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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Blvd.
Rockville MD 20850

WARNING LETTER

NOV 13 2008

VIA FEDERAL EXPRESS

Christopher D. Saudek, MD
601 N. Caroline Street
Outpatient Center, Room 2006
Baltimore, MD 21287

Dear Dr. Saudek:

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 July 10 through July 28, 2008, by an investigator from the FDA Baltimore District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation as a sponsor of and as a clinical investigator in the study titled (b)(4) (b)(4) under (b)(4) and (b)(4), complied with applicable federal regulations. The (b)(4) (b)(4) 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 requests prompt corrective action to address the violations cited and discusses your written response dated September 24, 2008, 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 several serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 50 – Protection of Human Subjects, Part 812 - Investigational Device Exemptions, and Section 520(g) (21 U.S.C. 360j(g)) of the Act. 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.

1. **Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50 [21 CFR 812.100, 21 CFR 312.40, 21 CFR 50.20, 21 CFR 50.25, and 21 CFR 50.27].**

   An investigator is responsible for obtaining and documenting informed consent from a subject using an Institutional Review Board (IRB)-approved consent form prior to involving the subject in the clinical investigation. You failed to ensure that informed consent was obtained from subjects and documented in accordance with federal regulations. Examples of these failures include, but are not limited to, the following:

   a.) The study protocol was amended on September 29, 2004, to add procedures for evaluation of under-response to insulin in the subjects. These new procedures included (b)(4) for subjects up to (b)(4) times in a (b)(4) period, and (b)(4) (b)(4) for subjects with apparent unresponsiveness to (b)(4). The October 10, 2003 consent form does not mention or describe the (b)(4) or (b)(4) (b)(4) or their associated risks. The IRB approved a revised consent form on October 14, 2004, describing the (b)(4) and (b)(4)

      i. Subject (b)(6) signed the October 10, 2003 version of the consent form on October 24, 2003, which did not list and describe the (b)(4). The subject had a (b)(4) in May 2005.
      ii. Subject (b)(6) signed the October 10, 2003 version of the consent form on October 20, 2003, which did not list and describe the (b)(4). The subject had a (b)(4) in February 2005.
      iii. Subject (b)(6) signed the October 10, 2003 version of the consent form on October 24, 2003 which did not list and describe the (b)(4). The subject had a (b)(4) in April 2005.

   b.) The IRB-approved consent forms used for the study lack a complete description of reasonably foreseeable risks and discomforts to the subjects.

      For example, the consent forms do not include the risk of (b)(4) which may require a (b)(4) to correct, as described in the study protocol. Subjects (b)(6) and (b)(6) required (b)(4), (b)(6) in (b)(6) and (b)(6), respectively, to replace the (b)(4)

   c.) None of the versions of the IRB-approved consent forms used for the study informed subjects that the (b)(4) used in the (b)(4) (under (b)(4)), is investigational.

In your response, you stated that study subjects will be re-consented with a revised consent form after it is approved by the IRB. Your response is inadequate as it lacks a corrective and preventive action plan to ensure that adequate consent forms are provided to study subjects prior to any study related procedures in the future. Please provide copies of policies/procedures that you have developed and implemented to ensure that adequate consent forms are provided to study subjects prior to any study related procedures. In addition, please maintain documentation that ensures that all applicable study personnel have reviewed these policies/procedures.

