DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Blvd.
Rockville MD 20850

WARNING LETTER

AUG 14 2008

VIA FEDERAL EXPRESS

Aniceta C. Mendoza, Chief of Nursing
Valley Baptist Medical Center IRB
1040 West Jefferson Street
Brownsville, TX 78520

Dear Ms. Mendoza:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection of the Valley Baptist Medical Center Institutional Review Board (IRB) from April 17 through 18, 2008, by an investigator from the FDA Dallas District Office. The purpose of this inspection was to determine whether the 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 the IRB's April 30, 2008, written response to the observations noted at the time of the inspection, and requests that the IRB 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 investigator presented an inspectional observations form FDA 483 for your review and discussed the observations listed on the form with you and the IRB Chair, Dr. Rose Gowen. The deviations noted on the FDA 483, the IRB's written response, and our subsequent review of the inspection report are discussed below:

1. **Failure to follow written procedures for conducting initial and continuing review of research and for reporting findings and actions to the investigator and the institution [21 CFR 56.108(a)(1)]; determining which projects require review more often than annually [21 CFR 56.108(a)(2)]; and 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 [21 CFR 56.108(a)(4)].

Examples of this failure include, but are not limited to, the following:

a. The IRB's written procedures state that, for the IRB's initial review of research, the clinical investigator must submit to the IRB information including a written protocol and a consent form. There is no documentation present in the IRB's files or in the approval letters sent to the clinical investigators for FDA-regulated studies approved by the IRB from 2005 through 2008 to indicate that informed consent forms were reviewed and approved by the IRB.

   In the IRB's response, which the IRB forwarded to the Dallas District Office on April 30, 2008, the IRB states that all approved consent forms "will be stamped with IRB approval on every page" as soon as possible. This response is not adequate in that the IRB has not indicated what corrective and preventive actions it will take to ensure that the IRB will follow its procedures as written and maintain documentation of consent forms submitted by investigators, that the consent forms for all studies previously approved by the IRB have been appropriately reviewed, and that the IRB will appropriately review consent forms submitted in future studies. Simply stamping all consent forms with "IRB approval" will not bring the IRB into compliance with the regulations.

b. The IRB's written procedures state (b)(4) (b)(4) However, the meeting minutes for (b)(4) at which renewal of a significant risk device study (b)(4) was discussed, and for (b)(4) at which approval of a new high risk study (b)(4) was discussed, report as actions and follow-up activities that information will be sent by mail "to the IRB Committee members who were not able to attend the meeting" and that the IRB should "Obtain a consensus from the IRB Committee to approve" the studies.

c. The IRB's written procedures state that the clinical investigator must (b)(4) (b)(4) There was no documentation in the IRB files to indicate that the IRB has enforced this requirement for all studies. For example, there were no records of receipt of any annual reports from the clinical investigator for the (b)(4) study that was initially approved by the IRB on March 22, 2006, or for the (b)(4) study that was initially approved by the IRB on July 13, 2006. According to the IRB's response, both of these studies are currently ongoing.

2. **Failure to follow written procedures for ensuring prompt reporting to the Food and Drug Administration of: (1) any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval [21 CFR 56.108(b)].**

   The IRB does not have any such procedures on file.

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].

The IRB's records indicate that several significant risk, FDA-regulated studies approved by the IRB have not been reviewed at least annually. Examples of this failure include, but are not limited to, the following:

a. The IRB initially approved the (b)(4) Study on February 8, 1999. The FDA investigator found only one record of annual review and renewal of IRB approval for this study, which is dated January 11, 2008.

b. The IRB initially approved the (b)(4) study on March 22, 2006. There is no record of any IRB reviews or renewals of approval since that date, even though the study is still ongoing.

c. The IRB files contain several unanticipated adverse event reports and a protocol deviation from the clinical investigator for the (b)(4) Study from August 2005 through March 2008, and Annual Reports for the (b)(4) Study for 2004 and 2005, yet there is no record that the IRB reviewed or evaluated any of these reports. In addition, the 2006 Annual Report for the (b)(4) Study was submitted to the IRB in February 2007, but there is no record that the IRB reviewed it until January 11, 2008.

In the IRB's response, the IRB provided a spreadsheet called a (b)(4) (b)(4) as a corrective action. This spreadsheet merely notes that, for the two studies listed above, the (b)(4) is "a report to be submitted annually." This response is not adequate in that the IRB has not indicated what corrective and preventive actions it will take to ensure that its procedures are in compliance with FDA regulations regarding continuing review of all regulated research, that the IRB's written procedures are followed, and that all FDA-regulated studies overseen by the IRB are appropriately reviewed at least annually.

Please also provide a complete listing of all clinical studies reviewed by the IRB since 1999 with your written response. This list should include the titles of the studies (with IDE or IND numbers if applicable), the names of the test articles, the names of the Clinical Investigators, dates of initial reviews and approvals, dates of continuing reviews, and current status of the studies.

