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JUL 23 2008

Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

WARNING LETTER

VIA FEDERAL EXPRESS

Alan L. Schneider, M.D.
1891 Effie Street
Los Angeles, CA 90026-1711

Dear Dr. Schneider:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your facility from February 22 through March 25, 2008, by investigators from the FDA Los Angeles District Office. The purpose of this inspection was to determine whether your activities and procedures related to your participation as the sponsor and as a clinical investigator in the clinical studies titled [redacted]

[redacted] and [redacted]

[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). It is, moreover, a significant risk device as defined in 21 CFR 812.3(m). This letter requests prompt corrective action to address the violations cited and discusses your April 30, 2008, 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 Form FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

Citations related to your role and responsibilities as the sponsor of [redacted] and [redacted].

Failure to include written procedures for monitoring the investigation and failure to ensure proper monitoring of the investigation. [21 CFR 812.25(e), 21 CFR 812.40, 21 CFR 812.43(d), and 21 CFR 812.46]

It is a sponsor's responsibility to ensure proper monitoring of the investigation, which includes selecting qualified monitors and securing compliance with the investigational plan and all applicable requirements and conditions of approval. 21 CFR 812.40, 21 CFR 812.43(d), and 21 CFR 812.46. The investigational plan shall include the sponsor's written procedures for monitoring the investigation. 21 CFR 812.25(e). Examples of your failures include, but are not limited to, the following:

[redacted]
The Investigational Plan, Section 3.9, Monitoring Procedure states, [redacted]

[redacted] During the FDA inspection you could not provide any documentation of the PI or of anyone else monitoring the investigation.

[redacted]
You failed to include a written procedure for monitoring in the investigational plan. In addition, during the FDA inspection, you could not provide any evidence of monitoring of the investigation.

In your response you acknowledge that there is a lack of study monitoring. You state that in future studies you will "employ an outside monitoring group." Your response is inadequate in that you did not provide a policy and procedure for evaluation of the outside monitoring group to ensure proper qualifications, as required by 21 CFR 812.43(d). In addition, your response lacked a plan to ensure your oversight. Although you may delegate the task of monitoring, as the sponsor you are ultimately responsible for ensuring proper monitoring of the investigation. 21 CFR 812.40 and 21 CFR 812.46. Please provide copies of policies and procedures that you are developing and implementing to ensure proper monitoring.

Failure to obtain FDA and IRB approval prior to implementing a change to the investigational plan. [21 CFR 812.35(a)(1)]

It is a sponsor's responsibility to obtain FDA approval and IRB approval (when appropriate) prior to implementing a change to the investigational plan, with certain exceptions. 21 CFR 812.35(a)(1). You failed to obtain approval from the FDA and the IRB for changes in the investigational plan prior to implementation. Examples of your failure include, but are not limited to, the following:

[redacted]
The investigational plan did not allow any [redacted]
[redacted] Subject [redacted] was taking [redacted] when enrolled

on [] and subject [] was taking [] when enrolled on [] Because this change to the investigational plan affected the validity of the data or information resulting from the completion of the approved protocol, it required FDA approval before implementation. 21 CFR 812.35(a). However, you never obtained FDA approval for this change and you only obtained IRB approval on [] after you had already implemented it.

In your response you state that you had mistakenly thought that, when you notified the IRB of changes to the investigational plan, the IRB would in turn notify FDA. You state that you now recognize the need to notify FDA of such changes. You also state that in future studies you will "utilize a consultant for the sole purpose of assuring compliance." Your response is inadequate in that it lacks a plan to ensure that both FDA and IRB approval are obtained when necessary prior to implementing a change to the investigational plan. Please provide copies of policies and procedures that you are developing and implementing to ensure that changes to the investigational plan are approved as necessary by the FDA and all reviewing IRBs prior to their initiation.

