HFE-35

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

MAR 6 2006

WARNING LETTER

VIA FEDERAL EXPRESS

David G. Greenhalgh, M.D.
Chief of Burns
Shriners Hospitals for Children Northern California
2315 Stockton Blvd.
Sacramento, CA 95817

Dear Dr. Greenhalgh:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your clinical site from September 2 to October 27, 2005 by an investigator from the FDA's Los Angeles District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study entitled [redacted] complied with applicable federal regulations. [redacted] is a device as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h). This letter also requests prompt corrective action to address the violations cited and discusses your written response to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval (PMA) applications, and Premarket Notification submissions (510(k)) are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 C.F.R.) Part 812 - Investigational Device Exemptions, and Part 50 - Protection of Human Subjects. At the close of the inspection, the FDA investigator presented an inspectional observations form FDA 483 for your review and discussed the observations listed on the form with you. The deviations noted on the FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

Failure to ensure an investigation is conducted in accordance with the signed agreement with the sponsor, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by the FDA or the IRB [21 CFR 812.100, 812.110(b)]

You failed to adhere to the above-stated regulations. You did not conduct the study according to the investigator agreement that you signed on June 26, 1999, and you did not follow the protocol provided to you by the sponsor on November 1, 1999. Instead of conducting the study according to the protocol, you revised or removed sections of the protocol prior to obtaining approval from the sponsor. Please note that the study protocol is part of the investigational plan as defined in 21 CFR 812.25(b). Examples of this failure include but are not limited to the following:

1. In your protocol dated 3/31/00, you added a site selection and randomization schedule under the heading "Design", which was designed to compare two sites of similar area and depth for each test. This design addition is not in the sponsor's original protocol nor did you receive approval for this change.

2. The amount of irrigation solution was changed in your protocol dated 6/22/00. Specifically, the sponsor's November 1, 1999 protocol states that [redacted] however, your protocol dated 3/23/01 was revised to [redacted] This change would affect wound chemistry and possibly healing.

3. The sponsor's original protocol required endpoint data to be collected for the following [redacted]

Your response states that since you did not receive the instruments to perform the biophysical measurement tests from [redacted] you believed that there were no expectations to perform the tests at your clinical site. However, this data was included in the original sponsor protocol and deleted from the eight protocols that you revised independently without discussion with the sponsor. Your response to these violations is inadequate. Please explain and provide documentation of the methods or procedures that will be used at your clinical site to ensure that protocol omissions do not reoccur in the future.

Your response explains that you did not intentionally violate the rules of an IDE since you were unaware that this was an official IDE study. In addition, you stated that you did not receive any feedback from the sponsor that omissions or errors had occurred. The investigator agreement that you signed on June 26, 1999, states that you will "Conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA." In addition, the IDE number is on the agreement along with it being identified as an FDA study.

Also, in your response, you state that the sponsor never informed you that you needed to complete protocol deviation reports since you were never asked for them. However, one of the responsibilities of an investigator as per 21 CFR 812.150 (a) (4) is to report "any

deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice should be given as soon as possible, but in no event greater than 5 working days after the event occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan." You failed to follow the federal regulations that the investigator agreement you signed on June 26, 1999 required you to uphold.

Your letter of November 7, 2005 states that you discussed changes in the protocol with the sponsor but failed to document these changes. You ensured us that in the future, documentation will be improved. You need to document changes according to the protocol requirements and federal regulations. Please develop and record a training and monitoring program for your staff's documentation practices, and please report this program to FDA in your response to this letter.

Failure to maintain accurate, complete and current records regarding the receipt, use or disposition of a study device [21 CFR 812.140 (a) (2)]

Examples of your failure to adhere to this requirement include, but are not limited to the following:

- Device accountability logs were not maintained by the investigator.
- Devices were stored in an unsecured area where employees not part of the study had access to them.

You agreed with this observation at the time of the close of the inspection and agreed to create and maintain a log of receipt and disposal of the study devices. Please explain and provide documentation of the methods or procedures that will be used at your clinical site to ensure that device accountability records are maintained.

Failure to maintain each subject's case history and exposure to the device, including all relevant observations [21 CFR 812.140(a)(3), 21 CFR 812.140(a)(3)(ii)]

Examples of your failure to adhere to these regulations include, but are not limited to the following:

- Page 14 of the original sponsor protocol indicates that photographs should be taken on zero, five, seven, fourteen, twenty-eight, ninety-one, one hundred and eighty-two, three hundred and sixty-five, and later post-operative days. Photographs were not taken or were not taken within the protocol time frames for three subjects ([redacted]). In addition, you eliminated post-operative photographs on day five in your subsequent protocols that had not received approval and there were no records that show when photographs were sent to the sponsor.

The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical study. It is your responsibility as a clinical investigator to ensure compliance with the Act and applicable regulations.

The inspectional report notes that you were not monitored by [redacted] but kept in touch with him via e-mails and telephone calls. The regulations in 21 C.F.R. Part 812 describe sponsor responsibilities as well as those of investigators. IRB responsibilities are spelled out in 21 C.F.R. Part 56, Institutional Review Boards. These three sets of responsibilities overlap to ensure appropriate conduct of clinical studies and the protection of the rights and welfare of participating subjects. Therefore, though the sponsor and IRB involved in your study may have been remiss in fulfilling their responsibilities, you are still held responsible for knowing and following the regulations pertinent to your activities as a clinical investigator in FDA-regulated studies.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the additional actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are the clinical investigator. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 C.F.R. 812.119.

You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at http://www.fda.gov/oc/ohrt/irbs/. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Send your response to: Viola Sellman, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch, 9200 Corporate Boulevard, HFZ-312, Rockville, Maryland 20850.

A copy of this letter has been sent to the San Francisco District Office at 1431 Harbor Bay Parkway, Alameda, CA 94502. Please send a copy of your response to that office.
If you have any questions, please contact Ms. Sellman at viola.sellman@fda.hhs.gov or (240) 276-0125.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health