DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 27 2003

WARNING LETTER

CERTIFIED MAIL - RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

William N. Sokol, M.D.
2011 W. Cliff Drive, Suite 7 & 8
Newport Beach, California 92660

Ref: 02-HFD-45-0501

Dear Dr. Sokol:

Between April 10 and May 9, 2001, Ms. Diane Van Leeuwen and Mr. Richmond K. Yip, representing the Food and Drug Administration (FDA), conducted an inspection of the following clinical studies in which you participated:

Protocol [redacted] – A Multinational, Randomized, Double-Blinded, Active-Controlled, Study for Evaluation of the Efficacy and Safety of Oral [redacted] Once a Day for 5 Days vs. Cefuroxime Axetil 250 mg Twice a Day for 10 Days in the Treatment of Acute Maxillary Sinusitis in Adults.

Protocol [redacted] – An Open Label Multicenter Non-Comparative Study of Oral [redacted] In The Treatment of Acute Bacterial Sinusitis In Patients Undergoing Sinus Aspirate.

Protocol [redacted] **(Glaxo Wellcome)** – A Randomized, Double-Blind, Parallel Group Trial Assessing the Efficacy and Safety of Fluticasone Propionate Inhalation Powder (250mcg QD) and Placebo In Subjects Greater Than 12 Years of Age With Chronic Asthma.

Protocol [redacted] **(Glaxo Wellcome)** – A Randomized, Double-Blind, Parallel-Group Study Evaluating The Protective Effects Of The Salmeterol Xinafoate/Fluticasone Proprionate Combination Product (50/100mcg BID via DISKUS) Against Bronchospasms Induced by Activity As Measured by Exercise Challenge Testing In Adolescent And Adult Subjects Who Require Chronic Inhaled Corticosteriod Therapy For The Treatment Of Persistent Asthma.

Protocol [redacted] **(Glaxo Wellcome)** - A Randomized, Double-Blind, Parallel-Group Study Evaluating The Protective Effects Of The Salmeterol Xinafoate/Fluticasone Proprionate Combination Product (50/250mcg BID via DISKUS) Against Bronchospasms Induced by Activity As Measured by Exercise Challenge Testing In Adolescent And Adult Subjects Who Require Chronic Inhaled Corticosteriod Therapy For The Treatment Of Persistent Asthma.

Protocol [redacted] - Randomized, Investigator Blinded, MultiCenter, Comparison, Of Two Dosings During [redacted] vs. Amoxicillin/Clavulanate For The Treatment Of Acute Maxillary Sinusitis.

This inspection is part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure the protection of the rights, safety, and welfare of the human subjects of these studies.

We note that at the conclusion of the inspection, our personnel presented and discussed with you the items listed on the Form FDA 483, Inspectional Observations. We have reviewed the inspection report; documents submitted with that report; your May 18, 2001 letter addressed to Dr. John R. Martin, Branch Chief, GCP 1, Division of Scientific Investigations, Center for Drug Evaluation and Research, in response to the Form FDA 483 inspectional observations; and your letter to the Chairman of [redacted] Institutional Review Board, dated June 18, 2001. We find your responses to be unacceptable.

Based on evaluation of the information obtained during the inspection, we have determined that you violated FDA regulations governing the proper conduct of clinical studies involving investigational new drugs and the protection of human subjects as published under Title 21, Code of Federal Regulations (CFR), Part 312 (copy enclosed). Our investigation revealed that you did not fulfill your obligations as a clinical investigator.

This letter provides you with written notice of the matters under complaint. A listing of the CFR violations follows. The applicable provisions of the CFR are cited for each violation.

1. **FAILURE TO CONDUCT YOUR STUDIES IN ACCORDANCE WITH THE APPROVED PROTOCOL [21 CFR 312.60]**

   You failed to conduct the studies in accordance with the approved protocol in that:

   Protocol [redacted]

   a. The case report forms (CRFs) submitted to the sponsor for at least 6 subjects [redacted] indicate that you performed the protocol-specified sinus punctures at Visit 1. However, during the inspection you informed the FDA investigators that you did not perform sinus punctures for any subjects in the study. You indicated that the procedure you actually performed was "rhinoscopically guided middle meatus aspiration". In your May 18, 2001 letter to the FDA, you confirmed that you substituted

middle meatus aspiration for the protocol-specified sinus puncture for all of the subjects enrolled at your site. Despite your belief that middle meatus aspiration is safer for the subjects, it is unacceptable that CFRs do not accurately reflect the procedure performed on the subjects. You must inform the sponsor and obtain approval from the sponsor prior to changing any protocol-specified procedure. You must inform the subjects correctly and accurately in their consent forms about the particular procedure you will perform and, if the procedure is changed from that specified in the protocol, the rationale for such change.

b. You collected specimens (by rhinoscopically guided middle meatus aspiration) from 3 subjects *after* study drug administration, instead of within 48 hours prior to study drug administration as specified by the protocol.

Subject	Date	Time of Drug Administration	Time of Specimen Collection
[redacted]	6/14/00	16:10	16:15
	5/15/00	15:00	16:00
	5/12/00	17:15	18:10

c. You did not obtain the blood pressure reading for subject[redacted] on Visit 1 as required by the protocol.

Protocol[redacted]

d. You did not perform protocol-specified sinus punctures prior to the start of study drug for subjects in this study. During the inspection, you indicated the procedure you actually performed was "rhinoscopically guided middle meatus aspiration". You confirmed the use of this procedure in your response of May 18, 2001. You did not inform the sponsor or obtain approval from the sponsor for this change in procedure.

Protocol[redacted]

e. You enrolled subject[redacted](1003) into the study although the subject did not meet the inclusion criteria of reversible airway disease, defined in the protocol as a ≥ 12% increase over baseline in FEV_1 within 30 minutes of the inhalation of 2 puffs (180mcg) of albuterol aerosol. The post medication pulmonary function test (PFT) performed June 23, 2000, indicated a 6.5% increase over baseline in FEV_1 at 36 minutes, and a 7.7% increase over baseline in FEV_1 at 46 minutes.

f. For the same subject[redacted](1003), you administered albuterol for the June 23, 2000 post medication PFT by nebulizer instead of by the metered dose inhaler required by the protocol.

Protocol[ ]

g. You failed to perform 60 minutes of post-exercise monitoring in accordance with the protocol. The protocol specified that during the exercise challenge test at Visit 4, each subject was to have pulmonary function testing and vital sign monitoring at 5, 10, 15, 30, and 60 minutes post-exercise. Subject[ ]was monitored for 15 minutes post-exercise and then sent home. You state in your letter of May 18, 2001, that the study coordinator was new, and that she mistakenly sent the subject home after noting a 20% decrease in the subject's FEV_1. We note that you acknowledge that a full 60 minutes of post-exercise monitoring should have been performed. As the principal investigator for the study, you are responsible for assuring that all employees are aware of protocol requirements and that they are obligated to follow the protocol.

2. FAILURE TO MAINTAIN ADEQUATE AND ACCURATE RECORDS [21 CFR PARTS 312.62(b)]

You failed to maintain adequate and accurate study records for Protocol[ ]in that:

a. The medical charts for[ ]and[ ]indicate that each of these subjects had prior sinus surgeries. These surgeries were not documented in the CRFs for either subject.

b. The concomitant medications, 1% oxymetazoline and 4% xylocaine, administered to obtain sinus samples, were not appropriately recorded as follows:

1) Subject[ ]The concomitant medications were not listed on the CRFs.

2) Subjects[ ]The concomitant medications were listed in the medical charts and in the CRFs, however they were not listed in study documents titled[ ]- *Source Document/Visit 1* created specifically for this study. We acknowledge that the protocol permitted the listing of concomitant medications directly into the CRF, and that the CRF would then become the actual source document. However, all forms or documents used in a study are considered study records, and are expected to contain the same information as the CRFs.

3) Subject[ ]The CRF for subject[ ]indicates that procedures conducted on July 10, 2000, including sinus x-ray, sinus puncture, blood and urine samples, and study drug administration, all took place at 15:30. During the inspection, you acknowledged that these procedures could not have occurred at the same time; however, this information was submitted to the sponsor as if the procedures were all conducted at 15:30.

3. **FAILURE TO OBTAIN INFORMED CONSENT FROM STUDY SUBJECTS [21 CFR 312.60 AND 21 CFR 50.25(a)]**

   Protocol[ ]and Protocol[ ]

   The consent form for both studies states that a sinus puncture would be performed at Visit 1 and, if necessary, at subsequent and post-therapy Visits. By your own admission, you did not perform sinus punctures. Therefore, subjects in these studies were not adequately informed of the procedures (i.e. rhinoscopically guided middle meatus aspiration) they were to undergo.

4. **FAILURE TO INFORM THE IRB OF CHANGES TO THE PROTOCOL [21 CFR 312.66].**

   Protocols[ ]and[ ]

   You failed to inform and obtain approval from[ ]Institutional Review Board[ ] for the changes in the protocols; specifically, your substitution of rhinoscopically guided middle meatus aspiration for protocol-specified sinus punctures in protocols [ ]and[ ] You also failed to inform and obtain approval from the[ ]IRB for the use of a nebulizer in place of a metered dose inhaler to administer Ventolin in protocol[ ]

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational drugs. We wish to remind you that as principal investigator, you are responsible for ensuring adherence to federal regulations and ensuring that the investigations are conducted according to the investigational plans.

Your violations of FDA regulations outlined above, particularly the protocol violations, resulted in the submission of inaccurate data to the sponsors of the referenced clinical studies, and the submission of unacceptable data to FDA. You must address these deficiencies and establish procedures to ensure that any on-going or future studies be conducted in compliance with FDA regulations. We plan to monitor your research activities to ensure that you have indeed implemented appropriate corrective actions and that your revised clinical investigation procedures comply with federal regulations.

Your May 18, 2001 letter, addressed to Dr. John R. Martin, Branch Chief GCP 1, Division of Scientific Investigations, Center for Drug Evaluation and Research, and your letter to the Chairman of[ ]Institutional Review Board, dated June 18, 2001, fail to provide us with assurances that in future studies you will adhere to the approved investigational plan as written.

Within fifteen (15) working days of receipt of this letter, you must notify this office in writing of the specific corrective actions you will take to address all of the deficiencies noted above and to

achieve compliance with the FDA regulations. If corrective actions cannot be completed within 15 working days, you may request an extension of time in which to respond by stating the reason for the delay and the time within which the corrections will be completed. We will review your response and determine whether it is adequate. Failure to provide adequate assurances of compliance with FDA regulations may result in further regulatory action without further notice.

Your reply should be sent to:

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Food and Drug Administration
7520 Standish Place, Room 125
Rockville, Maryland 20855

Sincerely yours,

Joanne L Rhoads M.D.

Joanne L. Rhoads, M.D., MPH
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research

Enclosure:
21 CFR part 312