

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
9200 Corporate Blvd.
Rockville MD 20850

MAY 15 2008**WARNING LETTER****VIA FEDERAL EXPRESS**

Robert Honeycutt/VP Ancillary Services
Sierra Providence Health Network IRB
Providence Memorial Hospital
2001 N. Oregon
El Paso, TX 79902

Dear Mr. Honeycutt:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection of your Institutional Review Board (IRB) from March 10 through March 14, 2008, by investigators from the FDA Dallas District Office. The purpose of this inspection was to determine whether your IRB is in compliance with applicable federal regulations. IRBs that review investigations of drugs and devices must comply with applicable provisions of Title 21, Code of Federal Regulations (21 CFR) Part 56-Institutional Review Boards, Part 50-Protection of Human Subjects, and Part 812-Investigational Device Exemptions. This letter also discusses your March 28, 2008, 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 56 - Institutional Review Boards, and Part 812-Investigational Device Exemptions. At the close of the inspection, the FDA investigators presented an inspectional observations form FDA 483 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 follow required written procedures [21 CFR 56.108(a)].

In order to fulfill the requirements of this regulation, each IRB shall follow written procedures for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution. You failed to adhere to the above-stated regulation. Examples of this failure include, but are not limited to, the following:

- a.) The IRB's written procedures state that both the study and its consent form must be approved before the study may proceed. The (b)(4) protocol was reviewed and approved by the IRB on (b)(4), but there is no documentation present in your files or in the letter sent to the clinical investigator for the study to indicate that the informed consent for the (b)(4) was reviewed and approved by the IRB.

In your response, dated March 28, 2008, you stated that "on a go-forward basis" the IRB minutes will reflect a vote on both the protocol and the informed consent, and that investigators will be informed that the protocol and informed consent must be submitted as separate documents. This response is not acceptable in that you have not provided a corrective and preventive action plan to ensure that the IRB's written procedures are followed as written or that the current procedures are adequate to ensure compliance with FDA regulations.

- b.) The IRB's written procedures state that a quorum of at least the majority of the voting committee members must be present at each meeting, and the quorum must contain at least one physician. Your meeting minutes for (b)(4) and (b)(4) at which renewal and approval of new clinical studies occurred, indicate that no physician member of the IRB was present at the meetings. In addition, the minutes for (b)(4) (b)(4) indicate that (b)(6) was a scientific member of the board, even though he is not listed as an IRB member on the (b)(4) roster.

In your response, you stated that you are currently searching for physicians to serve on the IRB. This response is not adequate in that you have not addressed the issue of holding IRB meetings without a quorum as defined by your procedures. Please provide written documentation of procedures that will be followed by the IRB to ensure that an appropriate quorum is present at each meeting, and actions that will be taken if the quorum requirements are not met.

- c.) The IRB's written procedures state, "(b)(4) (b)(4) (b)(4)." All the meeting minutes reviewed by the FDA investigators for the period of January 25, 2005 through September 28, 2006, indicate that clinical investigators were present during IRB votes to approve renewal of their studies. In addition, the meeting minutes for (b)(4) indicate that a member of the IRB voted to approve action on his own study.
- d.) The IRB's written procedures describe the required elements of informed consent. The copies of the informed consent forms in the IRB files for the (b)(4) and the

(b)(4) Study appear to be draft versions and are missing some of the required elements for informed consent as required by regulation [21 CFR 50.25]. No other versions of the consent forms were found in the IRB files.

In your response, you stated that informed consents that are not completely filled in will be returned to the principal investigator for review at the next IRB meeting. This response is not adequate in that you have not provided a corrective and preventive action plan to ensure that the IRB's written procedures are followed as written or that the current procedures are adequate to ensure compliance with FDA regulations regarding informed consent documents. The IRB should review a completed sample consent form, individualized for each study, to ensure that the consent document, in its entirety, contains all the information required by 21 CFR 50.25. The form approved by the IRB should be an exact copy of the form that will be presented to the research subjects.

2. Failure to prepare and maintain adequate documentation of IRB activities [21 CFR 56.115(a)].

In order to fulfill the requirements of this regulation, an IRB shall prepare and maintain adequate documentation of IRB activities, including the following: copies of all research proposals reviewed; written procedures for the IRB as required by 21 CFR 56.108; and minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings, actions taken by the IRB, the vote on these actions including the number of members voting for, against, and abstaining, the basis for requiring changes in or disapproving research, a written summary of the discussion of controverted issues and their resolution, and records of continuing review activities. You failed to adhere to the above-stated regulation. Examples of this failure include, but are not limited to, the following:

a.) Minutes of IRB meetings are inaccurate or incomplete. For example:

- The (b)(4), minutes state that there was a unanimous vote of 11 members to continue a study, but only 8 members are noted as present at the meeting.
- The (b)(4), minutes note that (b)(6) is both present and absent. If he was indeed absent, there was no quorum on that date.
- The (b)(4), minutes note a discussion of the (b)(4) study, but there is no record of a vote or action. The (b)(4) letter to the clinical investigator for the study notes that the IRB approved both the protocol and consent form at the (b)(4) meeting.
- The (b)(4), minutes indicate that the (b)(4) study was reviewed and unanimously approved for renewal "for (b)(4)." The letter sent to the clinical investigator on February 16, 2007, states that the IRB unanimously voted to close the study on (b)(4).
- The (b)(4), minutes list 19 studies as "updates" under "Old Business" with no record of action taken regarding each study. In addition, the minutes are labeled as "draft." No other version was found in your files.
- All the meeting minutes reviewed by the FDA investigators for the period of January 25, 2005, through September 28, 2006, list studies under "Old Business" requiring renewal, closure, or review of amendments or adverse event reports, with a general

statement saying that a motion was made and seconded regarding "the above protocols" to approve continuation, closure, or approve investigators for another term. There is no record of the documents reviewed or the number of members voting for or against each item.

