DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Blvd
Rockville MD 20850

95903d

JUN 22 2006

WARNING LETTER

VIA FEDERAL EXPRESS

Patricia Hardenbergh, MD
Chairperson, Vail Valley Medical Center IRB
181 West Meadow Drive, Suite 100
Vail, CO 81657

Dear Dr. Hardenbergh:

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 April 10 through April 14, 2006, by an investigator from the FDA Denver 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 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 requests prompt corrective action to address the violations cited.

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 Section 520(g) (21 U.S.C. 360j(g)) of the Act. 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. The deviations noted on the FDA 483 and our subsequent review of the inspection report are discussed below:

1. **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)].**

   Review of study documents and related IRB minutes indicates that you failed to ensure that the IRB reviewed all research for which it was responsible at least once per year. For example:

   a.) [redacted] initial conditional IRB approval was given

on 9/24/02 for one year. There was no IRB review between 9/24/03 and 7/8/04, when the study was renewed for one year. There has been no IRB review since the IRB approval expired on 7/8/05. IRB records list this study as active.

b.) [redacted] initial IRB approval was given on 9/17/02 for one year. There are no records to document any IRB reviews since that date. IRB records list this study as active.

c.) [redacted] initial IRB approval was given on 12/10/02 for one year. There was no IRB review until the study approval was renewed in December 2004.

d.) [redacted] initial IRB approval was given on 12/6/96 for one year. There are no records to document any IRB reviews from May 1997 through March 2001. IRB records list this study as active.

2. **Failure to ensure that no IRB member participates in the IRB's initial or continued review of any project in which the member has a conflicting interest [21 CFR 56.107(e)].**

You failed to ensure that IRB members with conflicting interests in the projects being reviewed did not participate. For example:

a.) [redacted] The Vice Chairman of the IRB, [redacted] lists "Chief, Scientific Affairs" [redacted] (the study sponsor) on his current CV. He is also listed as a participant in the study and as the author of the study Protocol. The IRB minutes for the 3/18/03 meeting do not document any reviews or discussions for this study, yet the IRB-approved consent form was stamped "Approved for use from 3/18/03 through 3/18/04 by [redacted]

b.) [redacted], is the author of the study Protocol and Chief of Scientific Affairs for the study sponsor. At the 3/18/03 IRB meeting, the progress report for the study was reviewed by the IRB. [redacted] voted to approve the continuing review, and signed the IRB re-approval letter dated 3/21/03.

3. **Failure to ensure that the IRB reviewed proposed research at convened meetings at which a majority of the members of the IRB were present, including at least one member whose primary concerns are in nonscientific areas, and that individuals invited to provide expertise for reviews do not vote with the IRB. [21 CFR 56.108(c) and 21 CFR 56.107(f)].**

You failed to ensure that, except when an expedited review procedure was used, the IRB reviewed proposed research at convened meetings at which the members present constituted a majority, including at least one member whose primary concerns were in the nonscientific areas, and that non-voting members of the IRB were not allowed to vote. For example:

a.) At the 3/15/05 IRB meeting, the minutes indicate that there were no non-scientific members present. In addition, only five of the ten listed members of the IRB were present, which was not a majority. Three new study Protocols were reviewed and approved at this meeting.

b.) At the 12/14/04 IRB meeting, the minutes indicate that only four of the nine listed members were present, which was not a majority. Four new Study Protocols were reviewed and approved at this meeting

c.) At the 12/14/04 IRB meeting, the minutes indicate that [redacted] Vail Valley Medical Center Vice President and a non-voting member of the IRB, was granted authority by the IRB to be the proxy for the IRB Chair and to vote for approval of new study Protocols.

d.) At the 12/13/05 IRB meeting, the minutes indicate that six of the ten IRB members were present. However, the "Outcome" section of the minutes indicates that only five members voted for or against approval for Study Protocols [redacted].

e.) The IRB minutes for the 6/22/04 meeting note that [redacted] abstained from voting on approvals for renewal of three study protocols, [redacted], due to a conflict of interest. However, [redacted] abstentions resulted in loss of the quorum, since only five of the eleven members of the IRB were able to vote for approval of these studies.