4. **Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. [21 CFR 56.108(c)].**

The IRB voted on FDA-regulated research when less than a majority of the members were present. Examples of this failure include, but are not limited to, the following:

a. At the (b)(4) IRB meeting, the minutes indicate that only (b)(4) of the IRB was present. Actions taken at this meeting included review and renewal of the (b)(4) Study.

b. At the (b)(4) IRB meeting, the minutes indicate that only (b)(4) of the IRB were present, one of whom did not vote due to a conflict of interest. Actions taken at this meeting included review and approval of a new clinical trial, the (b)(4)

study.

5. **Failure to require that information given to subjects as part of informed consent is in accordance with 21 CFR 50.25 [21 CFR 56.109(b)] and failure to require documentation of informed consent in accordance with 21 CFR 50.27 [21 CFR 56.109(c)].**

   The IRB failed to ensure that informed consent documents contain all the information required by 21 CFR 50.25. Examples of this failure include, but are not limited to, the following:

   a. There is no record of IRB review or approval of informed consent forms for at least (b)(4) studies reviewed by the IRB since 2003.

   b. The only version of the informed consent form in the IRB files for the (b)(4) Study is missing the name of the investigator, the IRB Chairman, and relevant contact information.

   c. The only version of the informed consent form in the IRB files for the (b)(4) (b)(4) study appears to be an incomplete draft. It is missing various information, including relevant contact information.

   In addition, the IRB's written guidelines, "Principal Responsibilities of the Investigator," state that an informed consent form must contain "all required HIPAA information specific to the proposed type of research," but do not require the consent form to contain all of the elements of informed consent described in 21 CFR 50.25.

6. **Failure to prepare and maintain adequate documentation of IRB activities, including copies of all research proposals reviewed, approved sample consent documents, and progress reports submitted by investigators [21 CFR 56.115(a)(1)].**

   Examples of this failure include, but are not limited to, the following:

   The IRB failed to maintain copies of all research proposals reviewed. For example, the (b)(4) (b)(4) Study, which is still ongoing, was initially reviewed and approved by the IRB on February 8, 1999. There are no records in the IRB's files related to any IRB activities for this study before May 5, 2005.

7. **Failure to prepare and maintain adequate documentation of IRB activities, including 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, and a written summary of the discussion of controverted issues and their resolution [21 CFR 56.115(a)(2)].**

   Minutes of IRB meetings are inaccurate and/or incomplete. For example:

   a. Minutes for IRB meetings on (b)(4) (b)(4) and (b)(4) (b)(4) note that FDA-regulated studies were approved or renewed, but there is no vote recorded on these actions including the number of members voting for, against, and abstaining, or a written

summary of the discussion of controverted issues and their resolution.

b. The IRB minutes for the period from (b)(4) through (b)(4) do not indicate which persons attending the meetings are IRB members and how many IRB members are missing, which makes it impossible to determine whether a quorum is present for each meeting.

c. A letter dated March 23, 2006, to a clinical investigator for the (b)(4) Study states that, at the IRB meeting on (b)(4) Western Institutional Review Board was approved as the IRB for this study. The minutes for this date state the only action was to "approve the proposed research study as presented" and make no mention of the IRB's decision to transfer IRB responsibilities to a Central IRB.

8. **Failure to prepare and maintain adequate documentation of IRB activities, including a list of IRB members identified by name, earned degrees, representative capacity, indications of experience, and any employment or relationship between each member and the institution. [21 CFR 56.115(a)(5)].**

No IRB membership rosters were found in the IRB's files, and the IRB has not prepared and maintained a list of IRB members identified by name, earned degrees, representative capacity, and indications of experience sufficient to describe each member's chief anticipated contributions to IRB deliberations.

In the IRB's response, it provided a current IRB roster listing (b)(4) names, which includes the information required by 21 CFR 56.115(a)(5). The roster appears to meet the requirements for IRB membership as outlined in 21 CFR 56.107. This response is only partially adequate in that it fails to provide a corrective and preventive action plan indicating what actions the IRB will take to ensure that it maintains a complete and accurate list of IRB members in the future.

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

It should also be noted that, if the IRB reviews or anticipates reviewing research involving children as subjects, the IRB must comply with the requirements of 21 CFR 50.50 and approve only those clinical investigations that satisfy the criteria described in 21 CFR 50.51, 50.52, or 50.53, and the conditions of all other applicable sections of 21 CFR part 50 subpart D.

Within **fifteen (15) working days** of receiving this letter, please provide **written documentation** of the actions the IRB has 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 the IRB to train all appropriate staff on any new procedures the IRB 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 the IRB. Please send the IRB's 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 the IRB's 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