DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

E. Clinton Lawrence, MD
1364 Clifton Road, Room 607
McKelvey Lung Transplantation Center
Atlanta, GA 30322

Ref: 06-HFD-45-0804

Dear Dr. Lawrence:

Between November 9, 2005 and November 29, 2005, Ms. Stephanie E. Hubbard, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of a clinical investigation (protocol[ ] entitled "A Phase III, Randomized, Double-blind, Placebo-controlled Safety and Efficacy Study of[ ]Treatment with an Open-label[ ]Arm in Patients with Pulmonary Arterial Hypertension") of the investigational drug[ ] performed for[ ].

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Hubbard presented and discussed with you Form FDA 483, Inspectional Observations. Your January 26, 2006 response to the Form FDA 483 does not adequately address these deficiencies, and the agency's concerns were not allayed by additional information we have considered since then. We wish to emphasize the following:

1. FAILURE TO PERSONALLY CONDUCT OR SUPERVISE THE CLINICAL INVESTIGATION [21 CFR 312.60].

When you signed the investigator statements (Form FDA 1572) for the above-referenced clinical investigation, you agreed to take on the responsibilities of a

clinical investigator at your site. Your general responsibilities (21 CFR 312.60) include ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety and welfare of subjects under your care; and ensuring control of drugs under investigation. You specifically agreed to personally conduct the clinical studies or to supervise those aspects of the studies that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as clinical investigator, you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that clinical trials were conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protected the rights, safety, and welfare of human subjects.

Despite numerous indications of problems with the conduct of studies for which you were responsible, you did not provide adequate supervision or institute actions to correct problems in a timely manner. In your written response to the 483 observations, dated January 23, 2006, you stated that you implemented corrective action after a second study monitor was assigned to your site in November, 2004, and alerted you to problems that had arisen in the conduct of the study. However, the monitoring log showed that your site was visited several times between June 11, 2003 and October 29, 2004 by a study monitor who identified numerous protocol deviations/violations for your site. In addition, in a letter dated January 7, 2005, the second monitor stated that he could find no notes from you since November of 2003 on any patients enrolled in this study. This timeline shows that as an investigator, you failed to have adequate involvement and oversight over this study during the course of the study.

2. FAILURE TO ENSURE THAT THE INVESTIGATION IS CONDUCTED ACCORDING TO THE SIGNED INVESTIGATOR STATEMENT AND INVESTIGATIONAL PLAN [21 CFR 312.60].

a. You failed to seek the sponsor's approval prior to implementing changes to the study protocol. Specifically the protocol states that weeks 1, 2, 4, 8, 10, 14, and 16 visits could be completed through telephone contact and blood sample collection at remote locations. We note that your site submitted a request dated October 15, 2004, to the IRB to replace these telephone contacts with letters, (i.e. questionnaires) that were to be sent to the subjects to fill out every two weeks. The IRB approved the use of the questionnaires on 10/25/04.

Our investigation found that in letters dated November 15, 2004 through November 24, 2004 to study subjects found in your study records, five subjects were sent these questionnaires. We note that in an email dated 12/15/04 found during the inspection, your research coordinator acknowledged that there was no written documentation at your site showing that approval for this change in the protocol had been granted by the study sponsor. In an email dated 12/17/04, the sponsor's representative stated that the purpose of biweekly phone contacts was to assure patient safety. The sponsor's representative granted the use of these

questionnaires but placed stipulations on their use. The above timeline of events demonstrates that your site implemented changes to the study protocol prior to receiving written approval by the sponsor.

b. You failed to ensure that subjects met all protocol required eligibility requirements prior to enrolling the subjects into the study, and further failed to complete all protocol required screening and baseline procedures prior to randomization of subjects. Specifically we note that 9 of 16 subjects enrolled at your site were ineligible and did not receive exemptions from the sponsor prior to enrollment:

   i. The protocol required that pulmonary function tests be performed within 3 months before study entry. We note that subjects 015, 024, 163, and 174 did not have pulmonary function tests performed within that 3 month window.

