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Via Federal Express

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WARNING LETTER

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

Timothy A.M. Chuter, M.D.
Division of Vascular Surgery
University of California, San Francisco (UCSF)
505 Parnassus Avenue
San Francisco, California 94143

Dear Dr. Chuter:

This Warning Letter informs you of objectionable conditions found during a recent Food and Drug Administration (FDA) inspection at your clinical site. This letter also discusses your written response to the noted violations and requests that you promptly implement additional corrective actions.

Jeffrey W. Shrifter, D.P.M., Timothy C. Grome, M.D., and Lance M. DeSouza, investigators with FDA's San Francisco District Office, conducted the inspection of your clinical site from November 17 through December 4, 2003. The purpose of the inspection was to determine if your activities as both sponsor and investigator complied with applicable FDA regulations in the following studies:

[REDACTED] and [REDACTED]

The products used in these studies are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(h) (the Act).

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

Our review of the inspection report prepared by the San Francisco District Office revealed 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," to you for review, and they discussed the listed deviations and several other issues with you. The deviations noted on the FDA-483, your written response to those deviations, and our subsequent inspection report review are discussed below.

1. You failed to adhere to the investigational plans and obtain FDA approval prior to implementing changes in the plans. [21 CFR 812.100, 812.110(b), 812.150(a)(4), and 812.35(a)]

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

- There is no documentation to show that you filed a supplemental application and received FDA approval to include [REDACTED] subjects in the IDE [REDACTED] protocol.
- Subject listings for IDE [REDACTED] [REDACTED] show "elective" repair of [REDACTED] for seven subjects and "urgent" repair of [REDACTED] for seven subjects. However, these figures are discrepant with those in the annual report, dated October 1, 2003, which lists nine subjects in the [REDACTED] urgent repair group and six subjects in the [REDACTED] elective repair group.
- There is no documentation that you obtained prior permission from FDA and the Committee on Human Research (CHR) for your "compassionate" use of the investigational device(s); there apparently was some confusion on your part over requirements relating to "compassionate" and "emergency" uses. The CHR serves as the Institutional Review Board for UCSF and the San Francisco Veterans Affairs Medical Center.
- On August 29, 2003, the Office of the Vice Chancellor, Research, University of California, San Francisco (UCSF), notified the FDA of the April 3, 2003, suspension of your protocols (IDE numbers [REDACTED]). The suspension was due to the concerns of CHR regarding the use of investigational devices under circumstances that may not have been covered by the approved protocols.
 - On December 20, 2002, you notified CHR of the death of a patient following "compassionate use." This patient was not enrolled in any of the IDE studies and the patient's [REDACTED] did not meet the inclusion criteria. The CHR felt that you may not have clearly differentiated between research use and emergency use, and you were not following your institution's policies regarding emergency use.
 - The CHR also found informed consent deficiencies, failure to adhere to the protocol(s), and incomplete records.
- Subject [REDACTED] did not meet the inclusion criteria for either IDE [REDACTED] or [REDACTED] because his or her [REDACTED] was not in the [REDACTED]. The consent document signed by Subject [REDACTED]

appeared to be from IDE [REDACTED] but it is unclear from your records under which protocol, if any, the subject was enrolled. On August 20, 2000, you notified FDA of the unapproved use of the device on a compassionate basis; it is unclear if you reported this deviation from your protocol(s) to CHR.

- Subject [REDACTED] should not have been enrolled and treated in the IDE [REDACTED] study because enrollment criteria were not satisfied.
- The protocol stipulated that a copy of the Informed Consent would be included in the study records, but this was not done in all instances.

2. You failed to maintain accurate, complete, and current records relating to your participation in the study(ies). [21 CFR 812.140(a) and (b)]

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

- Numerous case report forms (CRFs) were not signed and/or dated by the physician or research coordinator; other forms had missing data; and subject identifiers were not included on some of the forms.
- Subject listings for all three studies do not show any procedures done at either [REDACTED] in [REDACTED] or at the [REDACTED] in [REDACTED], though other documents indicate that study testing and/or procedures have been conducted at these sites.
- It is unclear from your records if CHR considered your three studies individually and, if so, who was considered the principal investigator for each. Specifically, two studies, [REDACTED] and [REDACTED] were apparently covered under the same CHR approval number (# [REDACTED]). The number [REDACTED] identified you as principal investigator; the number [REDACTED] identified Linda M. Reilly, M.D., as the principal investigator.
- It is unclear from your records what role [REDACTED] M.D., played in the studies. For instance, in an annual report for IDE [REDACTED] Dr. [REDACTED] was identified as an investigator. During the inspection, however, you identified Dr. Nowygrod as a study coordinator. Dr. [REDACTED]'s curriculum vitae identifies him as a principal investigator. If Dr. [REDACTED] was, in fact, a principal investigator for any of your studies, FDA was unable

to find an investigator agreement or financial disclosure statement for him.