In your response, you stated that, "on a go-forward basis, minutes will be maintained in more detail." This response is not acceptable in that you have not provided a corrective and preventive action plan to ensure that the IRB's written procedures are followed as written, that the current procedures are adequate to ensure compliance with FDA regulations, and that the minutes for IRB meetings are accurate and complete.

b.) You failed to prepare and maintain adequate written procedures to ensure that the IRB fulfills the requirements of the regulations for conducting initial and continuing review of research. Specifically, the IRB has no written procedures for the following:

- A procedure for ensuring prompt reporting to the Food and Drug Administration of any unanticipated problems involving risks to human subjects or others, and any instance of serious or continuing noncompliance with regulations or the requirements or determinations of the IRB.
- A procedure for reporting all IRB findings and actions to the investigator and the institution.
- A procedure for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the subjects.
- A procedure for determining which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review.
- A procedure for determining whether a sponsor's non-significant medical device study is significant risk (SR) or non-significant risk (NSR). In your response, you stated that the study sponsor will be required to provide the risk status of their product, which will be verified against the FDA database. This response is not acceptable. Unless FDA has already made a risk determination for the study, the IRB must review the sponsor's explanation of why the investigation is not a SR and make their own determination of SR or NSR. If the IRB's determination disagrees with the sponsor's then the IRB must report this to the clinical investigator or the sponsor as appropriate. In such a case, the investigation may not begin unless the sponsor obtains an Investigational Device Exemption (IDE) from FDA. This assessment of risk activity by the IRB must be documented in the meeting minutes.
- A procedure for determining which studies require review more often than annually. In your response, you stated, "each study protocol will be compared against any data in the FDA database that identifies those protocols that require more frequent review." This response is not acceptable. The IRB should determine that the frequency and extent of continuing review for each study is adequate to ensure the continued protection of the rights and welfare of research subjects. The factors considered in setting the frequency of review may include the nature of the study, the degree of risk involved, and the vulnerability of the study subject population. FDA recommends that the determination of frequency of review by the IRB be

documented.

- A procedure for reporting expedited review activities to the board.
- If the IRB reviews research involving children as subjects, the procedures should include the IRB responsibilities discussed in 21 CFR 50.50.

In addition, the following procedures are inadequate or incomplete:

- The section describing a quorum is missing the requirement that a non-scientific member must be present at every meeting.
- The section describing documentation of informed consent is missing the requirement that the form be dated, as well as signed, by the person giving consent.

3. Failure to conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year [21 CFR 56.109(f) and 812.64].

In order to fulfill the requirements of these regulations, an IRB shall conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. Your records indicate that, at the time of the FDA inspection, 12 of the 34 active studies approved by your IRB have not been reviewed for 17 months or more.

In your response, you stated that you have hired a temporary employee to bring the files up to date so you can have an IRB meeting in (b)(4) and do (b)(4) review of the studies. This response is not acceptable in that you have not provided a corrective and preventive action plan to ensure that the IRB's written procedures are followed as written, and that the current procedures are adequate to ensure compliance with FDA regulations regarding continuing review of research. Please also provide documentation of the (b)(4) meeting, including the actions and vote on FDA regulated studies that were past due at the time of the FDA inspection, and provide meeting minutes and copies of correspondence to the clinical investigators.

The violations described above are not intended to be an all inclusive list of problems that may exist at your IRB. The IRB is responsible for ensuring compliance with the Act and applicable regulations.

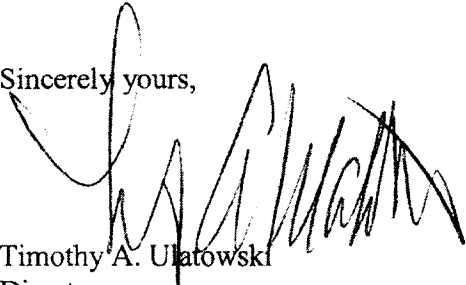
Within **fifteen (15) working days** of receiving this letter, please provide **written documentation** of the actions you have taken or will take to correct these violations and prevent the recurrence of similar violations. Please also explain and provide documentation of the particular methods or procedures that will be used at your IRB to train all appropriate staff on any new procedures you may implement to correct these deficiencies. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. 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 Boulevard, Rockville, Maryland 20850
Attention: Ms. Doreen Kezer, Chief, Special Investigations Branch.

A copy of this letter has been sent to the FDA Dallas District Office, 4040 North Central Expressway, Suite 300, Dallas, TX 75204. 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,



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