DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Alfred E. Abaunza, M.D.
Chief Medical Officer
West Jefferson Medical Center
Institutional Review Board
1101 Medical Center Boulevard
Marrero, LA 70072

Ref: 08-HFD-45-0204

Dear Dr. Abaunza:

Between July 23, 2007 and July 26, 2007, Ms. Barbara D. Wright, representing the Food and Drug Administration (FDA), inspected the Institutional Review Board (IRB) at West Jefferson Medical Center. The purpose of this inspection was to determine whether the IRB procedures for the protection of human subjects complied with Title 21 of the Code of Federal Regulations (CFR), Parts 50 and 56. These regulations apply to clinical studies of products regulated by FDA. We are aware that at the conclusion of the inspection, our investigator presented and discussed with you a Form FDA 483, Inspectional Observations.

From our review of the establishment inspection report, the documents submitted with that report, and your August 22, 2007 letter written in response to the Form FDA 483, Inspectional Observations, we conclude that the IRB did not adhere to the applicable statutory requirements and FDA regulations governing the protection of human subjects. We wish to emphasize the following:

1. **The IRB failed to excuse a member from participating in the initial review of a project in which the member had a conflicting interest, except to provide information requested by the IRB [21 CFR 56.107(e)].** Specifically,

   At the August 9, 2005 meeting of the IRB, Dr.[ ]an official voting member, presented his study entitled "A Multicenter, Randomized, Double-Blind Study Comparing the Clinical Effects of Intravenous[ ]with Placebo in Pediatric Patients (Ages 6 to 14 Years) with Acute Asthma." We note that the meeting minutes do not state that Dr.[ ]was excused from participating in the initial review or vote of his study. The minutes only noted

that a motion was made, seconded and carried to approve the proposal as presented.

2. **The IRB failed to follow written procedures for IRB functions and operations in accordance with 21 CFR Part 56.115(a)(6), 21 CFR 56.108(a)(1), and 21 CFR 812.66.**

   Pursuant to the above stated regulations, each IRB shall prepare, maintain, and follow written procedures for conducting initial and continuing review of research. The IRB failed to have written procedures in its manual "West Jefferson Medical Center Institutional Review Board Policy and Procedures" to determine if a device investigation is a significant risk (SR) device study or non-significant risk (NSR) device study. Specifically, the "Section VII – Functions and Operations, subsection A – Initial Review Process and subsection B – Criteria for IRB Approval" does not describe the criteria used by the IRB to make this determination.

   An IRB only has to make a SR or NSR determination for device studies presented as NSR studies to the IRB for review under 21 CFR 812.2(b)(1)(ii). The IRB considers the sponsor's brief explanation (21 CFR 812.2(b) (1)(ii)) of why the device is not a significant risk device when making the SR or NSR determination. In addition, in making the SR or NSR determination, the IRB considers the "significant risk device" definition [21 CFR 812.3(m)], the description of the device and how it is used, and any other material that the IRB requests from the sponsor. If the IRB determines the proposed NSR device study to be NSR, the IRB may proceed with its review in accordance with 21 CFR Part 56. However, if the IRB determines that the proposed NSR study is SR, then under 21 CFR 812.66 the IRB must notify the investigator, and where appropriate, the sponsor, about its determination. In this latter case, the sponsor cannot begin the study unless an application for an IDE is provided to FDA as described in 21 CFR 812.30(a). An IRB may verify FDA's approval of a significant risk device study by requesting a copy of the FDA's IDE approval letter from the investigator, who will obtain it from the sponsor. Significant risk device studies cannot proceed without FDA and IRB approval.

3. **The IRB failed to follow its written procedure for conducting continuing review of research [21 CFR 56.108(a)(1)].**

   a. The IRB's written procedures do not accurately reflect the current IRB practices in relation to continuing review. The current written procedures note that your IRB conducts continuing review of studies at least once a year to determine if the investigation still meets IRB approval criteria. In practice, however, we note that, your IRB does not send clinical investigators a written request until November of each year asking them to submit a written progress/summary report to the IRB by a given date in

December. Most all written progress/summary reports are then reviewed by the IRB at the first meeting of each calendar year.