2. **Failure to submit reports to FDA and all reviewing IRBs of the results of the evaluations of unanticipated adverse device effects (UADEs) within 10 working days after receiving notice of the UADE. Failure to provide complete, accurate, and current information about an investigation in response to a request from FDA [21 CFR 812.150(b)(1) and 21 CFR 812.150(b)(10)].**

   As a sponsor, you failed to adhere to the above-stated regulations. Examples of your failures include, but are not limited to, the following:

   a.) At least ten unanticipated adverse device effects (UADEs) have occurred during the study. Events were reported to FDA via MedWatch Reports, but not all were reported within the required 10 working day period. Some events were not reported to the IRB within the required 10 working day period. The following table summarizes these failures:

UADE	Subject	Date Site Aware of Event	Date of MedWatch Report	Date Reported to IRB
(b)(4)	(b)(6)		5/16/08	5/15/08
			1/9/07	1/9/07
			1/9/07	1/9/07
			8/18/06	8/18/06
			3/8/05	2/15/05

   b.) The IDE approval letter to you from FDA, dated July 30, 2003, notified you of your responsibilities as a sponsor of a significant risk device investigation. Enclosed with the IDE approval letter was an attachment, which listed your regulatory requirements, entitled "Sponsor's Responsibilities for a Significant Risk Device Investigation," notifying you of your responsibility to prepare and submit, among other information, "complete, accurate, and timely reports" of "unanticipated adverse device effects (with evaluation) to FDA, all IRBs, and investigators within 10 working days after notification by the investigator." You reported incomplete UADEs to FDA via MedWatch reports that failed to either identify the name of the investigational device or reference the IDE number. Please submit all future correspondence concerning the IDE study as an IDE supplement referencing the IDE number provided, rather than as a MedWatch report, to the IDE Document Mail Center at the Center for Devices and Radiological Health (CDRH), at the mailing address provided in the IDE approval letter and listed at 21 CFR 812.19(a)(1).

In your response, you stated that you will follow your SOP entitled "(b)(4) (b)(4) for reporting UADEs to

FDA. Your response is inadequate as it lacks a corrective and preventive plan to ensure that UADE reports are complete. As stated above, also please ensure that UADE reports are submitted to the IDE Document Mail Center at CDRH as IDE supplements rather than as MedWatch reports, which this SOP appears to allow for UADE reporting purposes. Please maintain documentation that ensures that all applicable study personnel have reviewed these policies/procedures.

3. **Failure to ensure an investigation is conducted in accordance with the investigational plan, applicable FDA regulations, and any conditions of approval imposed by FDA or the IRB [21 CFR 812.100 and 21 CFR 812.110(b)].**

As a sponsor-investigator, you are responsible for ensuring that an investigation is conducted according to the investigational plan, which includes the protocol, and to any conditions of approval imposed by an IRB or FDA. Examples of your failure to adhere to these regulations include, but are not limited to, the following:

The study protocol states that a Data Safety Monitoring Board (DSMB) will review data summaries prepared by you "every (b)(4) or more often if a study-related serious adverse event occurs." Your study records indicate that you provided study updates to the DSMB at intervals greater than six months:

i. The initial update was presented in person by you to the DSMB on (b)(4), and the second update was provided by mail (b)(4) later, on (b)(4)
ii. The third update was provided by mail (b)(4) later on (b)(4)
iii. The fourth update was provided by mail fourteen months later on (b)(4). This update included the statement that "since the last report in (b)(4), there have been 10 adverse events, 7 related to (b)(4)."
iv. There is no record of any update provided to the DSMB after (b)(4)

4. **Failure to submit an IDE supplemental application to FDA for approval of changes to an investigational plan. Failure to obtain FDA approval of the supplemental application before beginning part of an investigation [21 CFR 812.35(a) and 21 CFR 812.42].**

A sponsor must obtain FDA approval of a supplemental application for changes in the investigational plan that affect the rights, safety, or welfare of the subjects involved in the investigation, prior to implementing the change. You failed to adhere to the above-stated regulations. Specifically:

Your study records indicate that you amended the study protocol on September 29, 2004, to add procedures for evaluation of under-response to (b)(4) in the study subjects. These new procedures included (b)(4) for subjects up to (b)(4) in a (b)(4) period, and (b)(4) for subjects with apparent unresponsiveness to (b)(4). Both of these procedures increased the risks to the subjects enrolled in the study. The IRB approved the revised protocol and consent form on October 14, 2004, and you subsequently performed study–related (b)(4) and/or (b)(4) for evaluation of under-response to (b)(4) on at least (b)(4) subjects in 2005, as detailed above in **citation # 1**. However, FDA was not notified of this significant change to the investigational plan.

