DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

WARNING LETTER

Food and Drug Administration
Rockville MD 20857

NOV 29 2004

Certified Mail
Return Receipt Requested

Reference No: 04-HFD-45-1101

Anne Pickles
Vice President
Celsis Laboratory Group, St. Louis Division
6200 S. Lindbergh Blvd.
St. Louis, MO 63123

Dear Ms. Pickles:

Between April 28 and May 8, 2003, James I. Giefer, representing the Food and Drug Administration (FDA), inspected the following nonclinical laboratory studies conducted by your firm:

1. Protocol [ ] entitled "A 14 Day Dermal Repeated Intranasal Application Study in Rabbits Over the Period of Two Consecutive Weeks" of the investigational drug [ ] Nasal Cream, performed for [ ]
2. Protocol [ ] entitled "Primary Dermal Irritation – FDA Requirements, per 21 CFR 58" of the investigational drug [ ] Nasal Cream," performed for [ ]

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research, to ensure that the rights, safety, and welfare of the human subjects have been protected, and to verify compliance with Title 21 of the Code of Federal Regulations (CFR), Part 58--Good Laboratory Practice (GLP) regulations. The regulation at 21 CFR 58 applies to nonclinical laboratory studies of products regulated by FDA.

At the conclusion of the inspection, our investigator presented and discussed with [ ] the items listed on Form FDA 483, Inspectional Observations. Following our review of the establishment inspection report and related documents, including your letter dated May 15, 2003, we conclude that you violated FDA regulations governing the conduct of nonclinical laboratory studies. This letter provides you with written notice of the matters under complaint. The applicable provisions of the CFR are cited for each violation.

1. **Failure of testing facility management to assure that the test article and mixtures of the test article in a carrier were appropriately tested for identity, strength, purity, stability, and uniformity, as applicable [21 CFR 58.31(d)].**

You conducted studies [ ] and [ ] without obtaining necessary information about the characteristics of the test article administered. Specifically, you lacked information about the strength, purity, and composition of the test article provided by [ ] for use in these studies. You also failed to assure that the dose formulations [ ] Nasal Cream, [ ] prepared by the sponsor and administered in studies [ ] and [ ] were

tested for uniformity of the mixture, concentration of the test article in the mixture, and stability of the test article under the conditions of the study. Without knowing the actual dose of test article administered, your study director could not provide a meaningful assessment of study outcomes. For example, a conclusion of no toxicity for a given theoretical dose would be erroneous if the actual dose administered was sub-potent due to test article instability.

In your response to the Form 483, you suggested that you fulfilled the GLP requirement because the sponsor defined the test article characteristics and you obtained written verification that the sponsor had done the necessary testing. Your response fails to acknowledge that the written verification you received from [ ] did not adequately describe the test article. Characteristics such as strength, purity and composition were labeled "TBD" (to be determined).

2. **Failure to include characteristics of the test article in final study reports [21 CFR 58.185(a)(4)] and failure to include a description of all circumstances that may have affected the quality or integrity of the data in final study reports [21 CFR 58.185(a)(9)].**

The final study reports prepared by your study director for studies [ ] and [ ] did not include characteristics of the test article (e.g., strength, purity). As detailed in item 1 above, the sponsor's written verification that the necessary testing had been done is not adequate to satisfy the requirement that the final study reports contain the actual characteristics of the test article.

Characteristics of the test article are critical to the study director's assessment of study outcomes, and the absence of this information may have affected the quality or integrity of the data for studies [ ] and [ ] Thus, the final reports should have explained that you were lacking information about the characteristics of the test article.

3. **Failure to establish standard operating procedures to insure the quality and integrity of the data generated in the course of a study [21 CFR 58.81].**

You failed to establish standard operating procedures (SOPs) for the collection and identification of blood specimens taken from test systems, and for the processing of these blood specimens for laboratory testing. For example, in Study [ ] no valid results could be obtained from the original clinical chemistry and PT/PTT analyses for the group 1 and 2 termination specimens due to mislabeling (the serum specimens were labeled as plasma and vice versa). Additionally, in Study [ ] 20% of the blood specimens for hematology could not be analyzed because of clotting. Your response indicated that analysts were trained to bleed rabbits for another procedure [ ] Procedure for Antibody Production). Such training is not a substitute for written SOPs for the collection, identification, and processing of blood specimens for clinical chemistry, coagulation, and hematology analyses.

4. **Failure to conduct the nonclinical laboratory study in accordance with the protocol [21 CFR 58.130(a)].**

The protocol for Study[ ]required that, for sacrificed animals, "all organs will be weighed prior to placement into the[ ](protocol section 12.7). You failed to weigh the adrenals, thymus, pituitary, and thyroid.

5. **Failure to record data generated during the conduct of a nonclinical laboratory study directly, promptly and legibly in ink [21 CFR 58.130(e)].**

For study[ ] there was no documentation for the collection of blood for pharmacokinetic, clinical chemistry, and hematology measurements at termination. You also lacked source data to document the processing of blood specimens after collection.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. Your violation of the FDA regulations outlined above resulted in the submission of unreliable data to the sponsor, and the submission of unacceptable data to FDA. Your response dated May 15, 2003 addressed some of these deficiencies, however, your response did not provide adequate assurance that you have established policies and procedures to prevent recurrence of the violations cited above. For example, your response did not include details of the SOP you proposed to correct the numerous deficiencies concerning the identification, processing, and documentation procedures for blood specimens collected from test systems. You must correct the deficiencies noted above and establish procedures to ensure that any on-going or future studies will be conducted in compliance with FDA regulations.

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:
C.T. Viswanathan, Ph.D.
Associate Director, Bioequivalence
Chief, GLP & Bioequivalence Investigations Branch
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 116
Rockville, MD 20855
Telephone: (301) 827-5460

Sincerely,

Joanne L Rhoads M.D.

Joanne L. Rhoads, M.D., M.P.H.
Director
Division of Scientific Investigations
Office of Medical Policy
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