We note that the current process used by your IRB for the continuing review of studies allows for studies that had IRB approval to expire before the request is made by the IRB to the investigator to submit a summary report. Investigator Wright also noted that the IRB only sends out the written requests to investigators whose projects have cleared both the IRB and the Medical Executive Committee by the fall. If, however, a project has only recently been approved by the IRB but not the Medical Executive Committee your IRB will not request the investigator to send a written progress/summary report to you until the subsequent calendar year. Thus, a study can reach its expiration prior to the review of the study by the IRB at the continuing review phase. For example, we note that the study entitled "A Multicenter, Randomized, Double-Blind Study Comparing the Clinical Effects of Intravenous [ ] with Placebo in Pediatric Patients (Ages 6 to 14 Years) with Acute Asthma" was approved by the IRB at the August 9, 2005 meeting. In a letter dated November 13, 2006, after the IRB's approval had already expired (i.e. expiration, August 9, 2006), the IRB requested the investigator to submit a written summary report.

Also, we note that any studies that are reviewed and approved by the IRB after the November letter has been sent and before the first IRB meeting of the next calendar year will also not be reviewed until greater than one year after the study was initially approved. For example, if your IRB approves a study on December 1 of a given year after the November letter has been sent, then in November of the next calendar year, you would request that the clinical investigator submit a written progress/summary report by a given date in December. We note that by the time you review the study for continuing review at the first meeting of the subsequent calendar year, the study's original IRB approval would have expired. Thus, your IRB is not conducting continuing review of research at least once a year as described in your written procedure.

b. The IRB written procedures on continuing review state that the IRB requires investigators to submit written progress reports of their investigations to the IRB at least once a year. We note that two investigators failed to submit the written reports to the IRB by the December deadline date stated in your letter and that your IRB did not follow up with the investigators to ensure their compliance with the requirement. Specifically,

   i. As noted above, your IRB sent a letter dated November 13, 2006 to the investigator of the study "A Multicenter, Randomized, Double-Blind Study comparing the Clinical Effects of Intravenous [ ] with

Placebo in Pediatric Patients (Ages 6 to 14 Years) with Acute Asthma" requesting that the investigator submit a written progress report by December 22, 2006. The investigator, an IRB voting member, did not submit a written summary report to the IRB until February 6, 2007.

ii. The IRB sent a letter dated November 13, 2006 to the investigator of the study "Investigational Plan (Phase[ ]for the[ ]Study)" requesting a written progress report by December 22, 2006. Per the report to the Center, FDA Investigator Wright noted that as of the date of the FDA inspection (i.e. July 2007), the investigator had not submitted a summary report to the IRB as requested in the November 2006 letter.

4. **For other than expedited reviews, the IRB failed 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)].**

Specifically, we note that the meetings below did not have either a majority of members present and/or the presence of a nonscientific member:

a. At the January 4, 2005 meeting only 5 of 11 IRB members were present; thus a majority of the IRB members were not present at the meeting.

b. The nonscientific member was not present at the August 9, 2005 meeting. In addition, we note that Dr.[ ]a voting member, was conflicted during the discussion and vote of his study. As Dr.[ ]was conflicted, he was to be excused from participating in the review and approval of his study and thus no longer counted towards the majority of members present. Therefore, during the discussion and vote of his study, the IRB lost a majority of its members present at the meeting.

c. At the November 3, 2005 meeting only 3 of 11 IRB members were present. This meeting did not have a majority of the members present and also did not have a nonscientific member present.

d. At the February 7, 2007 meeting, there was not a nonscientist member in attendance.

5. **The IRB failed to conduct continuing review of research at intervals of not less than once per year [21 CFR 56.109(f)].** Specifically,

   a. The IRB approved the study entitled "A Multicenter, Randomized, Double-Blind Study Comparing the Clinical Effects of Intravenous[ ] with Placebo in Pediatric Patients (Ages 6 to 14 Years) with Acute Asthma" at the August 9, 2005 IRB meeting. The IRB did not request the investigator submit a written progress report until November, 2006 after the study's IRB approval had expired (i.e. expiration, August 9, 2006). The investigator submitted the written progress report to the IRB on February 6, 2007 and the IRB did not review and accept the report until February 7, 2007.

   b. In a letter dated March 3, 2005, the IRB informed the investigator that the study entitled an "Investigational Plan (Phase[ ]for the[ ]Study)" had been re-approved at continuing review. In the following year the investigator of this same study submitted a written progress report to the IRB on February 21, 2006. The IRB did not re-approve the study for continuing review until September 5, 2006.

