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DEPARTMENT OF HEALTH & HUMAN SERVICES



Public Health Service

Food and Drug Administration
2094 Gaither Road
Rockville MD 20850

WARNING LETTER

VIA FEDERAL EXPRESS

MAY 8 2007

Edward D. Verrier, MD
University of Washington Medical Center
1959 NE Pacific Street, Box 356310
Seattle, WA 98195-6310

Dear Dr. Verrier:

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 January 17 through February 2, 2007, by investigators from the FDA Seattle District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the study titled [redacted] under [redacted] sponsored by [redacted] complied with applicable federal regulations. The [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 discusses your February 17, 2007, written response to the observations noted at the time of the inspection, and requests that you promptly implement corrective actions.

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 several serious violations of Title 21, Code of Federal Regulations (21 CFR.) Part 812 -- Investigational Device Exemptions and Part 50 -- Protection of Human Subjects. At the close of the inspection, the FDA investigators presented a form FDA 483 -- "Inspectional Observations" 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:

- 1. Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50 and failure to document informed consent [21 CFR 812.100, 21 CFR 812.140(a)(3)(i), 21 CFR 50.20, and 21 CFR 50.27(a)].**

You failed to adhere to the above-stated regulations. Examples of this failure include but are not limited to the following:

- a.) You failed to ensure that information provided to a subject in order to obtain informed consent is in language understandable to the subject, as required by 21 CFR 50.20. Specifically, the medical record for subject [] states "Interpreter needed.. [] language." The consent forms signed by the subject on 3/15/04 and 7/18/05 are in English. There is no documentation in the study record that the consent forms were translated for the subject, or verification that the subject understood the consent forms.

In your response letter, dated February 17, 2007, you stated that "source documentation dated 15 March 2004 stated, 'Patient consented with interpreter present.'" This response is not adequate. Please provide us with a copy of this source documentation.

Investigators should carefully consider the ethical/legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented, the subject's consent will not truly be informed and may not be legally effective. When the study subject population includes non-English speaking people or the clinical investigator or the IRB anticipates that the consent interviews will be conducted in a language other than English, a translated consent document should be prepared with assurance that the translation is accurate. As required by 21 CFR 50.27, a copy of the written, IRB-approved consent document must be given to each subject. In the case of non-English speaking subjects, this would be the translated document. While a translator may be helpful in facilitating conversation with a non-English speaking subject, ad hoc oral translation of the consent document should not be substituted for an IRB-approved written translation. Under 21 CFR 50.27(b)(2), if consent information is to be presented orally and documented with a short form consent document, the IRB nonetheless must approve the written summary of what is to be said as well as the consent document, and there must be witness documentation of the oral presentation.

Your response also notes that an SOP is being developed regarding the informed consent process and documentation. This SOP should include a description of the procedures used for enrolling non-English speaking subjects. Please submit a final version of your SOP, and please explain and provide documentation of the particular methods or procedures that will be used at your clinical site to train all study staff on the new procedures.

- b.) The informed consent form was revised on April 21, 2004, adding, among other things, new information about an increase in the number of blood draws required for the study, and was approved by the IRB on May 11, 2004. The study sponsor required you to "reconsent" [] subjects who had signed the previous version of the form with the new version "when these subjects return for their next visit." However, your files indicate that the new consent form was sent to subjects by mail, and contain forms purportedly signed by [] of the subjects [] after the forms were sent to them by mail. Seeking consent by mail does not ensure circumstances in which the prospective subject has sufficient opportunity to consider whether or not to participate because it limits the subject's ability to ask questions about participation in the study. Furthermore, it can raise questions about whether the consent was in fact given by the subject at all.

2. **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 FDA or the IRB [21 CFR 812.100, 21 CFR 812.110(b)], 21 CFR 812.110(c)].**

You failed to adhere to the above-stated regulations. Examples of this failure include but are not limited to the following:

- a.) Protocol-required blood tests and procedures were not performed for at least of the subjects enrolled into the study. Specifically:
- i. Subject did not have Fractionated LDH (lactate dehydrogenase) evaluated at .
 - ii. Subject did not have LDH evaluated at discharge, and did not have Fractionated LDH evaluated at discharge, or .
 - iii. Subject did not have the NYHA functional class calculated at .
 - iv. Subject did not have Fractionated LDH evaluated at discharge, or , and did not have any blood tests performed at .