Failure to prepare and submit progress reports to FDA at regular intervals and at least yearly and failure to submit final reports to FDA. [21 CFR 812.150(b)(5) and 21 CFR 812.150(b)(7)]

The sponsor shall prepare and submit complete and accurate progress reports at regular intervals, and at least yearly, to all reviewing IRBs, and in the case of a significant risk device (as is your device), the sponsor shall also submit progress reports to the FDA. 21 CFR 812.150(b)(5). In the case of a significant risk device, the sponsor shall notify FDA within 30 working days of the completion or termination of the investigation and shall submit a final report to FDA and all reviewing IRBs and participating investigators within six months after termination or completion. 21 CFR 812.150(b)(7). Examples of your failures include, but are not limited to, the following:

[]
On [] the FDA conditionally approved [] You submitted progress reports to FDA on [] and [] However, you failed to submit progress reports to FDA, as required, in 2003, 2005, 2006, and 2007. Moreover, you reported the clinical trial to the IRB as closed on [] yet you neither notified FDA within 30 working days of the termination nor submitted a final report to FDA within six months after termination, as required.

[]
On [] the FDA conditionally approved [] You altogether failed to submit progress reports to the FDA at regular intervals, and at least yearly, as required.

In your response you state that you have submitted final reports to FDA for both studies and that you are now "fully aware of the requirements of filing annual progress reports." You further state that you will provide education to study staff involved in future studies to assure compliance. Your response is inadequate in that it lacks a corrective plan to ensure that, in future studies, progress reports will be submitted to the FDA at regular intervals,

and at least yearly. Please provide copies of policies, procedures, and additional plans that you are developing and implementing to ensure that progress reports will be submitted as required. In addition, please provide your written plan to ensure that the progress reports you submit are complete and accurate.

Failure to notify FDA and all reviewing IRBs of any request that an investigator return, repair, or otherwise dispose of any units of a device. [21 CFR 812.150(b)(6)]

Once a request is made that an investigator return, repair, or otherwise dispose of any units of the device, the sponsor shall notify FDA and all reviewing IRBs within 30 working days and state why the request was made. 21 CFR 812.150(b)(6). You failed to notify FDA and all reviewing IRBs of requests for device repairs.

[redacted]
Specifically, Subject [redacted] Days [redacted] and [redacted] Case Report Forms (CRFs) note, respectively, [redacted] and [redacted].
[redacted] During the FDA inspection you informed the FDA inspector that the device had an [redacted] malfunction during operation, which required that the [redacted] be replaced, and that after the replacement the [redacted] on subjects continued. You failed, however, to notify FDA and reviewing IRBs of this request for repair.

In your response you state that in future studies "any and all maintenance" will be reported to FDA and reviewing IRBs. Your response is inadequate in that it lacks a corrective plan to ensure notification of the FDA and all reviewing IRBs of all requests that an investigator return, repair, or otherwise dispose of any unit of a device. Please provide copies of policies and procedures that you are developing and implementing to ensure appropriate reporting.

Citations related to your role and responsibilities as the clinical investigator for the studies titled: [redacted]

[redacted]
[redacted] and [redacted]
[redacted]

Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50, failure to ensure that all essential elements of the informed consent were provided to each study subject, and failure to properly document informed consent. [21 CFR 812.100, 21 CFR 50.25, and 21 CFR 50.27]

It is an investigator's responsibility to ensure that informed consent is obtained in accordance with 21 CFR Part 50. 21 CFR 812.100. The informed consent shall be documented by the use of a written consent form approved by the reviewing IRB and signed and dated by the subject or subject's legally authorized representative at the time of the consent. 21 CFR 50.27. The consent document shall contain all of the basic essential

elements and any of the additional applicable elements identified in 21 CFR 50.25. In both studies you failed to obtain adequate informed consent, for example:

- A) Your consent document did not include all the essential elements set forth in 21 CFR 50.25.

