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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

Via Federal Express

APR 11 2005

WARNING LETTER

Kenneth J. Rosenthal, MD
Rosenthal Eye and Facial Plastic Surgery
310 East Shore Road, Suite 102
Great Neck, NY 10023

Dear Dr. Rosenthal:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a recent Food and Drug Administration (FDA) inspection at your firm. This letter also requests that prompt corrective actions be implemented in response to the violations cited. The inspection took place during the period from December 29, 2004 through January 19, 2005, and was conducted by Mr. Robert C. Steyert, an investigator with FDA's New York District Office. We also wish to acknowledge receipt of your letter to Mr. Jerome Woyshner, District Director of the FDA New York District Office, dated January 28, 2005, in which you responded to the inspectional observations.

The purpose of the inspection was to determine if your activities as a Clinical Investigator (CI) of human research studies complied with applicable FDA regulations, published in Title 21, Code of Federal Regulations, Part 50-Protection of Human Subjects, and Part 812-Investigational Device Exemptions [21 CFR 50 and 812]. The two clinical trials that were the subjects of the inspection were: [redacted] sponsored by [redacted], Inc. (IDE # [redacted], and [redacted], sponsored by [redacted], Inc. (IDE # [redacted]. The products used in the studies are devices as that term is defined in Section 201(h) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 321(h)] (the FDC Act).

The inspection was conducted under a program designed to ensure that data and information contained in applications for Investigational Device Exemption (IDE), Premarket Approval (PMA), Product Development Protocol (PDP), or Premarket Notification [510(k)] submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of the scientific investigation.

Our review of the inspection report prepared by the New York District Office revealed violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions. FDA Investigator Steyert listed his findings on a Form FDA-483, "Inspectional Observations," and discussed these findings with you at the conclusion of the inspection.

The deviations noted on the FDA-483, your written responses to those deviations, and issues from our

subsequent review of the inspection report are discussed below.

1. **Failure to maintain accurate, complete, and current records relating to your participation in an investigation [21 CFR 812.140(a)].**

   Responsibilities of clinical investigators include maintaining accurate, complete, and current records relating to the investigator's participation in an investigation.

   You failed to adhere to the above stated regulation. Examples of this failure include but are not limited to the following:

   a. **You failed to maintain complete records regarding the receipt, use, or disposition of a study device [21 CFR 812.140(a)(2)(iii)].** For example, during the inspection, you provided information to Mr. Steyert that indicated you received [redacted] study devices for the [redacted] study on 8/12/02. You subsequently enrolled [redacted] subjects into the study. However, you provided no records to document the specific devices that were returned to the sponsor or otherwise disposed.

   This was a repeat violation from an inspection that was conducted in October 2001, for which you subsequently received an Untitled Letter from FDA on December 12, 2001.

   Your written response to this observation is inadequate. You stated that documentation of test article accountability "was always maintained in the Operating Room Notebook and was available...We do acknowledge that during the exit interview we were unable to immediately remember its location in the study records." A Clinical Investigator's obligations include maintenance of complete records regarding the disposition of every device provided to you as part of a clinical trial. Furthermore, the FDC Act requires that you permit a reviewing FDA official access to records related to IDE studies [FDC Act § 704(e)]. The device accountability records were not provided to Mr. Steyert during the inspection nor did they accompany your response. If you have now located these records, please forward them to us with your response to this letter.

   b. **You failed to maintain accurate and complete records for each subject's case history and exposure to the device [21 CFR 812.140(a)(3)].** The study subjects' records contained numerous inaccuracies and inconsistencies. For example:

      i. [redacted] Study Patient [redacted]: the Preoperative Case Report Form, dated [redacted], noted that the required [redacted] was [redacted]. However, the [redacted] printout in this subject's file noted the count was '[redacted]' on [redacted], which was the 4-month post-surgical visit. There was no record of the Preoperative [redacted] in the subject's file.

      Your written response to this observation is inadequate. In your letter, you stated that this subject had an [redacted] done on [redacted] and that the entry of the incorrect test result onto the Case Report Form was "a clerical error." You also attached a photocopy of a [redacted] result dated [redacted]. We note that the study subject number "[redacted]" was

handwritten on this photocopy and, further, that [redacted] does not correspond to any visit date required by the protocol. It is unclear from your letter whether the test performed on [redacted] was also in error, since this test was not required by the protocol for this particular visit, and the results of this test were not recorded on the Case Report Form for the study visit on [redacted]. As a clinical investigator, you are responsible for ensuring that all information reported as part of a clinical study is accurate, and you are also responsible for supervising personnel to whom you have delegated certain study tasks.

ii. A monitoring report for the [redacted] study, dated 12/3-4/2004, noted that the Case Report Forms for nine study subjects had inconsistent and discrepant data, as compared to the source record, for such things as medications, [redacted], and complications. In addition, the report noted that clinical records were not available to verify specific study visit information reported on the Case Report Forms for subjects [redacted].