In your response, you stated that you have completed protocol deviation forms for each of the deviations listed above. This is not an adequate corrective action in that it does not address the records for all the subjects enrolled in the study. The FDA investigators reviewed only of the study subjects' records during their inspection, and found deviations in all records. Please provide us with evidence that you have reviewed the records of all study subjects, and have identified and reported all protocol deviations that may have occurred.

In addition, you provided us with a copy of a draft SOP titled "Collection and Documentation of Protocol-Required Data for Industry-Sponsored Clinical Trials." This procedure is not adequate in that it does not address any Clinical Investigator oversight or responsibility for accurate and complete implementation of the study protocols, but places all responsibility solely on the study coordinators. As a clinical investigator, you are responsible for ensuring proper conduct of the study and adherence to federal regulations. You may delegate study tasks to other qualified personnel, but you may not delegate your responsibility to ensure that all study tasks are correctly performed. Please submit a final version of your SOP, and please explain and provide documentation of the particular methods or procedures that will be used at your clinical site to train all study staff on the new procedures.

- b.) You failed to provide a consent form in the subject's native language for subject as required by the study sponsor and the IRB. Specifically, as noted above in citation 1a, the subject signed an English version of the consent form, even though the subject's records note that a translator is required because the subject speaks . Both the IRB and the study sponsor notified you on 8/7/06 and 8/11/06, respectively, that the subject must be reconsented with a consent form in but this was not performed.

In your response, you noted that "IRB was contacted on 14 February 2007, and my office is in active discussion with IRB to obtain instruction on what is necessary to remedy this

particular consent.” This response is not adequate in that you have not addressed the reason you did not respond to the sponsor’s and IRB’s requests in August 2006. Please explain and provide documentation of the particular methods or procedures that will be used at your clinical site to ensure that IRB and sponsor-required actions will be implemented for future studies. Please also notify us of what actions your IRB requires regarding this incident.

- c.) You failed to re-consent [] study subjects with a revised version of the consent form, as required by the study sponsor, as noted above in citation 1b. Specifically, there was no documentation in the study files that subjects [] and [] signed the revised consent form.
- d.) You failed to submit required study updates and requests for study renewal to the IRB in time to prevent lapses in study approval. Specifically, the IRB-approved renewal of the study expired on November 4, 2004, but was not approved for renewal until December 1, 2004. The following year, the IRB-approved renewal of the study expired on November 30, 2005, but was not approved for renewal until December 12, 2005. In both cases, your applications to renew the IRB approval were not submitted to the IRB “at least six weeks before the expiration date” as required by the IRB.
- e.) You failed to supervise use of the investigational device as required by 21 CFR 812.110(c) by allowing a physician who was not participating in the study to implant one of the study devices into a non-study subject on 10/22/03.

In your response, you stated that your site developed an SOP for Investigational Device Storage in 2004. Please explain and provide documentation of the particular methods or procedures that have been used at your clinical site to train all study staff on this procedure.

- f.) The Signature Authorization List, required by the study sponsor, was inaccurate and incomplete. This document is required in order to verify staff members who are authorized to perform study roles. Specifically:
 - i. Your initials and date were required for each name entered on the form. There were numerous versions of the document, some with your initials and no date, some dated only “4/25” or “7/18” with no year, and some initialed by other staff.
 - ii. Three different versions of the form, each dated by you as “1/18/07”, list [] as Research Coordinator with authorized study tasks listed. However, according to information you provided to the FDA investigators during the inspection, [] left the University of Washington in May 2006.
 - iii. Several of the forms are missing staff signatures and initials.