   In addition, we note that in a letter dated November 7, 2006, the Medical Executive Committee of West Jefferson Medical Center notified the investigator that they had also re-approved the study for continuing review and that had retrospectively backdated the IRB's re-approval for continuing review to March 1, 2006. We note that it is inappropriate for an institution to backdate the IRB's approval.

6. **The IRB failed to determine at the time of initial review that studies involving children are in compliance with 21 CFR Part 50 Subpart D, "Additional Safeguards for Children in Clinical Investigations" [21 CFR 56.109(h)].**

   Specifically, the IRB approved the study "A Multicenter, Randomized, Double-Blind Study comparing the Clinical Effects of Intravenous[ ]with Placebo in Pediatric Patients (Ages 6 to 14 Years) with Acute Asthma" at the August 9, 2005 convened meeting. The IRB did not make the findings or document that the study was in compliance with 21 CFR 50 Subpart D. In addition, during the FDA inspection of July 2007, your IRB secretary noted that the IRB was not aware of your responsibilities under 21 CFR 50 subpart D.

7. **The IRB failed to request sufficient information to determine whether studies meet the criteria for IRB approval of research at continuing review [21 CFR 56.111].**

   The IRB's written procedures note that investigators are to submit a written progress report to the IRB of their investigation at least once a year. In the letter sent to investigators to remind them to submit a written progress report, the IRB only requests information that includes the number of patients enrolled during that year, their outcomes, any changes to the approved research and other pertinent information. We note that because the letter request fails to specify any necessary details concerning these categories of information, the contents of these written progress reports are left to the discretion of the investigator and can include limited to no information about adverse and/or serious adverse events, protocol deviations, current protocol and informed consent document in use, recruitment materials being utilized, changes in risk/benefit identified by the investigator or sponsor during the course of the study, etc. Thus, the IRB failed to request sufficient information to determine whether studies met the criteria for IRB approval under 21 CFR 56.111 at continuing review.

8. **The IRB failed to prepare the minutes of IRB meetings in sufficient detail to show actions taken by the IRB, the vote on actions, including the number of members voting for, against and abstaining [21 CFR 56.115(a)(2)].** Specifically,

   a. In all the IRB meetings that took place in 2005-2006 and the meeting on February 7, 2007, the minutes were not prepared in sufficient detail to show the vote on the IRB actions, including the number of members voting for, against and abstaining on the actions. We note that the statement "motion made, second and carried to approve" was used for all studies that were approved by the IRB.

   b. The IRB meeting minutes do not detail all of the actions taken by the IRB. Specifically,

      i. In the review of records related to the study "A Multicenter, Randomized, Double-Blind Study Comparing the Clinical Effects of Intravenous[ ]with Placebo in Pediatric Patients (Ages 6 to 14 Years) with Acute Asthma", we note that the IRB sent a letter to the clinical investigator informing him that the IRB reviewed and accepted his summary report and study closure notification at the February 7, 2007 meeting. However, there was no mention of this study in review of the minutes for the February 7, 2007 meeting.

ii. The investigator for the study "Investigational Plan (Phase [ ] for the [ ] Study)" submitted a summary report to the IRB in a letter dated February 2, 2005. In a letter dated March 3, 2005, the IRB informed the investigator that the study had received continuing approval. There is no mention of this study in the March 1, 2005 IRB meeting minutes.

c. During the January 4, 2005 and January 3, 2006 IRB meetings, the minutes indicate that the IRB held one vote to approve collectively all studies that were undergoing continuing review. However, the minutes for these meetings do not indicate votes for IRB action on the individual studies, including the numbers of members voting for, against, or abstaining.

This letter is not intended to be an all-inclusive list of deficiencies regarding your IRB's responsibilities. Within fifteen (15) working days of your receipt of this letter, the FDA requests that you address these deficiencies in writing and inform us of corrective actions and procedures that you have or will take to prevent and ensure that similar violations will not occur in any on-going or future studies. Please note that at the appropriate time FDA will conduct additional inspections to ensure that adequate corrective actions have implemented.

We appreciate the cooperation shown Investigator Wright during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Leslie K. Ball, M.D.
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/s/

LESLIE K BALL
02/25/2008