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WARNING LETTER

VIA FEDERAL EXPRESS

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

Peter A. Engelhard, D.O.
President
Apex International Health
446 Arthur Godfrey Rd.
Miami Beach, FL 22140

JUN 14 2004

Dear Dr. Engelhard:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site. This letter also discusses your written response to the noted deviations and requests that you implement prompt corrective actions. Ms. Luz Collado, an investigator from FDA's Florida District Office, conducted the inspection from February 5 through February 10, 2004. The purpose of the inspection was to determine if your activities both as a sponsor and investigator of the study entitled [REDACTED] complied with applicable FDA regulations. Data from this study was submitted to the FDA in support of a marketing application. The investigational article used in your study is a device as defined in Section 201 (h) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321 (h)].

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

Our review of the inspection report prepared by the district office revealed serious violations of Title 21 Code of Federal Regulations (21 CFR), Part 812-Investigational Device Exemptions, Part 50-Protection of Human Subjects, and Section 520(g) of the Act [21 U.S.C. 360j(g)]. At the close of the inspection, Ms. Collado presented a Form FDA 483 "Inspectional Observations" to you for review and discussed the listed deviations and several other issues with you. The deviations noted on the Form FDA 483, your written response to those deviations, and our subsequent inspection report review are discussed below:

Failure to adhere to the general and specific responsibilities of a sponsor [21 CFR 812.40 and 812.43(d)].

Sponsors have numerous regulatory responsibilities, including the responsibilities for ensuring proper monitoring of the investigation and for selecting monitors qualified by training and experience to monitor the study in accordance with the protocol and FDA regulations. [21 CFR 812.40, 812.43(d)]. You failed to fulfill these responsibilities, as

our inspection found no evidence that you selected qualified monitors, or that the study had in fact been monitored at all.

Failure to adhere to the general and specific responsibilities of a clinical investigator [21 CFR 812.100 and 812.110(b)].

You failed to conduct the study according to the investigational plan, as required by 21 CFR 812.100 and 812.110(b). For example:

- You failed to conduct the study according to the investigational plan by not following up on all subjects at the times specified in the protocol. The protocol required follow-up visits at 6-months after treatment. Your records indicated that examinations for several subjects were late. For example, Subjects [REDACTED], [REDACTED], and [REDACTED] had their follow up visits at 8 months, 9 months, and 1 year respectively. The records also indicated that you did not contact subjects about their missing visits in a timely manner. For example, you contacted subjects [REDACTED] and [REDACTED] in January 2004, 3 months after their 6-months visit was due.

We agree that study subjects may fail to complete required follow-up visits, particularly those subjects who reside outside the geographic area in which you are conducting the study and have to travel considerable distance. However, there was no documentation to demonstrate that you or your staff attempted to contact subjects who missed their scheduled visits required by the protocol in a timely manner. There was also no system in place to alert staff to follow up on those who missed their scheduled visits. Missing follow up visits may unnecessarily expose subjects to the risks associated with an investigational device.

We note that you have implemented a procedure to follow up on subjects who fail to make required visits or to have those visits in established timeframes, which also includes a system for documenting your efforts to contact them. This corrective action appears adequate. However, in the future, in selecting subjects for an investigation, you should consider subjects for whom there is a reasonable expectation that they will be available for each examination scheduled, including follow-up visits.

- The protocol also required laboratory blood tests at the 6-months visit. However, the records for some subjects such as [REDACTED] indicated that you conducted their 6-months follow up visit by telephone, and they did not have the required laboratory tests. Others (subjects [REDACTED], and [REDACTED]) did not have their required blood tests during their 6-months office visit.

Although some subjects interviewed by telephone had their required blood tests completed by their primary care physician, there were no copies of their laboratory results in their records to indicate that these tests had been performed or to indicate the results. You also failed to document in their records those subjects that refused to have blood drawn at their 6-month office visit.

We note that you are reviewing all subjects' charts. For those subjects who had required laboratory tests through their primary care physician, you are requesting access to their medical records to obtain any missing laboratory results so that you can complete their files. This appears to be adequate to correct the incomplete files. However, you should identify the steps you will take to assure that in the future, all files contain all required examination and/or laboratory reports.