[redacted]
On [redacted] FDA notified you that your informed consent document was inadequate and that, prior to enrolling any additional subjects, you must revise your consent document by, among other changes, adding a statement that [redacted] and by correcting and expanding upon your description of the risks of [redacted] and your procedures for managing these risks. These changes were required under 21 CFR 50.25. Yet, prior to making the necessary changes, you enrolled an additional eighteen subjects, specifically Subjects [redacted] and [redacted]

- B) You failed to obtain consent from subjects using the written consent form approved by your reviewing IRB, as required under 21 CFR 50.27. Examples of this failure include:

[redacted]
The consent document used for eighteen of [redacted] subjects enrolled was not the consent document approved by your reviewing IRB, the Western Institutional Review Board (WIRB). Specifically, Subjects [redacted] and [redacted] signed a consent document stamped as "Approved by [redacted]"

In your affidavit you state, "I, nor am I aware of my staff have not back-dated or signed any other records with earlier dates than the date of my signature." Consent documents had subject signature dates that preceded the document approval date. For example, Subject [redacted] signed an additional consent document on [redacted] that was stamped as "IRB approved [redacted]" Please clarify how the subjects' signatures occurred prior to the document approval date.

- C) In both studies, you failed to properly document informed consent for subjects. Specifically, on a majority of the informed consent forms, the subject's signature was dated by you rather than by the subject. In your affidavit you state that it was "common practice" for you to date the subject's signature as well as your own.

You state in your response that you have provided "[a]dequate training" on obtaining proper informed consent and that you will ensure that each subject or the subject's legally authorized representative dates the consent document at the time of consent. This response is inadequate in that it lacks a corrective action plan to ensure that informed consent is obtained as required. Please provide copies of policies and procedures that you are developing and implementing to ensure that informed consent is obtained in accordance with 21 CFR Part 50.

Failure to obtain proper informed consent from subjects prior to their participation in the studies. [21 CFR 50.20 and 21 CFR 812.100]

It is an investigator's responsibility to ensure that informed consent is obtained in accordance with 21 CFR Part 50. 21 CFR 812.100. Under 21 CFR 50.20, an investigator cannot involve a human subject in FDA-regulated research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative, with certain exceptions. 21 CFR 50.20. In both studies you failed to ensure that informed consent was obtained prior to involving subjects in research. Specifically, you failed to ensure that informed consent was obtained from subjects prior to performing clinical screening procedures solely for the purpose of determining their eligibility for research. Examples of this failure include, but are not limited to the following:

[redacted]
1) Subject [redacted] was performed on [redacted] but the subject did not sign the consent document until [redacted]

2) Subject [redacted] screening interview history and physical, [redacted] and [redacted] were performed on [redacted] but the subject did not sign the consent document until [redacted].

1) Subject [redacted] screening history and physical, [redacted] and [redacted] were performed on [redacted] but the subject did not sign the consent document until [redacted]

2) Subject [redacted] and [redacted] were performed on [redacted]. The screening history, physical, and randomization were performed on [redacted] with the investigational device was received between [redacted] and [redacted]. These study related tests and investigational [redacted] were all performed before the subject signed the consent document on [redacted]

In your response you state that "[a]dequate training regarding need for informed consent prior to study, screening, or metric testing was provided" and that you have reinstated Good Clinical Practice (GCP) training for all study personnel. Your response is inadequate in that it lacks a corrective plan to ensure adequate informed consent is obtained prior to any study related procedures. Please provide copies of policies and procedures that you are developing and implementing to ensure that written informed consent is obtained and documented prior to any study related procedures.

Failure to conduct the investigation according to the signed agreement, the investigational plan, and applicable FDA regulations. [21 CFR 812.100 and 21 CFR 812.110(b)]

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for

protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. 21 CFR 812.100 and 21 CFR 812.110(b). In both studies, you failed to conduct the investigation in accordance with the investigational plan. You enrolled subjects who did not meet the eligibility criteria set forth in the investigational plan. Examples of your failure include, but are not limited to, the following:

- [redacted]
- 1) The inclusion criteria states that at baseline the [redacted] is not to exceed [redacted] with a maximum of [redacted] on each of the following: [redacted] and [redacted]. Subject [redacted] baseline/screening [redacted] dated [redacted] noted a [redacted] of [redacted] on item [redacted].
 - 2) The inclusion criteria requires the subjects [redacted] to be [redacted] or less at baseline. For Subject [redacted], the [redacted] result is documented as [redacted] on the Screening Visit CRF. The actual [redacted] however, was [redacted] which makes this subject ineligible for inclusion in the study.

