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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Blvd.
Rockville MD 20850

WARNING LETTER

VIA FEDERAL EXPRESS

SEP 30 2008

Blaine Douglas
CEO/Wellmont Holston Valley Medical Center
201 W. Ravine Road
Kingsport, TN 37660-3725

Dear Mr. Douglas:

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 May 15 through July 24, 2008, by an investigator from the FDA New Orleans 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, many of which are recurrences or continuations of violations cited in a Warning Letter sent from FDA to your IRB in June 2006 as a result of an inspection conducted in February 2006, and discusses your written response to the noted violations dated August 11, 2008. As described below, under 21 CFR 56.120, FDA is imposing restrictions on your IRB.

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 violations of Title 21, Code of Federal Regulations (21 CFR) Part 56 - Institutional Review Boards. At the close of the inspection, the FDA investigator presented an inspectional observations form FDA 483 to Dr. C. Robert Bice, the IRB Chairman, for his review and discussed the observations listed on the form with him. The deviations noted on the FDA 483, the written response, and our subsequent review of the inspection report are discussed below:

1. **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)].**

This is a recurrence of a violation cited at the last IRB inspection and in the last Warning Letter issued to you in 2006.

At the majority of meetings since the last FDA inspection concluded in February 2006, the IRB voted on FDA-regulated research when less than a majority of members without conflicting interests were present. Examples of this failure include, but are not limited to, the following:

a.) The minutes for both the October 9, 2007, meeting and the November 13, 2007, meeting indicate that only six of the thirteen listed members of the IRB were present, which was not a majority.

b.) The minutes for at least thirteen of the IRB meetings held since March 2006 indicate that, though a majority of members were present, abstentions by one or more members of the IRB due to a conflict of interest resulted in loss of the quorum, since less than a majority of the members of the IRB were able to vote.

The response letter from Dr. Bice, dated August 11, 2008, stated that the observation was "due to lack of full time IRB support." The letter also notes that a full time IRB support person will be hired and on the job by October 1, 2008. This is not an acceptable response, as it does not address the issue of holding IRB meetings and votes without ensuring that a majority of IRB members are present and not conflicted out of voting. Please provide written documentation of procedures that will be followed by the IRB to ensure that you follow FDA requirements for each meeting and for each vote, and actions that will be taken if the quorum requirements are not met. If the number of non-conflicted members able to attend a meeting does not constitute a majority of IRB members, you should reschedule the meeting.

2. **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)].**

This is a recurrence of a violation cited in the last IRB inspection and in the last Warning Letter issued to you in 2006.

Minutes of IRB meetings are inaccurate and/or incomplete. Examples of this failure include, but are not limited to, the following:

a.) The IRB minutes do not always accurately record which members are present or absent. For example:
   i. The minutes for the April 11, 2006 meeting list (b)(6) twice and record her as both P (present) and A (absent).
   ii. The minutes for the July 11, 2006 meeting note that "(b)(6) chaired the meeting in the absence of Dr. Robert Bice, Chairman," However, the listing of voting members records Dr. Bice as "P."
   iii. The minutes for the August 8, 2006 meeting note that Dr. Bice "called the meeting to

order," but the listing of voting members records him as "A."

iv. The sign-in sheet for the July 10, 2007 meeting contains signatures for (b)(6) and (b)(6) However, the listing of voting members in the minutes records both (b)(6) and (b)(6) as "A."

v. The listing of voting members in the minutes for both March 11, 2008 and for April 8, 2008 record (b)(6) as "A." However, the minutes later note that (b)(6) (b)(6) "presented the (b)(4) protocol activity" and abstained from voting.

b.) Minutes of IRB meetings do not accurately record votes on actions, including the number of members voting for, against, and abstaining. For example:

i. The April 11, 2006, IRB meeting minutes note, "the IRB with 8 members voting and 2 abstentions approved" several new protocols and protocol amendments. However, the listing of voting members records only nine present.

ii. The December 12, 2006, IRB meeting minutes note that two of the nine voting members present at the meeting abstained from voting on (b)(4) protocol activity. However, the minutes note, "the IRB with 6 members voting yea approved" several new studies and protocol amendments, and does not account for the missing vote.

iii. The October 11, 2006, IRB meeting minutes note, "The IRB after further discussion approved the revisions/updates/amendments," for eight studies, without a record of the number voting for, against, or abstaining.

iv. The December 11, 2007, IRB meeting minutes document the presentation of four new studies, but there is no record of any actions taken by the IRB. Updates for two of these studies were approved (without a quorum) at the March 2008 meeting. These four studies appear on the IRB's list of approved studies dated April 2008. However, there is no record that the IRB voted on or approved these studies or their consent forms.