- The protocol indicated that subjects should receive 1 to 6 ml of [REDACTED] per injection. You failed to follow the investigational plan by injecting several subjects with more than the maximum allowable amount. For example, subjects [REDACTED] received 9 ml per injection and patient [REDACTED] received 9, 10, and 11 ml.

We acknowledge that you submitted information to the FDA and IRB in your Interim Study and Progress Reports about the protocol deviations relating to injecting more than the maximum allowable amount of [REDACTED] described in the protocol. Although you did not receive specific directions to submit a supplemental application or revised protocol for review and approval, investigators are required to obtain sponsor approval prior to changing or deviating from an investigational plan, under 21 CFR 812.150(a)(4), and sponsors are in turn responsible for obtaining approval for a supplemental application from FDA and/or the IRB prior to implementing a change to the investigational plan, under 21 CFR 812.35(a). In this study, you served as both the sponsor and the investigator. We recognize that you have subsequently submitted a revised protocol to the IRB. In the future, you should take steps to ensure that protocol changes are appropriately reviewed before they are implemented.

You also failed to fulfill your obligation as an investigator to ensure compliance with all applicable FDA regulations, including part 50, governing informed consent. [21 CFR 812.100, 812.110(b).] For example:

- You documented consent from several subjects in your study using informed consent forms unapproved by your IRB, in violation of the requirements of 21 CFR 50.27(a). These included subjects [REDACTED] and [REDACTED].
- In addition, these unapproved informed consent forms did not contain all of the basic elements of informed consent as required by 21 CFR 50.25. Specifically, these forms did not indicate that blood testing would be required under the protocol. Under 21 CFR 50.25(a)(1), the subject must be provided with a description of the procedures to be followed in the study, and under 21 CFR 50.25(a)(2), the subject must be informed of any reasonably foreseeable discomforts which the subject may experience.

Your response indicates that you are re-consenting these subjects with the current IRB-approved and stamped version of the consent form. Please provide FDA with information on how you intend to prevent this problem with future studies.

Failure to maintain complete, accurate and current records [21 CFR 812.140(a)(2), (a)(3) and (b)(2)].

Investigators must maintain complete, accurate and current records related to the receipt, use, or disposition of a device, and sponsors must maintain complete, accurate, and current records of the disposition of devices. [21 CFR 812. 140(a)(2), (b)(2). You failed to fulfill these requirements, for example, because

The device inventory records did not include the batch number or other code mark of each device received and used in the study, as required by 812.140(a)(2)(i) Additionally, there was a discrepancy between the actual and documented inventory on hand. Whereas the actual inventory consisted of [REDACTED] vials of [REDACTED], the documented inventory indicated [REDACTED] vials. Consequently, you do not have accurate records of the disposition of all the investigational devices, as required by 812.140(a)(2)(iii) and 812.140(b)(2).

We note that you are attempting to reconcile inventory records with patient records to account for the missing vials used in study subjects and to institute better methods for accounting for investigational devices received.

Investigators are also required to maintain complete, current, and accurate records of each subject's case history and exposure to the device. 812.140(a)(3).

You failed to maintain complete records of several subjects' exposure to the device by failing to include the injection times, as required by 812.140(a)(3)(iii). Subjects [REDACTED], and [REDACTED] are examples.

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

Please advise this office, in writing, within fifteen (15) working days after receiving this letter of the additional, specific steps you plan to take to correct these violations and prevent the recurrence of similar violations. Failure to respond may result in the FDA taking regulatory action without further notice to you. FDA may also initiate proceedings to disqualify you from further activity as a clinical investigator, in accordance with 21 CFR 812.119. Please direct your response to the following address: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance,

Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Viola Sellman.

We are also sending a copy of this letter to FDA's Florida District Office, 555 Winderley Place, Suite 200, Maitland, FL 32751, and request that you also send a copy of your response to that office. If you have any questions, please contact Ms. Sellman by phone at (301) 594-4723, ext. 127, or by email at vx@cdhr.fda.gov.

Sincerely yours,



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

cc:

Essex Institutional Review Board, Inc.

~~446 Arthur Godfrey Road~~ 181 Main Street
~~Miami, Florida 33140~~ Lebanon, NJ 08833