



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

JUN 18 2003

WARNING LETTER

Via Federal Express

William Stevenson, M.D.
Brigham and Women's Hospital
75 Francis Street, Suite TR03
Boston, Massachusetts 02115

Dear Dr. Stevenson:

The purpose of this letter is to inform you of the objectionable conditions found during a Food and Drug Administration (FDA) inspection at your clinical site and to request a reply. Dr. Kristina Joyce, Ms. Karen McNabb-Noon, and Mr. Mutahar Shamsi of the New England District Office conducted the inspection between January 27 and February 3, 2003.

The purpose of the inspection was to determine if your activities as a clinical investigator in the study entitled [REDACTED] sponsored by [REDACTED] complied with applicable FDA regulations. [REDACTED] and [REDACTED] is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 321(h)].

The inspection was conducted under an FDA compliance program designed to ensure that data and information contained in requests for Investigational Device Exemption (IDE), Premarket Approval Application (PMA), and Premarket Notification (510(k)) submissions are scientifically valid and accurate. Another objective of the program was to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations. The aforementioned study was conducted under IDE [REDACTED] and supported PMA [REDACTED].

Our review of the establishment inspection report prepared by the New England District Office reveals violations of the requirements of Title 21, Code of Federal Regulations (CFR), Part 50 – Protection of Human Subjects and Part 812 – Investigational Device Exemptions. At the conclusion of the inspection, Dr. Joyce listed her findings on a Form FDA-483 “Inspectional Observations,” and discussed these findings with you. [REDACTED] and Mr. Shamsi of FDA were also present at this meeting.

In a February 24, 2003, facsimile to Dr. Joyce, you acknowledged the observations noted on the FDA-483 and described plans to take corrective actions to address the protocol deviations and device accountability issues. However, your response to the FDA-483 does not contain an adequate corrective action plan with specific times for completion and supporting documentation for corrections already made. FDA considers your violations to be particularly concerning as we observed similar device accountability deficiencies, as well as other deviations, during an inspection conducted from April 21-28, 1998. In a June 1, 1998, letter to FDA, you promised to correct those deficiencies and comply with FDA regulations. Despite those assurances, FDA review of the inspection report finds persistent deficiencies in device accountability as well as other violations, including violations of human subject protection requirements. These violations are summarized below.

1. Failure to obtain informed consent [21 CFR 50 and 21 CFR 812.100]

You failed to obtain informed consent from two subjects in the study prior to treating them with the investigational device, as required by 21 CFR section 812.100 and 21 CFR part 50. Your records indicate that the only consent forms for these two subjects were completed after the subjects' treatment. In addition, one of these subjects signed an outdated consent form. As a clinical investigator, you must seek consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether to participate and that minimize the possibility of coercion or undue influence [21 CFR 50.20].

██████████ and ██████████ told the FDA investigators that these two subjects verbally consented to the study prior to beginning treatment. However, you do not have any records demonstrating that the requirements of 21 CFR 50.27(b)(2) were met, including requirements that the Institutional Review Board (IRB) approved a short form written consent document stating that the elements of informed consent have been presented orally to the subject, that the form was given to these subjects at the time of consent, or that both the subject and a witness signed the form. There is also no record that the IRB approved a written summary to be presented orally to the subject, as required by 21 CFR 50.27(b)(2).

2. Failure to conduct the study in accordance with the investigational plan [21 CFR 812.100 and 21 CFR 812.110(b)]

As a clinical investigator, you are responsible for ensuring that the investigation is conducted according to the investigational plan, as required by 21 CFR 812.100 and 21 CFR 812.110(b). Your records reveal numerous instances where study procedures necessary to evaluate the safety and effectiveness of the device, including laboratory testing, were either not performed at all or were not performed within the timeframes for follow-up examinations described by the study protocol. Eleven subjects did not have complete laboratory testing or assessments during the baseline period. Five subjects were not assessed by telephone at one week after procedure. Two subjects were not seen within

the scheduled follow-up period at one month. Two subjects were not followed at three months. Five subjects were not seen within the scheduled follow-up period at three months. One subject was not followed at six months. Six subjects were not seen within the scheduled follow-up period at six months.

You also failed to fulfill your device control responsibilities under the investigational plan. You did not ensure that the investigational devices were maintained under controlled access storage. The devices were received by hospital staff not part of the clinical investigation. These persons were allowed to handle the devices before the devices were inventoried by study staff. Hospital personnel who were not clinical study staff, including a laboratory technician, had keys to the storage area where the devices were kept. In addition, devices received from the sponsor were not completely accounted for or logged on the Device Shipment, Receipt, and Inventory Form in a timely manner, as required by the investigational plan.

3. Failure to prepare and maintain accurate, complete, and current records relating to the receipt, use, and disposition of the investigational devices [21 CFR 812.140(a)(2)]

In addition to the failure to use the device control documents required by the investigational plan, you failed to prepare and maintain accurate, complete, and current device accountability records, as required by 21 CFR 812.140(a)(2). Specifically, records of investigational devices returned to the sponsor contained inaccurate information regarding lot numbers and quantities.

The above deviations are not intended to be an all-inclusive list of deviations that may exist in the clinical study. We recommend that you review your records for other deficiencies and correct them accordingly. It is your responsibility to comply with federal regulations. Delegating work to research staff does not relieve you of the responsibility to supervise the clinical investigation. You are responsible for the accuracy and completeness of the study records and for any discrepancies found in the records.

Please respond to this letter within 15 working days, including documentation supporting the specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. In your response, provide a complete list of your open investigational studies and postmarket studies, including the name of the study sponsor, the date of IRB approval, and application number. As already noted, your February 24, 2003, response to the FDA-483 is not sufficient, as it does not provide adequate documentation of your proposed corrective actions for some of the violations noted above, and does not address the human subject protection issues raised in this letter.

Failure to respond to this letter and take appropriate corrective action could result in enforcement action without further notice. In addition, FDA could initiate disqualification proceedings in accordance with 21 CFR 812.119.

A copy of this letter has been sent to the Food and Drug Administration, New England District Office, One Montvale Avenue, 4th Floor, Stoneham, Massachusetts 02180. We request that a copy of your response be sent to the New England District Office and to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 2098 Gaither Road, Rockville, Maryland 20850, Attention: Kevin M. Hopson, Consumer Safety Officer. If you have any questions or require additional time to respond, please call Mr. Hopson at (301) 594-4720, extension 128.

Sincerely yours,



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

cc: PURGED COPIES

Elizabeth Hohmann, M.D.
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