In Dr. Bice's response, he stated that a roster is being signed at all meetings, and will reflect the actual members attending the meetings. He also noted, "the clerical errors will be alleviated when a full time IRB support person is hired." This is not an acceptable response, as it does not address the issue of ensuring the overall accuracy of IRB meeting minutes. In addition, as noted above, one of the examples includes a case in which the signed roster did not agree with the list of IRB members recorded as present in the minutes. Please provide written documentation of procedures that will be followed by the IRB to ensure that the meeting minutes will be an accurate and complete reflection of IRB activities.

3. **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 research for significant risk studies that did not meet the criteria of minimal risk or minor changes in approved research during the period (of one year or less) for which approval is authorized. Examples of this failure include, but are not limited to, the following:

a.) The IRB records contain a note that, since the February 13, 2007, meeting was canceled, Dr. Bice approved the renewal of at least four significant risk studies. None of these approvals meet the criteria for expedited review since the research involves more than minimal risk and the approval was for renewal of the studies, not for minor changes to

them.

b.) The July 10, 2007, IRB meeting minutes contain a comment that Dr. Bice approved the (b)(4) "due to the cancellation of the June IRB meeting" and "the IRB with 7 voting members ratified the approval made by Dr. Bice." This study does not meet the criteria for expedited review since the research involves more than minimal risk and the approval was for a new study, not for minor changes to an ongoing study.

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

This is a recurrence of a violation cited in the last IRB inspection and in the last Warning Letter issued to you in 2006.

You failed to ensure that IRB members with conflicting interests in the projects being reviewed did not participate except to provide information to the IRB. Examples of this failure include, but are not limited to, the following:

a.) The minutes of nearly every IRB meeting since 2006 contain statements noting that IRB members (b)(4), (b)(6) and (b)(6) "both abstained from voting on oncology protocol actions." However, documentation in the minutes regarding the votes on actions regarding new (b)(4) studies or renewal of ongoing (b)(4) studies indicates that these two people voted for approvals. For example:

i. The IRB meeting minutes for January 9, 2007, show that eight voting members were present at the meeting, including (b)(6) and (b)(6). With their abstentions, there should have been only six members voting. However, the actions taken for approval of 7 protocol amendments/revisions, 2 new studies, and 8 ongoing studies state, "The IRB with 9 members voting approved" the revisions, new studies, or continuation of the ongoing studies.

ii. The IRB meeting minutes for April 10, 2007, show that eight voting members were present at the meeting, including (b)(6) and (b)(6). With their abstentions, there should have been only six members voting. However, the actions taken for approval of 3 new studies and 2 ongoing studies state, "The IRB with 7 members voting approved" the new study or continuation of the ongoing study.

iii. The IRB meeting minutes for August 14, 2007, show that seven voting members were present at the meeting, including (b)(6) and (b)(6). With their abstentions, there should have been only five members voting. However, the action taken for approval of 16 protocol amendments and/or revisions to the consent forms states, "The IRB with 7 members voting approved" the study revisions and amendments.

iv. The IRB meeting minutes for March 11, 2008, show that eight voting members were present at the meeting, including (b)(6). (b)(6) was listed as absent. With (b)(6) abstention, there should have only been seven members voting. However, the actions taken for approval of 2 protocol amendments/revisions, 1 new study, and 22 ongoing studies state, "The IRB with 8 members voting approved" the revisions, new study, or continuation of the ongoing studies. The actions taken for approval of 4 other new studies states, "The IRB with 9 members voting approved" the new studies.

b.) The minutes of nearly every IRB meeting since 2006 contain statements noting that either IRB member (b)(6) or (b)(6) "abstained from voting on (b)(4)." However, documentation in the minutes regarding the votes on actions regarding new cardiology studies or renewal of ongoing cardiology studies indicates that these two people voted for approvals. For example:

i. The IRB meeting minutes for January 9, 2007, show that eight voting members were present at the meeting, including (b)(6). With her abstention, there should have been only seven members voting. However, the actions taken for approval of 1 protocol amendment/revision and 5 ongoing studies state, "The IRB with 8 members voting approved" the revisions or continuation of the ongoing studies.

ii. The IRB meeting minutes for April 10, 2007, show that eight voting members were present at the meeting, including (b)(6). With her abstention, there should have been only seven members voting. However, the actions taken for approval of 1 protocol amendment/revision and 1 new study state, "The IRB with 8 members voting approved" the revisions or new study.

iii. The IRB meeting minutes for August 14, 2007, show that seven voting members were present at the meeting, including (b)(6). With her abstention, there should have been only six members voting. However, the actions taken for approval of 1 protocol amendment/revision and 2 ongoing studies state, "The IRB with 7 members voting approved" the revisions or continuation of the ongoing studies.

iv. The IRB meeting minutes for March 11, 2008, show that eight voting members were present at the meeting, including (b)(6). With his abstention, there should have only been seven members voting. However, the actions taken for approval of 3 protocol amendments/revisions and 2 ongoing studies state, "The IRB with 8 members voting approved" the revisions, or continuation of the ongoing studies.

