Patients" of the investigational drug [ ]performed for[ ]

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety and welfare of the human subjects of those studies have been protected. At the conclusion of the inspection, Ms. Sykes presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your response to the Form FDA 483 dated November 2, 2004.

Based on our evaluation of the inspection report, the documents submitted with the report, an affidavit signed by you on August 26, 2004, and your response to the Form FDA 483, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing your conduct of clinical investigations and the protection of human subjects. A listing of the major violations noted during the inspection supporting our conclusion follows. The applicable provisions of the Code of Federal Regulations (CFR) are cited for each violation.

1. **Failure to protect the rights, safety, and welfare of subjects under your care [21 CFR 312.60].**

An investigator is responsible for protecting the rights, safety, and welfare of the subjects under the investigator's care. Our investigation indicates that, for the 43 subjects you enrolled in the above-referenced study, you failed to protect their rights, safety, and welfare by exposing them to unnecessary trauma and risk of adverse effects. The above-referenced study was designed to evaluate the effectiveness of[ ](an

investigational topical anesthetic containing[ ]for use as local dermal anesthesia for vascular access (e.g., blood draws) in pediatric patients. Subjects between the ages of 3 and 17 were to be randomized to receive either the investigational topical anesthetic or a placebo. The protocol inclusion criteria specified that enrollment of subjects was limited to patients who required a vascular access procedure on the antecubital surface. Notwithstanding this criterion, none of the 43 pediatric subjects you enrolled required a vascular access procedure. The subjects were subjected to a needle stick solely for the purpose of evaluating their pain response to the stick. Those subjects who received the study drug were needlessly subjected to some degree of pain from the needle stick depending on how effective the drug was, and potential infection at the site of the needle stick. Those who did not receive the study drug were needlessly subjected to the pain associated with a needle stick, and potential infection at the site of the needle stick.

2. **Failure to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].**

As discussed above, the protocol inclusion criteria limited enrollment to subjects who required a vascular access procedure. None of the subjects you enrolled required such a procedure. You maintain that you changed the enrollment criteria because subjects that received only a needle stick (no blood draw) would have a more consistent pain response than subjects from whom blood was being drawn. In your November 2, 2004 response to the Form FDA 483, you state that the change in the inclusion criteria was made with the knowledge of the sponsor[ ]clinical monitor, and in accordance with a[ ]study agreement which allowed for deviations from the protocol. However, you were not able to provide any documentary evidence to support your assertion that[ ]was notified of the protocol change. The available documentation seems to indicate that [ ]did not become aware of your protocol change until after you enrolled the last subject.

3. **Failure to promptly report to the IRB all changes in research activity and failure to ensure that no changes were made in the research without IRB approval [21 CFR 312.66].**

As discussed in violation #2 above, you acknowledge that you changed the protocol to permit enrollment of pediatric subjects who did not require a vascular access procedure. An investigator is required to promptly report to the IRB all changes in the research activity and to not make any changes in the research activity without IRB approval (21 CFR § 312.66). In your response to the Form FDA 483, you acknowledge that the IRB was not made aware of the change in enrollment criteria until after the completion of the study. We note that the change you implemented - subjecting healthy, normal pediatric subjects not requiring a vascular access procedure to needle sticks solely for the purpose of evaluating their pain response - required IRB approval. In particular, IRB review was

needed to evaluate potential changes in the IRB's assessment of risks under 21 CFR part 50, subpart D - Additional Safeguards for Children in Clinical Investigations.

4. **Failure to maintain adequate and accurate 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)].**

Records for 12 of your subjects reviewed during FDA's investigation were found to contain inaccuracies. The eligibility section of the case report forms submitted to the sponsor for each of these subjects indicated that subjects required a vascular access procedure (in the check boxes adjacent to the statement "Patient requires a vascular access procedure on the antecubital surface" the "YES" box was checked). In addition, source documents describing the procedure done on each of these subjects indicated that subjects had a "Blood Draw." As discussed in violations #1 and 2 above, subjects enrolled at your site did not require a vascular access procedure and did not have blood drawn.

5. **Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject to whom the investigational drug was administered [21 CFR 312.60].**

The informed consent for participation in a clinical study is required to include, among other things, a description of the procedures to be followed during the study (21 CFR § 50.25(a)(1)). For protocol [ ] the consent forms for parents and adolescents and the assent form for children did not accurately describe the procedures to be followed. These forms stated that a vascular access procedure (e.g., blood draw) would be performed after administration of the investigational therapy [ ] or a placebo). However, blood draws were not performed. Instead, a needle stick was performed solely to induce pain.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of this investigational drug. It is your responsibility as the investigator of record to ensure adherence to FDA regulations.

On the basis of the above violations, FDA asserts that you have failed to protect the rights, safety, and welfare of subjects under your care. You must address these violations and establish procedures to ensure that any on-going or future studies will be in compliance with the regulations.

Please inform this office, in writing, within 15 working days of your receipt of this letter, of the actions you have taken or plan to take to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in further regulatory action.

Your written response and any pertinent documentation should be addressed to:

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Sincerely yours,

Joanne L Rhoads M.D.

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Director
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