During the FDA inspection, you told the FDA investigator that you did not know you were the sponsor of this study, and you were not aware of the requirement to submit protocol amendments to FDA for approval. We remind you that the original IDE approval letter addressed to you, dated July 30, 2003, included an attachment entitled "Sponsor's Responsibilities for a Significant Risk Device Investigation," which describes your regulatory requirements under 21 CFR 812.35(a) and 812.42. Your responsibilities established by these regulations, as a sponsor of a significant risk device investigation, are listed in the attachment under the heading "Supplemental Applications," including submission to, and approval by, FDA for changes in the investigational plan that may affect the rights, safety, or welfare of the subjects.

In your response, you stated that any future changes to the investigational plan will be submitted to FDA for approval prior to implementation. Your response is inadequate as it lacks a corrective and preventive action plan to ensure that any future changes to the investigational plan will be submitted to FDA for approval prior to implementation. Please provide copies of policies/procedures that you have developed and implemented to ensure that future changes to the investigational plan will be submitted to FDA for approval prior to implementation. In addition, please maintain documentation that ensures that all study personnel have reviewed these policies/procedures.

5. **Failure to submit progress reports to FDA for a significant risk device study at least yearly [21 CFR 812.150(b)(5)].**

   The IDE regulations require that sponsors of a significant risk device study submit progress reports to FDA at least annually. FDA granted approval of the IDE on July 30, 2003, and you initiated study enrollment in February 2004. The July 2003 IDE approval letter from FDA reminded you of your regulatory requirements as a sponsor to provide an annual progress report to FDA, and provided you with a suggested format. No progress report was submitted to CDRH in 2005. You submitted your first IDE progress report on March 6, 2006, and the second on May 7, 2007. CDRH has not received your IDE progress report for 2008.

Your response states that you understand the requirement for submission of progress reports in accordance with FDA regulations and that you will submit annual reports to CDRH. Your response is inadequate in that it lacks a corrective and preventive action plan to ensure that progress reports are submitted to FDA at least annually. Please provide copies of policies/procedures that you have developed and implemented to ensure that progress reports are submitted to FDA at least annually. In addition, please maintain documentation that ensures that all study personnel have reviewed these policies/procedures.

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 sponsor and as a clinical investigator to ensure compliance with the Act and all applicable regulations.

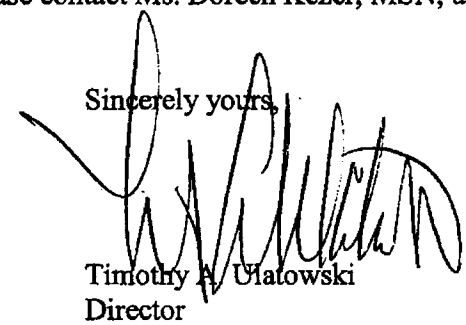
Within **fifteen (15) working days** of receiving this letter, please provide written documentation of the additional actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are the clinical investigator and/or 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 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, Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-311, Rockville, Maryland 20850. In addition, please provide a complete list of all clinical trials in which you have participated for the last five years, including the name of the study and test article, the name of the sponsor, the number of subjects enrolled, and the current status of the study.

A copy of this letter has been sent to FDA's Baltimore District Office, 6000 Metro Dr., Suite 101, Baltimore, MD 21215. We request that a copy of your response also be sent to that office.

If you have any questions, please contact Ms. Doreen Kezer, MSN, at 240-276-0125 or at Doreen.Kezer@fda.hhs.gov.

Sincerely yours,



Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
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cc (unpurged):

Alicia Y. Greene
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IRB/Purged Copy to: