DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Nasim Golzar, MD
26516 Crenshaw Blvd
Palos Verdes Peninsula, CA 90274-3970

Ref: 08-HFD-45-0204

Dear Dr. Golzar:

Between July 24, 2007 and August 22, 2007, Ms. Yvette Lacour-Davis representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations of the investigational drug [ ] performed for [ ]

1. Protocol [ ] entitled "Prospective, Randomized, Double-Blind, Three-armed, Multi-Center, Comparative Trial to Evaluate the Efficacy and Safety of [ ] BID for 7 days vs. [ ] BID for 10 days vs. Cefuroxime axetil 250 mg PO BID for 10 days in the Treatment of Acute Bacterial Sinusitis".

2. Protocol [ ] entitled "Prospective, uncontrolled, open label, multi-center clinical trial evaluating the efficacy and safety of [ ] BID for 10 days in the teatment of patients with community acquired pneumonia".

3. Protocol [ ] entitled "Prospective, randomized, double-blind study comparing [ ] BID for 5 days with Azithromycin for 5 days (500 mg PO day 1, then 250 mg PO OD days 2-5) in the treatment of patients with acute exacerbation of chronic bronchitis".

This inspection is a part of 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 the study have been protected.

From our review of the establishment inspection report, the documents submitted with that report and your September 18, 2007 letter written in response to the Form FDA 483, "Inspectional Observations", we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical

investigations and the protection of human subjects.

We are aware that at the conclusion of the inspection, Ms. Lacour-Davis presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. **You failed to obtain informed consent of each human subject in accordance with 21 CFR 50 [21 CFR 312.60].**

   Specifically, 21 CFR 50.20 states that except as provided in 21 CFR 50.23 and 21 CFR 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. In addition, except as provided in 21 CFR 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB [21 CFR 50.27(a)].

   The following violations were noted in reference to Protocol [ ]

   a. Four of 23 subjects (4011, 4015, 4019, and 4021) had protocol-specified baseline laboratory blood samples drawn prior to signing and dating the informed consent document.

   b. The IRB approved informed consent document required documentation of the actual time in which legally effective informed consent of the subject was obtained. There was no documentation of the actual time in which subjects 4016, 4017 and 4018 signed and dated the consent forms. In addition, we were unable to verify that these subjects signed and dated the informed consent forms prior to any protocol specified procedures being conducted on them.

   In your September 18, 2007 written response, you noted that in all cases the subject had been verbally consented prior to any study procedures being performed. Verbal consent, however, is inadequate. The exceptions in 21 CFR 50.23 and 21 CFR 50.24 to the informed consent requirements, as well as the exception in 21 CFR 56.109(c) to use of the written consent form approved by the IRB, did not apply to the conduct of this study.

2. **You failed to ensure that the studies were conducted according to the approved protocols [21 CFR 312.60].**

   a. The following violations were noted for Protocol [ ]

      i. The protocol specified that to be included in the study the patient must have a clinical diagnosis of acute sinusitis with signs and symptoms present for > 7 days but < 28 days as defined by A) radiographic and B) clinical criteria. The radiographic evidence for inclusion in the study included the presence of any of the following: evidence of air-fluid levels, opacification, and/or ≥ 6 mm mucosal thickening. Ten of the 30 enrolled subjects [43007, 43009,

43011, 43012, 43013, 43014, 43015, 43019, 43021, and 43030] failed to meet the protocol required radiographic documentation for inclusion in the study. Specifically, x-rays for these subjects failed to demonstrate acute sinusitis.

ii. The protocol specified that subjects who received systemic antimicrobial agents for more than 24 hours within 7 days prior to enrollment had to be excluded from the study. Subject 43002 was enrolled in the study on 12/12/00 even though the subject had been taking Doxycycline during this exclusionary time period.

iii. For 9 of 30 subjects (43001, 43002, 43003, 43004, 43005, 43006, 43009, 43013, and 43014), a paranasal[ ]view x-ray was not done at the Test of Cure visit, as required by the protocol.

In your September 18, 2007, written response, you noted that the patients all had clinical signs and symptoms highly suggestive of acute bacterial sinusitis and would have been treated with antibiotics regardless of enrollment in the study. This answer is inadequate. FDA regulations require that investigators enrolling subjects into FDA regulated clinical research studies follow the investigational plan to help ensure that data collected during the study is reliable and that the rights, safety and welfare of research participants are protected.

b. Protocol[ ]specified that subjects who were prematurely withdrawn from the study were to have a complete clinical assessment, a sputum specimen collected for gram stain, culture and susceptibility testing, and all safety laboratory investigations performed as required by the protocol. The protocol further noted that if an alternate antimicrobial agent was prescribed, this testing should be performed prior to initiation of therapy with the alternate agent. In addition, the protocol specified that these prematurely withdrawn subjects were to have a clinical assessment, including a chest x-ray performed 2 to 4 days after the last dose of therapy with the alternate antibiotic. We note that Subjects 17001 and 17003 were prematurely withdrawn from the study, but did not have their sputum collected, nor did they have post alternate antibiotic chest x-rays taken as required by the protocol.