      In your written response dated January 23, 2006, you stated that you reviewed the entries but did not use a calendar, and that you depended on your research coordinator to confirm the dates. As the principal investigator, it is your responsibility to have oversight over this study and to ensure that all eligibility requirements are met prior to enrolling subjects into the study.

   ii. The protocol excluded subjects from the study if they had uncontrolled systemic hypertension as evidenced by systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mg Hg. In addition, the protocol specified that the blood pressure be taken as a part of the baseline evaluation. We note that there was no baseline blood pressure taken for subject 095 at study entry, that the blood pressure used for the source data baseline visit was taken from a pulmonary consult dated several days prior to enrollment of the subject into the study, and that the blood pressure identified in the pulmonary consult (186/126) would have excluded the subject from participation in the study.

   iii. The protocol excluded subjects that had taken any new type of treatment for pulmonary arterial hypertension within 30 days before study entry. The concomitant medication source document found at your site shows that subject 095 was taking both Lasix and Aldactone for pulmonary arterial hypertension within several days prior to study entry. It was noted in records obtained at your site that the sponsor did not grant exception for this subject to be enrolled into the study.

      In your written response dated January 23, 2006, you stated that Lasix is not a primary treatment for pulmonary arterial hypertension but is used for peripheral edema; hence you felt no exception was required. We note, however, that your site's concomitant medications source record which shows that both Lasix and Aldactone were prescribed to the subject for pulmonary arterial hypertension (PAH). In addition we note that when your site was queried about whether or not the sponsor granted exception for

enrollment of this subject due to use of Lasix, your records show that no exception was granted.

iv. The protocol required that subjects included into the study, have a cardiac catheterization test showing a pulmonary vascular resistance (PVR) > 3 mm Hg/L/min, performed within 6 months before study entry. We note that subject 184 did not have a cardiac catheterization test prior to enrollment into the study.

In your written response dated January 23, 2006, you stated that you personally retrieved and reviewed the raw data from the patient's medical record and catheterization report and found that the calculated PVR exceeded 3 mm Hg/L/min. We note that you did this only in response to the FDA Form 483. Our investigation found no evidence that you performed this calculation prior to enrollment of the subject.

v. The protocol required that subjects have baseline physical examinations performed. We note that subjects 001, 095 and 129 did not have complete physical examinations performed as a part of their baseline evaluation.

In your written response dated January 23, 2006, you stated that you felt that vital signs shown within the research note for subject 001 were an adequate baseline physical examination and that both subject 095 and 129 had physical examinations documented in their medical records. We note that the protocol states that physical examinations must be done as a part of the baseline evaluation which can occur on the same day as screening or at any time within 7 days of the initiation of the study drug. The protocol further states that physical examinations, including taking the vital signs (sitting blood pressure, respiratory rate, heart rate and temperature), height and body weight must be done. The FDA field investigator noted that during the course of the audit, both she and your current research coordinators examined the medical records for subject 095 and 129 and were unable to find any physical examinations for these two subjects that would qualify them as having a complete baseline physical exam. Furthermore information placed into the source records for subject 095's baseline physical examination for this study, was taken from a pulmonary consult dated several days prior to enrollment of this subject into the study.

vi. The protocol required that women of child-bearing potential be using two forms of medically acceptable contraception and have a negative pregnancy test at screening and monthly thereafter. We note that subject 126 was noted to be of child bearing potential at screening; however there was no documentation that she was using any form of medically acceptable contraception. In your January 25, 2006 letter you noted that her husband had a vasectomy 18 years ago.

vii. The protocol specified that an ECG was to be performed at screening. We note that subject 184's source document states that no ECG was performed for this subject.

3. FAILURE TO MAINTAIN ADEQUATE RECORDS OF THE DISPOSITION OF THE DRUG [21 CFR 312.62(a)]

You failed to maintain adequate records of the disposition of the drug, including the dates, quantity, and use by subjects. Our investigation was unable to find drug accountability logs for 10 of 16 subjects enrolled at your site and found numerous discrepancies concerning drug dispensation in your source documents. Specifically, we note the following:

a. In a note to file dated 08/10/05 and signed by you, you stated that the previous study coordinators did not maintain the drug accountability log for subjects enrolled in this study. In an addendum to this note to file dated 10/31/05, you further stated that individual patient records (logs) were kept for the first 7 subjects and the site did not maintain a central drug accountability log for the 9 subsequent patients. During the investigation we found that only 6 subjects' drug accountability logs were maintained at the site.