4. **Failure to maintain minutes of IRB meetings in sufficient detail to show attendance at the meetings and the vote on actions, including number of members voting for, against, or abstaining [21 CFR 56.115(a)(2)]**

a.) During the 6/14/05 IRB meeting, no vote was recorded in the minutes for approval of new Study Protocol [redacted]

b.) The IRB records contain three different sets of minutes for the 6/14/05 IRB meeting. Each of the three sets of minutes documents different attendees at the meeting.

c.) During the 12/13/05 IRB meeting, the minutes indicate that there were six voting members present. However, for Study Protocols [redacted] and [redacted], the recorded votes were five for approval and zero against. One of the members was documented as having seconded the motion to approve the studies but there were no voting sheets filled out by this member. There is no documentation as to whether this member abstained or left the meeting.

d.) The IRB minutes for the 3/18/03 meeting do not document any reviews or discussions for [redacted] this study, yet the IRB-approved consent form was stamped "Approved for use from 3/18/03 through 3/18/04 by [redacted]

5. **Failure to use expedited review procedures only for certain kinds of research involving no more than minimal risk or for minor changes in approved research [21 CFR 56.110].**

The IRB granted approval by expedited review of new research for studies that did not meet the criterion of minimal risk. For example:

a.) On 1/6/05, the IRB granted initial approval by expedited review for a new [redacted] to be conducted at Vail Valley Medical Center. The reason given for expedited review was that it was a multicenter study and had already been reviewed and approved by one or more other institutional review boards. The nature of this study and the reason for expedited review do not meet the criteria for expedited review.

b.) On 12/14/04, the IRB granted initial approval by expedited review for two new Study Protocols, [redacted] These studies do not meet the criteria for expedited review because they were not documented as being minimal risk or involving minor changes to already approved research.

6. **Failure to prepare and follow written procedures for conducting the review of research, including periodic review, and for ensuring prompt reporting to appropriate institutional officials and the FDA of any serious or continuing non-compliance with these regulations or the requirements or determinations of the IRB [21 CFR 56.108(a)&(b) and 56.115(a)(6)].**

You failed to ensure that the IRB prepared and followed written procedures for the conduct of IRB activities. For example:

a.) There were no written procedures for determining which projects require review more than once per year.

b.) The IRB's written procedures state that the clinical investigator must submit a progress report to the chairman at semi-annual intervals. There was no documentation in the IRB files to indicate that the IRB has enforced this requirement for all studies. For example, the studies noted above in citation number (1.) had no evidence that semi-annual progress reports were submitted to the IRB.

c.) The IRB has no written procedures for ensuring prompt reporting to appropriate institutional officials and the FDA of any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB.

d.) The IRB's written procedures state that research "will be reviewed at convened meetings at which a majority of the IRB are present...which majority shall constitute a quorum." The IRB has not enforced this requirement, as evidenced by the examples noted above in citation number 3.

e.) The IRB's written procedures for Expedited Review state that the IRB "may utilize expedited review for research that meets the definition of minimal risk and other criteria established by the FDA and/or the Department of Health and Human Services." The IRB failed to adhere to this requirement, as evidenced by the examples noted above in citation number 5.

7. **Failure to prepare and maintain 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 [21 CFR 56.115(a)(5)].**

   You failed to ensure the IRB prepared and maintained a current and accurate list of IRB membership. Specifically:

   a.) IRB membership rosters were found in the IRB records for 2006 (with ten voting members) and for 2002 (with eleven voting members) only. There were no rosters for the years 2003 through 2005.

   b.) IRB minutes documented varying numbers of total members for each meeting, ranging from five members at the 6/14/05 meeting to eleven members at the 6/22/04 meeting.

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.

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. 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 Denver District Office, 6th & Kipling St., Denver, CO 80225-0087. 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