c. The following violations were noted for Protocol[ ]

i. Protocol version #1, amendment #1, (dated October 15, 2000) specified that for a course of therapy to be microbiologically valid, inclusion in the study required that at least one causative organism be identified in an appropriate pre-treatment sputum specimen (i.e. epithelial cells $\leq$ 10/low power field (lpf), WBC $\geq$ 25/lpf). Protocol version #2, amendment #2, (dated December 8, 2000) [hereinafter "the protocol"] further clarified this inclusion criterion noting that if the sputum sample at enrollment had < 25 WBC/lpf, obtaining another sputum sample that demonstrated > 25 WBC/lpf would be acceptable, provided that the patient has received no more than 48 hrs of study medications at the time the second sputum sample was collected.

Subjects 4001 and 4004 were enrolled in the study even though their sputum samples did not have the protocol required inclusion criterion of > 25 WBC/lpf.

ii. The protocol specified that at the time of enrollment, a medical history was to be obtained, including past history of respiratory illnesses, smoking history, an inquiry regarding any underlying illness or conditions, and general health status. A complete medical history was not obtained for Subjects 4001, 4002, 4003, and 4004 as required by the protocol.

iii. The protocol specified that at the time of enrollment, a baseline urinalysis test would be performed. Subjects 4001 and 4002 did not have this test as required by the protocol.

iv. The protocol specified that within 48 hrs prior to enrollment, the subject must provide a purulent or muco-purulent sputum by deep expectoration for gram stain, culture, and susceptibility testing. Subject 4010 was unable to produce the protocol required sputum specimen for enrollment; however you still dispensed study medication to this subject.

v. The protocol specified that at the Test of Cure visit, subjects were to have a serum pregnancy test. Subjects 4002, 4003, and 4007 did not have the test as required by the protocol.

In your September 18, 2007, written response, you noted that patients coming into the office with an acute infection need to be treated quickly. You further stated that study participants had to be screened, enrolled and randomized in a manner that is typically much faster than for other types of non-infectious disease clinical trials; hence there was no in-depth review of screening with all lab and x-ray data in hand before randomization. This answer is inadequate. FDA regulations require that clinical investigators enrolling subjects into FDA regulated clinical studies follow the investigational plan to help ensure the reliability of data collected during the study and that the rights, safety and welfare of research participants are protected.

3. **You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b)].**

a. The clinical signs and symptoms of disease that you reported in the electronic case report form for protocol #[ ]could not be verified against information within the source documents for the 17 of 30 subjects enrolled in the study: 43001, 43002, 43004, 43005, 43006, 43007, 43008, 43009, 43010, 43011, 43012, 43013, 43014, 43015, 43016, 43017, and 43019. A memorandum to file dated 2/12/2001, found during the FDA inspection, noted that "[C]urrently, for all study visits up to 2/12/2001, all specific sinusitis symptoms, and the subsequent ratings entered in the[ ]system, have on occasion no supporting documents. Going forward, all specific sinusitis

symptoms, or any visit specific data entered into the[ ]system shall have supporting documents." FDA confirmed the lack of source documents during its inspection. We note that all 17 subjects noted above were enrolled into the study prior to 2/12/2001.

b. We note that there was discrepant information between the case report form and the source documentation for the baseline clinical signs and symptoms of disease at the pre-therapy visit on 1/24/01, for Subject 4001 enrolled in protocol #[ ]Specifically, on 4/12/01, you signed and dated a change to the case report form for Subject 4001, which noted that the subject had moderate and not mild wheezing. However, the P.V. Family & Immediate Medical Care source document completed for the pre-therapy visit on 01/24/01 only noted that Subject 4001 had increased wheezing at this visit and did not note the extent of the wheezing.

4. **You failed to maintain adequate investigational drug disposition records with respect to quantity [21 CFR 312.62(a)].**

Specifically, the Inventory Drug Disposition Log for Subject # 17001 enrolled in protocol #[ ]lists the number of tablets returned as 15 on 12/30/00. However, the electronic Case Report Form, lists the number of tablets returned by the subject 12/30/00 as 12 tabs.

5. **You failed to assure Institutional Review Board (IRB) continuing review of clinical investigation [21 CFR 312.66].**

Specifically, 21 CFR 312.66 requires clinical investigators to assure that all changes in the research activity are promptly reported to the IRB. An amendment to Protocol [ ]was made on October 16, 2000. However, during the FDA inspection you failed to provide a copy of the IRB approval of the October 16, 2000 amendment. Thus, you have failed to demonstrate that you promptly reported this change in research activity to the IRB.

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 Tejashri Purohit-Sheth, M.D., at 301-796-3402; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

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Sincerely yours,

{See appended electronic signature page}

Leslie Ball, MD
Director
Division of Scientific Investigations
Office of Compliance
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Leslie Ball
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