This was a repeat violation from an inspection that was conducted in October 2001, for which you subsequently received an Untitled Letter from FDA on December 12, 2001.

2. **Failure to ensure an investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations [21 CFR 812.100].**

Responsibilities of clinical investigators include ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, and for protecting the rights, safety and welfare of subjects under the investigator's care [21 CFR 812.100].

a. [redacted] Study Patient [redacted]: an [redacted] of the affected [redacted] was not performed pre-operatively as required by the protocol.

b. A monitoring report for the [redacted] study, dated 12/3-4/2004, noted that several study procedures required by the protocol were not performed, including:

i. [redacted] measurements for subjects [redacted];

ii. [redacted] counts for subjects [redacted];

iii. Manual [redacted] measurements for subject [redacted].

3. **Failure to ensure submission of complete, accurate, and timely progress reports as required by the reviewing IRB [21 CFR 812.150(a)].**

Responsibilities of clinical investigators include submitting progress reports on the investigation to the reviewing IRB at regular intervals [21 CFR 812.150(a)(3)], and providing upon request by a reviewing IRB, accurate, complete, and current information about any aspect of the investigation [21 CFR 812.150(a)(7)].

You failed to adhere to the above stated regulations. Examples of these failures include but are not limited to the following:

a. [redacted] was the IRB of record for the [redacted] study. [redacted] required study status updates from you every six months to maintain IRB approval. Your study records indicated that the progress report that was due on 10/6/03 was not sent to the IRB until 1/21/04, despite several reminders from the IRB. The progress report that was due on 10/6/04 was not sent to the IRB until 11/26/04.

Your written response to this observation is inadequate. In your letter, you stated that you "did not recognize at the onset of the study that a quarterly report was expected" and that you were not aware of your omission "until contacted with a late notice." However, the letters from the IRB indicate that the progress reports were requested before the "Final Notice" requests were sent. Specifically, the January 13, 2004, letter from the IRB states "The Board understands you have been contacted several times," and the November 17, 2004, letter from the IRB indicates they were enclosing "another copy" of the progress report form for your completion. Furthermore, as a clinical investigator, it is your responsibility to understand any conditions of IRB approval, including frequency of progress reports.

The deviations presented in this letter are not intended to be an all-inclusive list of objectionable practices that may exist at your clinical site. It is your responsibility to ensure adherence to each requirement of the Act and all pertinent Federal regulations when conducting clinical research, and to ensure that any study staff or personnel who are delegated study tasks are knowledgeable regarding the Investigational Plan and are directly supervised by you.

Please acknowledge receipt of this letter **within 15 working days**, including supporting documentation of the specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies.

In addition, please provide a complete list of all clinical trials in which you have participated for the last five years, including the name of the study and test article, the name of the sponsor, the number of subjects enrolled, and the current status of the study.

Our review of the inspection results also noted that you use an electronic medical record (EMR) system to maintain medical and other clinical data for your patients, including study subjects. You told Mr. Steyert that data obtained during study visits are entered directly into the EMR, and no paper records are used. A follow-up letter from you to Mr. Steyert, dated January 31, 2005, detailed the name of the EMR system and the means by which study subject information is entered. Please note that Title 21, Code of Federal Regulations, Part 11, "Electronic Records; Electronic Signatures" outlines specific requirements that must be met for any system that is being used to maintain required records. In addition to the information requested above, please submit the following:

- documentation of the validation of your EMR system to ensure accuracy, reliability, and the ability to detect invalid or altered records;
- documentation of the ability to generate accurate and complete copies of records suitable for

inspection, review, and copying by the agency;

- documentation of a secure, computer-generated, time-stamped audit trail that can independently record the date and time of operator entries and actions that create, modify, or delete electronic records, and to verify that record changes do not obscure previously recorded information.

Failure to respond to this letter and take appropriate corrective action could result in regulatory action without further notice. Please respond in writing to:

Food and Drug Administration
Center for Devices and Radiological Health, Office of Compliance
Division of Bioresearch Monitoring, Special Investigations Branch (HFZ-311)
2094 Gaither Road, Rockville, Maryland 20850
Attn: Michael E. Marcarelli, PharmD/Director

A copy of this letter has been sent to FDA's New York District Office, Food and Drug Administration, 158-15 Liberty Avenue, Jamaica, NY 11433. We request that you copy the district on your response.

Sincerely yours,

Larry D. Sommer for

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health