b. The protocol required that the investigator is responsible for implementing a system for documenting study drug accountability at the clinical site and that patient accountability for the study drug will be ensured through patient interviews and study drug reconciliation at selected visits, before dispensing study drug supplies for the next visit interval. You failed to maintain adequate and accurate records concerning the amount of study drug consumed, missed, discarded or returned. For example,

i. For subject 001 we note several discrepancies:

1) The Subject[ ]Accountability Log documents the return of 90 tablets from 144 tablets dispensed on 10/27/03. However, the[ ] Drug Accountability Logs case report form reports that 78 tablets were returned.

In your written response dated January 23, 2006, you stated that the correct entries were originally entered on the case report form and then changed to incorrect answers. We can not determine the accuracy of this explanation because it was your own research coordinator with primary oversight over this study, who made the changes in the case report form.

2) The[ ]Accountability Log shows that 126 tablets were dispensed to this subject on 7/21/03 with a notation "took Day 1– then drug held until Day 14" and 27 tablets returned on 9/5/03. This contradicts the information in the[ ] Drug Accountability Logs

case report form which shows that 144 tablets were dispensed on 7/21/03 and 0 tablets returned on 10/3/03.

In addition, we note that there were discrepancies found within the source documents for why subject 001 did not take study drug from days 2-13. A data clarification form dated 1/24/05 was sent to your site asking clarification as to why the patient skipped the 14 doses of study due to "Drug Holiday from Day 2-13". A hand written note on this data clarification form stated that per all available source records, it was unclear why the patient held the drug from day 2-13. We note that the response given by you to the query contradicts the research notes found in subject's source records. The research note dated 7/21/03 states that the patient took 1st dose of drug on this day. Dr.[ ]was noted to have prescribed an antibiotic for treatment of the subject's illness and subsequently placed a hold on the study drug for 2 weeks due to possible synergistic effect of Biaxin on[ ]

3) We note that the[ ]Drug Accountability Logs case report form for this subject had many cross-outs with correction dates of 2004 even though the subject was dispensed drug from July – October, 2003.

ii. Subject 015's[ ]Accountability Log documents the return of 33 tablets on 2/2/04. This however, contradicts the[ ]Drug Accountability Logs case report form that the 33 tablets were returned on 01/16/04.

iii. For subject 095, there is contradictory information concerning the disposition of the drug during week 12-18. The source document worksheet for week 18 states that the subject ran out of drugs before she could come in even though she had been dispensed 144 tablets. Per your response to the data clarification form dated 1/4/05 questioning the drug accountability for week 12-18 for this subject, you stated that the unused tablets were discarded by the patient.

In your written response dated January 23, 2006, you stated that this query was answered by a contract coordinator and it was unclear why the response says "pt. discarded". We can not determine the accuracy of this explanation because it was your own research coordinator with primary oversight over this study, who originally documented the drug accountability for week 18 for this subject.

iv. The[ ]Drug Accountability Logs case report form for subject 113 reported that 15 of the 144 tablets dispensed on 06/07/04 were returned by the subject on 7/21/04; however, the Clinical Materials Return Forms document the return of only 9 tablets.

v. The drug accountability source worksheets for subjects 174 and 184 at Week 18 were not completed. Therefore the information in the[ ]Drug Accountability Logs case report form for this time period could not be verified through the subject's source data.

vi. The[ ]Drug Accountability Logs (DAL) case report form for subject 199 documents the return of 6 tablets on 09/15/04, 15 tablets on 10/28/04 and 48 tablets on 11/30/04. This contradicts the amount of drug returned to the site per the Clinical Materials Return Form, which documents the return of 6, 9, and 32 tablets.

vii. The[ ]Drug Accountability Logs (DAL) case report form for subject 230 documents the return of 15 tablets on 10/07/04, 15 tablets on 11/18/04 and 0 tablets on 1/06/05. The Clinical Materials Return Forms document the return of 6, 27, and 0 tablets.