In Dr. Bice's response, he stated that the specific example cited in the form FDA 483, which refers to the IRB meeting minutes on August 14, 2007, was again "due to lack of full time IRB support" and that a full time IRB support person will be hired and on the job by October 1, 2008. This is not an acceptable response, as it does not address the issue of ensuring consistent and accurate meeting minutes and documenting compliance with FDA regulations regarding conflict of interest.

5. **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)].**

This is a recurrence of a violation cited in the last IRB inspection and in the last Warning Letter issued to you in 2006.

Examples of this failure include:

a.) The IRB membership rosters do not always correspond with the list of IRB members recorded in the minutes for IRB meetings. For example:

i. The minutes for the March 14, 2006, IRB meeting lists eleven members, including (b)(6) and (b)(6). However, the March 2006 IRB roster lists only nine

voting members, and does not include (b)(6) or (b)(6) .

ii. The August 2006 IRB roster lists eleven voting members, including (b)(6) However, the August 8, 2006 IRB meeting minutes lists ten voting members, and does not list (b)(6) .

iii. The March 2007 IRB roster lists twelve voting members, including (b)(6) and (b)(6) . However, the April 10, 2007, IRB meeting minutes lists only ten voting members, and does not include (b)(6) . In addition, (b)(6) is listed as a non-voting member.

b. The IRB rosters provided to the FDA investigator during the inspection do not contain all of the required information. For example, in the rosters for March 2007 and January 2008, the representative capacity of each member (as scientific or non-scientific) is unclear, as is the employment or relationship between each member and the institution (the entries for several members in the "affiliation with institution" column are blank).

In Dr. Bice's response, he stated that "the clerical errors will be alleviated when a full time IRB support person has been hired." This is not an acceptable response. Please 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, with provisions for timely updates of the roster when changes in membership occur. Please also submit an accurate, complete, and current IRB roster for our review.

6. Failure to follow required written procedures for conducting initial and continuing review of research [21 CFR 56.108(a)].

This is a recurrence of a violation cited in the last IRB inspection and in the last Warning Letter issued to you in 2006.

The IRB failed to follow written procedures, as required by 21 CFR 56.108(a)(1). Examples of this failure include, but are not limited to, the following:

a.) The IRB Policy and Procedures states, "(b)(4) (b)(4) (b)(4) ." As noted above in **citation # 1**, the IRB met numerous times and approved research without meeting the requirements for a quorum.

b.) The IRB Policy and Procedures states that the IRB may use the expedited review procedure to review either or both of the following: "(b)(4) (b)(4) (b)(4) " As noted above in **citation # 3**, the IRB's records indicate that expedited review procedures were used inappropriately for approval of research not meeting these criteria.

c.) The IRB Policy and Procedures states, "(b)(4) (b)(4)

(b)(4) " As noted above in **citation # 4**, the IRB's meeting minutes indicate that members of the IRB voted on approvals for studies in which they have a conflict of interest.

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.

We note that the IRB meeting minutes for August 8, 2006, indicate that Dr. Bice had approved a request for compassionate use of the "(b)(4) on July 28, 2006. The minutes also state that the IRB approved the physician's "future requests up to twelve months" for compassionate use of this device. The IRB should understand that prior FDA approval is needed before any protocol deviation, including a compassionate use of an investigational device that is significant risk subject to an IDE. The sponsor of the device study must submit an IDE supplement to FDA requesting approval for a protocol deviation in order to treat a patient under compassionate use. The physician should not treat the patient identified in the supplement until FDA approves use of the device under the proposed circumstances. FDA recommends that the IRB implement written procedures for dealing with future compassionate use requests to ensure that the sponsors and clinical investigators are in compliance with the regulations. Information regarding recommended procedures for compassionate use can be found at http://www.fda.gov/cdrh/devadvice.

As noted, most of the violations discussed above are recurrences or continuations of violations found during the February 2006 inspection and reflected in FDA's June 29, 2006, Warning Letter to you. The IRB has also failed to implement all of the corrective and preventative actions promised after the 2006 inspection and letter, to assure future compliance with FDA regulations.

As a result of the IRB's continuous non-compliance with FDA regulations, FDA hereby directs that no new subjects be enrolled into ongoing studies subject to 21 CFR Part 56 that are reviewed by your IRB, as provided by 21 CFR 56.120(b)(2). This restriction will remain in effect until FDA has evidence of adequate corrective actions and notifies you in writing that the IRB's corrective actions are satisfactory. In addition, FDA may withhold approval of new studies subject to 21 CFR Part 56 that are reviewed by your IRB, as provided by 21 CFR 56.120(b)(1).

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 provide a complete listing of all clinical studies reviewed by the IRB since 2006 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.

Failure to respond to this letter and take appropriate corrective action will result in the continuation of the restriction described above and could result in the FDA taking further regulatory action, including the initiation of disqualification proceedings in accordance with 21 CFR 56.121. 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 New Orleans District Office. Please send a copy of your response to that office at: 404 BNA Drive, Building 200, Suite 500, Nashville, TN 37317.

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

Sincerely yours,

Larry D. Spears for

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