- [REDACTED] M.D., stated in a November 19, 2003, letter to you that he had performed over 40 surgeries at both [REDACTED] and [REDACTED] implanting the [REDACTED] device. However, Dr. [REDACTED] did not submit an Investigator Agreement or final disclosure statement until November 19, 2003, which was after he had already performed surgeries with the device.
- A discharge evaluation form demonstrates that Subject [REDACTED] (IDE [REDACTED]) had a falling hematocrit and was given two units of packed red blood cells, but this information was crossed out and "error" was written above it. However, the dictated hospital discharge summary states that this subject did have a falling hematocrit and was given two units of packed red blood cells.
- The October 1, 2003, annual progress report indicated that deviations from protocol for IDEs [REDACTED] and [REDACTED] had been reported individually as they occurred, though source documents did not identify any specific protocol deviations.
- In numerous cases, there was no documentation that various tests/assessments were performed per schedule. Because many CRFs were missing this information, it is unclear if required follow up was done or simply not documented.
- There was no log of serious adverse events for the studies.

In your response you claimed that data collection in terms of recordkeeping suffered from understaffing of the [REDACTED] research unit as well as inadequate systems of quality control. You outlined changes instituted to address these problems.

3. You failed to adequately document informed consent, including required information in the consent document, and you failed to maintain signed consent forms for all subjects. [21 CFR 50.27, 50.25(a)(5) and (a)(7), 812.100, and 812.140(a)(3)]

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

- In many cases the identity of the person who explained the research study to subjects (Section J) was missing.
- There were numerous instances in which the question regarding the subject's consent to have the procedures recorded was left unanswered.

- The consent form for Subject [REDACTED] (IDE [REDACTED]) lacked a witness signature. Subject [REDACTED] (IDE [REDACTED]) signed and dated the consent form on February 4, 2002; the witness had signed the form one day earlier. Subject [REDACTED] (IDE [REDACTED]) signed and dated the consent form November 16, 2002; the witness dated the form one day later.
- Signed consent forms for the following subjects could not be located: [REDACTED] (IDE [REDACTED]), [REDACTED] (IDE [REDACTED]), and [REDACTED] (IDE [REDACTED]). Subject [REDACTED], whose procedure was conducted on [REDACTED], re-signed a consent form on November 19, 2003.
- There was no contact identified on the consent forms to answer questions about a person's rights as a research subject.
- There was erroneous information in the protocol and consent form for the study [REDACTED] (versions dated January 26, 2002, and October 15, 2002). The protocols stipulate that only members of the study team will have access to subjects' records; there is no mention that FDA may inspect the records. Also, it is stated that the sponsoring company [REDACTED] may have access to the subjects' records, even though FDA records indicate that you, not [REDACTED] are the sponsor of this study.

In your written response, you claimed that some elements of informed consent were missing because they predated HIPAA regulations. You then provided revised consent forms; however, there is still no statement about who to contact with questions regarding a research subject's rights.

4. You failed to prepare and submit complete, accurate, and timely reports. [21 CFR 812.150(a)(1), 812.150(b)(1) and 812.150(b)(2)]

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

- There was no documentation that you, as a sponsor, notified FDA and all reviewing IRBs of the suspension of your protocols by CHR.
- Subject [REDACTED] (IDE [REDACTED]), whose procedure was conducted [REDACTED] died on [REDACTED] of intra-abdominal bleeding due to a guide wire injury. The injury was reported to CHR on December 20, 2002, within CHR's 10-day requirement. You sent a letter dated November 15, 2002, to FDA informing of this death, although this date was prior to the subject's death.

- Subject [REDACTED] (IDE [REDACTED]) died of intracranial bleeding on [REDACTED]. FDA was not notified until October 2, 1998, approximately 8 months after the death. It is unclear when CHR was notified because the death information CRF is undated.
- Subject [REDACTED] (IDE [REDACTED]) was diagnosed with [REDACTED] on [REDACTED] and died [REDACTED]. There was no documentation found reporting this death to CHR. CHR approval letters state that "all deaths, whether or not they are directly related to study procedures, must be reported."
- Subject [REDACTED] (IDE [REDACTED]) experienced an adverse event on June 28, 2000. The severity of the event, action taken, and outcome were not included on the CRF. Also, the subject's primary care physician notified you that the subject died on [REDACTED] but it is unclear whether you reported this information to the CHR or FDA.
- Subject [REDACTED] (IDE [REDACTED]) died of cardiac disease on [REDACTED]. An adverse event report, made to CHR on April 23, 2003, specified that FDA had been notified; however, there was no documentation that you did in fact notify FDA.