In your written response dated January 23, 2006, you stated that that the original drug use in the drug accountability log was correct and you did not know why the correct information was changed to incorrect information. We note that those entries to which you stated are incorrect were made to drug accountability log by your own research coordinator after the subject had completed and returned all study drugs.

4. FAILURE TO PREPARE AND MAINTAIN ADEQUATE AND ACCURATE CASE HISTORES [21 CFR 312.62(b)].

a. You failed to follow the protocol-specified guidelines for conducting the 6 min walk test which states that the start and stop times for the walk should be recorded. We note that per the monitoring site records, you and your investigative team were trained on the study prior to its initiation. We note that the following subjects did not have start and stop times for their 6 min walk:

i. Subject 001- The start/stop times for the 6 min walk was not documented at Screening (7/14/03), week 6 (9/5/03), week 12 (10/10/03), and week 18 (11/21/03).

ii. Subject 002 - The start/stop times for the 6 min walk were not documented at Screening (7/22/03), week 6 (9/11/03), and week 12 (10/23/03).

iii. Subject 095 - The start/stop times were not completed for this subject at week 14.

iv. Subject 184 - The start/stop times for the 6 min walk was not documented at screening (7/15/04) and week 6 (8/27/04).

In a letter dated November 6, 2003, the study monitor identified that your site was not recording the actual walk time as required by the protocol. We note further

that in a memo to file dated 1/13/04 and signed by you, that you stated that the 6 min walk test used by [ ] includes a stop watch to ensure that the patient was tested for an exact 6 minutes and that the hospitals form does not include recording the actual start and stop times. You subsequently stated that as of the beginning of November 2003, a new source document form was created for the [ ] trial to include the recording of actual start and stop times. In the review of source documents obtained at your site, we note, however, that the following walk tests that occurred after the beginning of November 2003, still did not have start/stop times documented: Subject 001 – week 18 (11/21/03); Subject 095 – week 14 in lieu of week 12 (07/09/04); Subject 184 – screening (7/15/04) and week 6 (8/27/04) . In addition we note that source documents show that at least one subject (002), had a 7 min walk test at week 18 not a 6 min walk test.

b. There was a discrepancy noted between information in the source documentation and case report form for subject 002. The source data stated that the Borg Index and World Health Organization (WHO) functional classification were documented for subject 002 at week 6; however the case report form for subject 002 stated that this was "ND" (not done).

5. FAILURE TO PROMPTLY REPORT TO THE IRB ALL UNANTICIPATED PROBLEMS AFFECTING THE RISK TO HUMAN SUBJECT OR OTHERS [21 CFR 312.66].

We note that you failed to promptly report to the IRB three Serious Adverse Events (SAE) that occurred at your site.

a. The source documents show that subject 129 was admitted to the [ ] Hospital for Atrial Septal Defect (ASD) repair and right pulmonary valve baffle on 7/14/04. Per your site's SAE record, your site learned of this SAE on 7/14/04 but did not notify the IRB until 12/14/04.

b. The source documents show that subject 199 had a case of atrial fibrillation on 8/4/04. This SAE was not reported to the IRB until 12/10/04. We note that in your letter to the IRB dated 12/10/04, the subject had this SAE in August, 2004, was admitted to [ ] Hospital for cardioversion, and was being followed by your co-principal investigator, for his condition.

c. The source documents show that subject 174 was admitted to [ ] Hospital in [ ] for evaluation of fluid retention and congestive heart failure on 10/20/04. Per your site's SAE record, your site learned of this SAE 10/20/04 but you did not notify the IRB until 11/10/04.

In your written response dated January 23, 2006, you stated that for subject 174 that there are long pages of phone notes by your research coordinator dated 10/27/04 indicating that this is the date that your site learned of the event and the IRB was subsequently notified on 11/10/04. Your written response to this finding, however is

in contrast to the SAE record found at your site during the FDA audit showing that your site learned of this SAE on 10/20/04.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You must address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you must notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Leslie K. Ball, M.D., at (301) 594-1032, FAX (301) 827-5290. Your written response and any pertinent documentation should be addressed to:

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Gary Della'Zanna
Director
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gary DellaZanna
11/3/2006 12:34:47 PM