In your response you state you have reinstated Good Clinical Practice (GCP) training for all study personnel. Your response is inadequate in that it lacks sufficient detail and supporting documentation. Please provide a copy of the training and documentation that all study personnel have completed the training. Please also provide copies of policies and procedures that you are developing and implementing to ensure that the investigation is conducted properly.

Failure to maintain accurate, complete, and current case histories. [21 CFR 812.140(a)(3)]

An investigator is responsible for maintaining accurate, complete, and current records of each subject's case history and exposure to the device, which encompasses the case report forms (CRF) and supporting data. 21 CFR 812.140(a)(3). Case histories shall contain all relevant observations, including records concerning adverse device effects. 21 CFR 812.140(a)(3)(ii). In both studies, you failed to maintain accurate, complete, and current records of subject's case histories as required. Examples of these failures include, but are not limited to, the following:

- A) Case histories for each subject concerning all relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), are not all accurate and complete.
[redacted]
- 1) Subject [redacted] Days [redacted] and [redacted] CRFs note "Yes" in response to "Update Adverse Events?" but there are no adverse events identified in the case histories or in the CRFs.
- 2) Subject [redacted] Visit Day [redacted] and [redacted] Visit [redacted] CRFs note "Yes" in response to "Update Adverse Events?" but there are no adverse events identified in the case history or in the CRFs.

[redacted]
Subject [redacted] Days [redacted] and [redacted] CRFs noted "Yes" in response to "Update Adverse Events?" but there are no adverse events identified.

B) Subject's records (including CRFs and supporting data) were not all accurate and complete.

- [redacted]
- 1) Subject [redacted] Screening CRF dated [redacted] documented a [redacted] total [redacted] of [redacted] but the actual [redacted] was [redacted]. In addition, the [redacted] dated [redacted] documented a [redacted] of [redacted] but the values added up to [redacted].
 - 2) Subject [redacted] Screening CRF dated [redacted] documented [redacted] for [redacted] [redacted] and [redacted] but the underlying evaluation forms could not be located.

Because [redacted] and [redacted] were used to determine each subject's eligibility, miscalculations may have led to the inclusion of subjects who did not meet the eligibility criteria. In addition, because the primary outcome variable for this study is based on the change in [redacted] miscalculations directly affect the quality and integrity of the data.

- [redacted]
- 1) Subject [redacted] Day [redacted] CRF notes vital signs before and after [redacted] as [redacted] but there are no values documented.
 - 2) Subject [redacted] Day [redacted] and [redacted] CRFs lack documentation of the protocol-mandated blood pressure and heart rate before and after the procedure.

In your response you state that study personnel have been or will be instructed regarding proper record keeping and that "per nursing standard all errors will be appropriately lined out initialed and dated." Your response is inadequate in that it lacks sufficient detail and supporting documentation. Please provide a copy of the training and documentation that all study personnel have completed the training. Please also provide copies of policies and procedures that you are developing and implementing to ensure proper recordkeeping. 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 study sponsor 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 study sponsor. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. Send your response to: Attention: Doreen Kezer, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance,

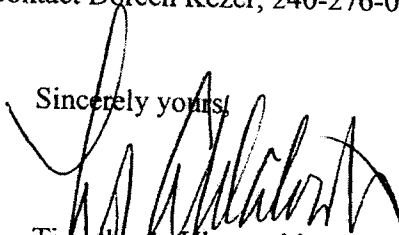
Page 9 Alan L. Schneider, M.D.

Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-310, Rockville,
Maryland 20850.

A copy of this letter has been sent to Los Angeles District Office. Please also send a copy
of your response to that office at 19701 Fairchild, Irvine, CA, 92612.

If you have any questions, please contact Doreen Kezer, 240-276-0125, or e-mail
doreen.kezer@fda.hhs.gov.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Timothy A. Ulatowski', written over the typed name below.

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