In your written response, you claimed that prior to October 2001 you were unaware that you were required to report deaths to the IRB, unless related to the device/procedure. You claimed you did report all adverse events caused either by the [REDACTED] or by a complication of [REDACTED]. Since October 2001, you said you had promptly reported all deaths to the IRB, regardless of cause. You also claimed that the date of the death notification to FDA of Subject [REDACTED] was a typographical error.

5. You failed to properly monitor the studies and to select qualified monitors. [21 CFR 812.40 and 812.43(d)]

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

- There were no standard operating procedures for monitoring or for selecting appropriate monitors for your studies.
- There was no evidence that the studies had been monitored.
- There was no documentation that the study coordinator(s) had received adequate training.

In your written response, you indicated that, since February 2003, periodic audits of your studies have been performed by [REDACTED]. You also provided their outline for device audits.

We have shared the inspectional findings with the Office of Device Evaluation. You should be aware that they may be requesting additional information from you about your studies.

We are aware that the UCSF Quality Improvement Unit, Human Subjects Protection Program, Office of Research, reviewed your protocols after the CHR at UCSF had suspended them in April 2003. Additional study deficiencies were identified in their report and will not be repeated here.

The above-described deviations are not intended to be an all-inclusive list of deficiencies found in your clinical studies. When conducting clinical investigations of products regulated by FDA, whether acting as a sponsor, an investigator, or both, it is your responsibility to adhere to each requirement of the Act and all applicable federal regulations.

Within 15 working days of receiving this letter, please provide written documentation of the additional, specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. You should address the following issues in your response:

- If you had prior approval from FDA to include [REDACTED] on protocol IDE [REDACTED] please forward this documentation. If not, explain why you felt the inclusion of [REDACTED] was appropriate.
- Identify the clinical sites for each study. Your subject listings only identify UCSF and VAH. If procedures were done at [REDACTED] and [REDACTED], please provide copies of IRB approval. Also identify the principal investigator and co-investigator for each of the studies at each of the sites.
- Clarify how many subjects were enrolled in each of your IDEs and at what site. Also, account for any patients treated under emergency or compassionate use, and confirm whether or not they were included in your IDEs. If not, how were these patients accounted for and were they followed up per protocol?
- Reconcile the difference in the numbers of urgent [REDACTED] and elective [REDACTED] contained in your subject listings as compared to the information presented in your October 2003 annual report.
- Explain how you differentiate between "compassionate" and "emergency" use. If you received prior approval from FDA for compassionate use, provide documentation.

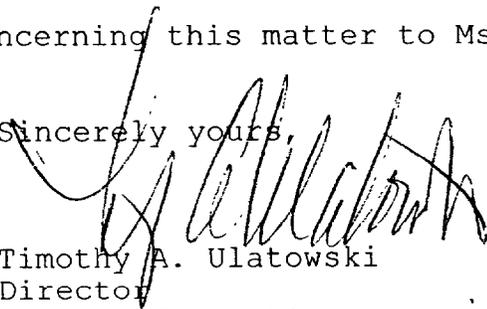
- Verify that all serious adverse events and deaths have been reported, including those for subjects in your IDE studies as well as those treated under emergency or compassionate situations.
- You stated during the inspection that one Canadian patient on the IDE [REDACTED] protocol had not been reported. Please explain.
- Clarify the roles and responsibilities of Drs. [REDACTED] and [REDACTED] for each study.
- Explain what you considered to be a protocol deviation in your studies and how/to whom you reported the deviations. Please provide documentation that the deviations were reported.

Any submitted corrective action plan should include projected completion dates for each action to be accomplished. Failure to respond to this letter or take appropriate corrective action could result in the FDA taking regulatory action against you without further notice. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 CFR 812.119.

Send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch I (HFZ-311), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Barbara Crowl. A copy of this letter has been sent to FDA's San Francisco District Office, 1431 Harbor Bay Parkway, Alameda, California 94502. We request that a copy of your response also be sent to that office.

Please direct all questions concerning this matter to Ms. Crowl at (301) 594-4720, ext. 168.

Sincerely yours,



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