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APR - 3 2000

WARNING LETTER
Via Federal Express

Thomas S. Tooma, M.D.
Laser Vision Correction
3501 Jamboree Road, Suite 1100
Newport Beach, California 92660

Dear Dr. Tooma:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection of your clinical site, to discuss your written response to the deviations noted, and to request a prompt reply with regard to the remaining issues. The inspection took place during the period of December 22, 1999 and January 13, 2000, and was conducted by Mr. Allen F. Hall, an investigator from FDA's Los Angeles District Office. The purpose of the inspection was to determine if your activities as a clinical investigator of [REDACTED] for [REDACTED] comply with applicable FDA regulations. [REDACTED] are devices as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notifications [510(k)] 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 scientific investigations.

Our review of the inspection report submitted by the district office revealed serious violations of requirements of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions, Part 50 - Protection of Human Subjects, and Section 520(g) of the Act. You received a form FDA-483, "Inspectional Observations," at the conclusion of the inspection that listed the deviations noted and discussed with you. We acknowledge receipt of your response dated January 28, 2000, which addresses each of the form FDA-483 items. The deviations noted on the form FDA-483 and our subsequent review of the inspection report and your response to the FDA-483 items are summarized below.

Failure to conduct the study in accordance with the investigational plan and the signed investigator's agreement with the sponsor [21 CFR 812.100 and 812.100(b)]

You failed to conduct the study in accordance with the investigational plan and the investigator's agreement, including failure to adhere to the inclusion/exclusion criteria outlined in the study protocol. For example, the investigational report includes information about your use, outside of study conditions, of a device you have agreed to treat as investigational and your willingness to treat subjects who have exited studies for their convenience. For the investigational study of the [REDACTED], item 1 on the investigator agreement (copy enclosed), which you signed, reads "[REDACTED] is an investigational procedure and the [REDACTED] is an investigational device." You performed enhancement treatments on subjects [REDACTED] and [REDACTED] using this laser, even though prior laser surgery is one of the exclusion criteria for the study. In your response you state that treatment of subject [REDACTED] fell under "the previously FDA-approved limits for this device." According to item 1, this is a contradiction. Moreover, [REDACTED] do not presently have approval for use in any [REDACTED] procedures.

With regard to those subjects for whom you performed enhancement surgery outside of the [REDACTED] protocol, you state that these subjects had first exited the study and that federal regulations and the study protocol allow subjects to exit the study for any reason, at any time. It is true that subjects are free to leave a study at any time. However, as a clinical investigator it is your responsibility to assure that potential subjects fully understand that the integrity of the study is dependent upon subjects completing the protocol and that they agree to participate as fully as possible. According to the inspectional report, the reason listed for exiting the study on the subject chart for [REDACTED] "due to the patient's intolerance to wait." To allow a subject to exit the study because he/she is impatient to have an enhancement procedure that the protocol does not allow, and then to treat them immediately with a different excimer laser, sends the wrong message. Of the subject files reviewed, three subjects received enhancements outside of the study, after exiting the study. In all three cases, the date for both their exit from the study and the enhancement surgery is the same. Moreover, the inspection report notes that the sponsor had notified you in a letter dated October 13, 1999, that the use of other laser systems for retreatments was inappropriate. To have done so for any study subjects, even those who officially exited the study, indicates that your intentions as a clinical investigator differ from what is expected by both the sponsor and FDA.

Failure to follow the general requirements for obtaining informed consent (21 CFR 50.20)

You administered informed consent for a [REDACTED] trial for [REDACTED] to a subject from the [REDACTED] study who required enhancement due to overcorrection, despite the fact that one of the exclusion criteria for the [REDACTED] study is previous [REDACTED] surgery. Your response states that the subject never really thought that he/she was part of a study and, in fact, this subject's information was never included

in study files. You also state that potential subjects and the counseling staff do not know at the time of the informed consent process if the subject will meet the necessary criteria. The protocol for the [REDACTED] study, in section [REDACTED] Patient Entry (copy enclosed), states that after evaluation of the patient with regard to study requirements, written informed consent will be obtained and the patient will then be enrolled in the study. Acceptance of a signed informed consent for this study is therefore intended to constitute enrollment in the study.

Moreover, according to the inspection report, you stated that employees designated to administer the informed consent process were not qualified to review the patient's medical history record and would not know of the subject's prior surgery. Item 4 on the investigator agreement states, "The full responsibility for administering adequate informed consent rests entirely and exclusively with the surgeon." It is therefore your responsibility to assure that those you delegate to take part in the consent process are adequately and properly informed.

A previous FDA inspection, in March 1998, revealed treatment of study subjects without proper informed consent and protocol violations that included treatment of subjects outside of the inclusion/exclusion criteria and use of the [REDACTED] outside of the prescribed temperature and humidity range. You responded that you would take corrective actions on all issues. Present findings, including those described above, indicate that your studies are not being conducted as expected by FDA.

For your information, an investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations. Clinical investigators are to conduct themselves in a manner conducive to promoting the integrity of the clinical investigations they have agreed to supervise. Please amend your organizational procedures regarding clinical investigations for which you are the principal investigator. These procedures need to include measures to assure that personnel responsible for the informed consent process are knowledgeable of the inclusion/exclusion criteria of the study in question and have access to pertinent information about the potential study subject. The informed consent process, moreover, needs to stress the importance of the subject adhering to the study requirements. While the subject always has the right to exit the study at any time, those with a high drop-out probability should not be recruited into the study. Once these procedures have been amended, a training program needs to be arranged for all personnel who have responsibilities with regard to investigational studies. Please send a copy of your revised procedures to the address given below, as well as a proposed schedule for personnel training.

Also, you need to cease use of study informed consent documents for your patients who are not study subjects. The inspectional report notes that your Clinical Research Director, [REDACTED], stated during the inspection that consent forms for patients who will undergo non-investigational procedures were in development. Please send us a copy of these forms.

Please send the information requested above, within 15 working days of receipt of this letter, to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Jean Toth-Allen, Ph.D. Failure to respond could result in further regulatory action without additional notice, including initiation of investigator disqualification procedures.

A copy of this letter has been sent to FDA's Los Angeles District Office, 19900 MacArthur, Suite 300, Irvine, California 92715. We request that a copy of your response also be sent to that office.

If you have any questions, feel free to contact Jean Toth-Allen, Ph.D. at (301) 594-4723, ext. 141.

Sincerely yours,



Lillian J. Gill
Director
Office of Compliance
Center for Devices and Radiological
Health

Enclosures

cc:

 (purged copy)


Emory S. Martin, Chair (purged copy)
Research Consultants' Review Committee
4009 Banister Lane
Austin, Texas 78704

 (purged copy)
