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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Blvd.
Rockville MD 20850



WARNING LETTER

VIA FEDERAL EXPRESS

MAY 23 2007

Gustav R. Eles, DO
Allegheny General Hospital
320 East North Ave.
Pittsburgh, PA 15212

Dear Dr. Eles:

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 February 22 through March 7, 2007, by an investigator from the FDA Philadelphia District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the study titled [REDACTED]

[REDACTED], under [REDACTED], sponsored by [REDACTED], complied with applicable federal regulations. The [REDACTED] used for this study 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 March 8, 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. At the close of the inspection, the FDA investigator 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:

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)].

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

- a.) All [redacted] of the subjects enrolled in the study had information in their study records that they may have failed to meet eligibility criteria. Specifically:
 - i. Subject [redacted] had a [redacted] performed on 8/26/05, which indicated [redacted]. The protocol specifically excluded subjects with [redacted]. In addition, this [redacted] was performed over 4 months prior to study enrollment, while the protocol required this procedure to be performed within 60 days of the study procedure that was performed on 1/12/06.
 - ii. Subject [redacted] had a [redacted] performed on 11/9/05, which was more than 60 days prior to the study procedure that was performed on 1/26/06.
 - iii. Subject [redacted] had a [redacted] performed on 1/10/06, which indicated [redacted]. The study protocol required subjects to have [redacted] for inclusion in the study.
 - iv. Subject [redacted] had elevated pre-study [redacted] tests, which the laboratory report noted as [redacted] on 1/30/06, the same date as the study procedure. In addition, the pre-study [redacted] and showed [redacted], which the report noted as indicative of [redacted] within 30 days of study enrollment was listed as an exclusion criterion in the study protocol.
 - v. Subject [redacted] had a pre-procedure blood pressure of 204/87 on 3/8/06, the same date as the study procedure. The study protocol excluded subjects with severe hypertension as defined by blood pressure greater than 180 systolic and/or 110 diastolic.

There was no documentation in any of these study subjects' records to indicate that you evaluated their eligibility for enrollment in the study.

- b.) The protocol required that all subjects receive a dosage of [redacted] daily - at least 72 hours prior to the procedure, or a [redacted] - at least 4 hours prior to procedure, and a dosage of [redacted] daily - at least 72 hours prior to the procedure, or a [redacted] - at least 4 hours prior to the procedure. The protocol further states "[redacted] must be given to the subject using the recommended doses." [redacted] of the [redacted] subjects enrolled in the study had no documentation that these pre-procedure medications were properly administered. Specifically:
 - i. Subject [redacted] received only [redacted] 30 minutes before the procedure.
 - ii. Subject [redacted] received only [redacted] 90 minutes before the procedure.
 - iii. Subject [redacted] received only [redacted] 30 minutes before the procedure.
 - iv. Subject [redacted] received only [redacted] the morning of the procedure.

- v. Subjects [REDACTED] received only [REDACTED] 90 minutes before the procedure.
- c.) The protocol required that [REDACTED] testing be performed at specified times following the study procedure. Three of the [REDACTED] enrolled subjects missed one or more of these tests. Specifically:
 - i. Subjects [REDACTED] - the [REDACTED] tests were not performed.
 - ii. Subject [REDACTED] - the [REDACTED] and the [REDACTED] tests were not performed.
- d.) Follow-up study visits were performed late or were missed for [REDACTED] of the [REDACTED] enrolled subjects. Specifically:
 - i. Subjects [REDACTED] had their 6-month follow-up visits over one month outside the protocol-specified time-frame.
 - ii. Subject [REDACTED] had no 6-month follow-up visit.

In your response, you stated that these visits were performed late due to your extended absence because of [REDACTED] and because there was no approved sub-investigator to whom you could delegate the responsibility. You provided a corrective action plan that included hiring a Physician Assistant to assist you with future subject follow-up visits, and having the study coordinator notify the study sponsor when there is a lack of an investigator, to obtain approval to use a non-study physician to perform the visits. This is not an acceptable corrective action. At the time the [REDACTED] subjects noted above were due for their 6-month visits, there were three other physicians listed on the Signature Log as "sub-investigators", any of whom could have performed the visits. In addition, your study records indicate that your study coordinator, who is a Registered Nurse, performed the follow-up visits with no record of any oversight by you or another physician.

- e.) The study protocol stated [REDACTED] the [REDACTED] or placement of the [REDACTED] be delegated to an interventionist that has [REDACTED]. You failed to supervise use of the investigational device by allowing a physician who was not participating in the study and was not approved by the sponsor to implant one of the study devices into Subject [REDACTED].

As a Clinical Investigator, you are required to follow the study protocol exactly as it is written, unless the protocol is amended by the study sponsor or the study sponsor gives prior written approval for a protocol deviation. As a Clinical Investigator, you are also responsible for ensuring that all study staff are adequately trained and qualified to perform study tasks delegated to them. 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. Additionally, you and your sub-investigators also signed an Investigator Agreement in which you agreed to conduct the study according to the protocol and all applicable regulations.

Please provide us with documentation of a corrective action plan, such as a written procedure for ensuring study protocol compliance, written verification of training of study staff on study procedures and requirements, and/or internal study reviews or audits to ensure that such protocol violations have not occurred with other subjects and/or other studies, and that

corrective actions have been implemented to prevent recurrence of the problems for future studies.

Please also provide documentation that all protocol deviations that occurred during this study have been reported to your IRB and the study sponsor.

In addition, you failed to supervise the study so as to ensure that your general responsibilities as a clinical investigator were fulfilled. Your general responsibilities as a clinical investigator include 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. For example, in addition to the protocol deviations noted above, the study records indicate that your study coordinator, who is a Registered Nurse, performed nearly all of the 30-day, 6-month, and 12-month follow-up visits for the subjects in this study. There was no documentation to indicate that you reviewed or evaluated any of the information collected by the nurse during these visits. During the FDA inspection, your study nurse explained to the FDA investigator that she performed the follow-up visits because you do not maintain an office at Allegheny General Hospital. Please provide us with a plan for future studies that will ensure you can adequately supervise study personnel and procedures that are performed at this site.

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.

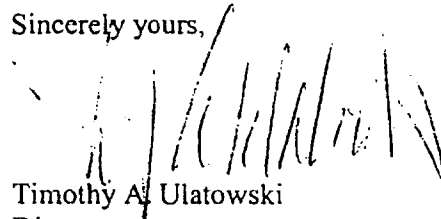
You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action 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 Philadelphia District Office, 900 US Customhouse, 2nd and Chestnut Streets, Philadelphia, PA 19106. 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,

A handwritten signature in black ink, appearing to read "Timothy A. Ulatowski". The signature is written in a cursive style with some loops and flourishes.

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

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IRB/Purged Copy to:

Matthew R. Quigley, MD/IRB Chair
Allegheny General Hospital IRB
320 East North Avenue
Pittsburgh, PA 15212

Sponsor/Purged Copy to:

