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## Inspections, Compliance, Enforcement, and Criminal Investigations

Snow, Lamar L. M.D. 9/29/10



Department of Health and Human Services

Public Health Service  
Food and Drug Administration  
Silver Spring, MD 20993

### WARNING LETTER

**CERTIFIED MAIL  
RETURN RECEIPT REQUESTED**

Ref: 10-HFD-45-09-03

L. Lamar Snow, M.D.

**(b)(6)** (home address)

Dear Dr. Snow:

Between April 27 and May 7, 2009, Ms. Barbara Wright, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of clinical investigations [protocol 008, parts A and B, both entitled "A multi-center randomized, double-blind, placebo-controlled trial of ibuprofen injection (IVIb) for treatment of pain in post-operative adult patients"] of the investigational drug ibuprofen (Amelior), performed for Cumberland Pharmaceuticals.

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, the documents submitted with that report, and your written response dated October 16, 2009, 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. Wright presented and discussed with you Form FDA 483, Inspectional Observations.

**1. You failed to ensure that the investigation was conducted according to the signed investigator statement, in that you failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].**

When you signed the Statement of Investigator (Form FDA 1572) for the above referenced clinical trial, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities as a clinical investigator include ensuring that the clinical trial 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 [21 CFR 312.60]. By signing Form

FDA 1572, you specifically agreed to personally conduct the clinical trial or to supervise those aspects of the trial that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as a 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 the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protects the rights, safety, and welfare of human subjects.

We note that your failure to adequately supervise this study led to significant problems identified below with the conduct of the study.

**2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].**

a. The primary efficacy endpoint of the protocol was to measure the reduction in the requirement for morphine use in the 24 hours following surgery measured by total morphine usage compared to placebo. We are unable to determine the total morphine dose administered to subjects as documented in the hospital records, compared to the documents in the subjects' files. Examples include, but are not limited to, the following:

i. Regarding Subject 3255, enrolled in protocol 008, part A, there are discrepancies in the total administered dose of morphine, as reflected in hospital records and the Case Report Form (CRF). The CPI-CL-008 Post Operative Pain Source Document and the CRF contain documentation of morphine administered consistently 40 or 41 minutes after the hour (e.g., 1340, 1440, 1541, 2241, etc.), and indicate that the subject was given a total dose of 37 mg of morphine between **(b)(6)**. However, summing up the doses in the hospital Post Anesthesia Care Unit (PACU) report printed on **(b)(6)** (full year not legible) and the hospital Morphine Patient Control Analgesia (PCA) report reveals that the subject received a total of 18 mg of morphine between **(b)(6)**. In addition, based on the hospital's narcotic waste documentation, only a total of 15 mg of morphine was administered to this subject. A CRC Notes form in the subject's case history addresses the discrepancy in the hospital records but does not offer any explanation; furthermore, it does not address the discrepancy between the total doses of morphine reflected in these hospital records and the CRF.

ii. Regarding Subject 7060, enrolled in protocol 008, part B, the CRF contains documentation to indicate that the subject was given a total of 20 mg of morphine between **(b)(6)**. However, hospital records indicate that the subject received a different total amount of morphine. For example, the hospital PACU report dated **(b)(6)**, indicates that the subject received a 10 mg dose of morphine; and the hospital Medication Administration Record (MAR) reveals that a total dose of 31.75 mg of morphine was administered to the subject via patient controlled analgesia between **(b)(6)**. Viewed together, these two hospital records (the MAR and PACU reports) indicate that the subject received a total dose of 41.75 mg of morphine, not the 20 mg reported in the CRF.

iii. Regarding Subject 6057, enrolled in protocol 008, part B, the CRF contains documentation to indicate that the subject was given a total of 26 mg of morphine between **(b)(6)**, in the 24 hours following surgery. However, the hospital PACU report dated **(b)(6)**, revealed that the subject received a 4 mg dose of morphine; and the hospital MAR revealed that a total dose of 39 mg of morphine was administered to the subject via PCA between **(b)(6)**. Viewed together, these hospital records indicate that the subject received a total dose of 43 mg of morphine, not the 26 mg reported in the CRF.

iv. Regarding Subject 8058, enrolled in protocol 008, part B, the CRF indicates that the subject was given a total of 48 mg of morphine (40 mg from PCA and 8 mg from PACU) between **(b)(6)**. However, the PCA Patient Assessment 24 Hour Flowsheet indicates that a total dose of 17 mg of morphine was administered to the subject via PCA between **(b)(6)**, not the 40 mg reported in the CRF.

b. Regarding protocol 008, part A, there were discrepancies between the hospital records and other documentation in Subject 2256's file regarding the time of study drug administration. Specifically, the hospital MAR indicates that Dose 2 of the study drug was to be administered at 14:20, but was given at 15:30. However, the CPI-CL-008 Post Operative Pain Source Document indicates that the subject received Dose 2 from 14:20-14:50.

c. Regarding protocol 008, part B, there was a discrepancy between the hospital records and other documentation in subject 5059's file regarding the time of Imitrex administration, a concomitant medication. Specifically, the hospital MAR indicates that Imitrex was given at 8:00 a.m. on **(b)(6)**. However, the concomitant medications page of the CRF indicates that Imitrex was dispensed at 9:40 a.m.

**3. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].**

a. Protocol 008, part A specified that if any adverse event (AE) occurs during or after dosing with the study drug, the investigator will record the following information on the appropriate pages of the CRF: the AE; whether or not the AE was judged to be study drug related; the date and time of occurrence; date and time of resolution (or a statement to indicate that it is still ongoing); severity of the AE; seriousness of the AE; relationship of the AE to study drug administration; treatment used; and outcome of the AE. The Discharge Summary noted that Subject 1252 had an episode of about 48 hours of vomiting requiring intravenous fluids. However, vomiting was not reported as an adverse event on the CRF.

b. Protocol 008, part A specified that the study will be double-blind and that the subject, investigator, and sponsor will be blinded to the assigned treatment until all subjects have completed the protocol and after the study database has been analyzed. The protocol also specified that a subject's treatment assignment will be revealed only in the case of an emergency, when it would be imperative for the assignment to be known. Despite the absence of any indication that an exception was warranted, the hospital Medication Administration Record (MAR) for Subjects 2251 and 4251 revealed their particular treatment arm (400 mg of ibuprofen) to study staff, in violation of the protocol.

c. Protocol 008, part A specified that a physical examination was required during the screening/baseline period (Hour -72 to Hour 0). The protocol-required screening/baseline physical examination for Subject 2251 was performed on January 18, 2006. However, the surgery and subsequent treatment with study drug did not take place until **(b)(6)**, which is more than 72 hours from the date of the screening physical examination.

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 should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken 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 Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity (formerly Lewin), M.D., M.P.H.  
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Good Clinical Practice Branch I  
Division of Scientific Investigations  
Office of Compliance  
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Building 51, Room 5354  
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Sincerely yours,  
{See appended electronic signature page}  
Leslie K. Ball, M.D.  
Director  
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Reference ID: 2838662

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/s/

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LESLIE K BALL  
09/29/2010

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