In your response, you stated that you are in the process of developing a new Investigator Agreements SOP, to include instructions on the Delegation of Authority Log. The draft version of this SOP that you provided is not adequate, in that you have not addressed the issues and problems with the Signature List/Delegation of Authority Log, that were observed during the inspection. Please provide a corrective action plan to address these issues, and please explain and provide documentation of the particular methods or procedures that will be used at your clinical site to train all study staff on the new procedure.

3. Failure to maintain accurate, complete, and current records relating to your participation in the investigation [21 CFR 812.140(a)].

You failed to adhere to the above-stated regulation. Examples of this failure include but are not limited to the following:

- a.) You failed to maintain accurate, complete, and current records of receipt, use, or disposition of the study device, as required by 21 CFR 812.140(a)(1). Specifically, for the Study Device Accountability Records:
- i. The “date received” was missing for of the study devices sent to your site.
 - ii. The “date returned to the sponsor if not used” was missing for of the study devices.
 - iii. The “Use By” dates (UBD) were inaccurate and inconsistent. Specifically:
 - The packing list for device number , shipped on 5/29/03, listed the UBD as 8/28/03, but the accountability log listed the UBD as 11/25/03.
 - The packing list for device number listed the UBD as 10/16/03, but the log listed the UBD as 1/28/04.
 - The packing list for device number listed the UBD as 10/9/03, but the log listed the UBD as 1/14/04.
 - For the three examples listed above, the device numbers on the packing list were changed by hand. There is no documentation of who made these changes, or when and why the changes were made. These changes resulted in the UBD inconsistencies.

In your response, you stated that you are in the process of developing a new device receipt and accountability log and SOP. Please submit a final version of your SOP and the log, and please explain and provide documentation of the particular methods or procedures that will be used at your clinical site to train all study staff on the new procedures.

- b.) Study subjects’ records were not accurate, complete, and current. Specifically:
- i. For subject , Protocol Deviation forms were not signed by you for occurrences on 10/18/04 and 3/26/04.
 - ii. For subjects and , Case Report Form Query forms were not completed or signed.
 - iii. For subject , you signed a 5-page “Enrollment Report” form on 1/8/06 that was primarily blank. This subject was implanted with the study device on 8/5/04.
 - iv. Subject signed the consent form after the study nurse signed the consent as “Investigator.” Specifically, the subject’s signature is dated 3/15/04, while the study nurse’s signature is dated 3/12/04.

In your response, you stated that a protocol-required data procedure will be developed. Please submit a final version of this procedure, and please explain and provide documentation of the particular methods or procedures that will be used at your clinical site to train all study staff on the new procedure.

In addition, the Investigator’s Agreement for the study, dated by the study sponsor as May 28, 2003, and which you signed but did not date, is blank under the section for “Other Participating Investigators.” However, according to your study records, numerous co-investigators participated in

the study, implanted the study device, and collected study data.

In your response, you stated that the Investigator Agreement has been amended and you will submit it to the sponsor. Please provide us with a copy of the amended form once it has been fully executed. You also stated that you are in the process of developing a new Investigator Agreements SOP, to include instructions on the Delegation of Authority Log. Please submit a final version of your SOP, and please explain and provide documentation of the particular methods or procedures that will be used at your clinical site to train all study staff on the new procedure.

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.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the 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 CFR. 812.119.

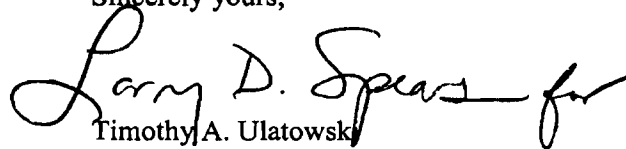
You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Please send your response to:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Bioresearch Monitoring, HFZ-311
9200 Corporate Blvd., Rockville, Maryland 20850
Attention: Ms. Doreen Kezer, Chief, Special Investigations Branch.

A copy of this letter has been sent to the FDA Seattle District Office, 22201 23rd Drive, SE, Bothell, WA 98021. Please send a copy of your response to that office.

If you have any questions, please contact Ms. Doreen Kezer at 240-276-0125 or at Doreen.Kezer@fda.hhs.gov.

Sincerely yours,



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