DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

APR 17 2000

WARNING LETTER
Via Federal Express

Michael B. Limberg, M.D.
Limberg Eye Center
1270 Peach Street
San Luis Obispo, California 93401

Dear Dr. Limberg:

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 January 27 and February 14, 2000, and was conducted by Mr. William R. Bowman, 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 Paradigm Medical Industry's Photon Laser Phacolysis System comply with applicable FDA regulations. This system is a device 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 a copy of your response to Mr. Bowman dated February 24, 2000. The deviations noted on the form FDA-483, our subsequent review of the inspection report, and your response to the FDA-483 items are discussed below. The deviations noted include:

Failure to obtain Institutional Review Board (IRB) approval before starting the study [21 CFR 812.110(a)].
Two (2) subjects were treated with the investigational device prior to the date of study approval by the reviewing IRB.

Failure to obtain consent forms for all study subjects (21 CFR 812.100).
One of the laser subjects and 11 out of 29 of the control (ultrasound) subjects in the study did not sign the study informed consent document. The inspection report notes that you stated that you were not originally aware that the control subjects needed the study informed consent but were informed of that by the study monitor. Although control subjects received standard care, the need for specially timed post-operative visits and the fact that their files are open to review by the FDA must be agreed to prior to the surgical procedure.

Failure to conduct the study according to the investigational plan [21 CFR 812.100 and 812.110(b)].

- The most current version of the protocol was not available at the time of the inspection. The need to take corneal endothelial cell photographs or counts at 1 day and 1 week post-operative was not included in the version presented during the inspection. The inspection report notes that you were aware of this requirement and had discussed with the sponsor elimination of need for these counts until non-invasive procedures to do so were in place. There is no documentation of this discussion. Moreover, the IRB was not informed of the absence of this testing.

- 8 out of 24 subjects treated with the investigational laser did not meet the inclusion/exclusion criteria for the study. This included subjects who did not meet the age criteria; had a cataract grade outside of the acceptable range; and had poorer visual acuity than required.

- UCVA and/or BSCVA evaluations were not performed at all required visits.

- Endothelial cell photographs were not retained for all subjects.

- Adverse effects were not reported to the sponsor in the required timeframe after occurrence.

Failure to maintain complete and accurate records [21 CFR 812.140(a)].
Information on some of the case report forms (CRFs) did not agree with the computerized subject records and vice versa for those records that were originally captured on the CRF and then transcribed to the computerized source records. Moreover, UCVA readings are incorrectly entered for some BSCVA results on CRFs that only have provision to record the BSCVA.

The deviations listed above are not intended to be an all-inclusive list of deficiencies that may exist in your clinical study. It is your responsibility as a clinical investigator to ensure that an investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations.

Your response states that IRB approval had been confirmed by telephone prior to start of the study. There is no documentation of such a phone conversation in your records. Moreover, the letter of approval from the reviewing IRB (copy enclosed) states "Institutional Review Board approval granted to Dr. Limberg on August 18, 1998." There is no mention in the letter of verbal confirmation of approval at an earlier date.

With regard to the hardness of the cataract, Mr. Bowman notes that you informed him that the readings recorded are PSC results and that these are not a measure of the hardness of the cataract. However, these are the same numbers you entered on the CRFs. The exclusion criteria listed in the study protocol states that "Subjects will be excluded that: A. present with Grades +3 and +4 cataracts." The sponsor therefore expects that the information included on the CRF is a cataract grade, i.e. a measure of the hardness of the cataract. If the CRFs for your subjects include a number representing a different measure, the sponsor is categorizing your results incorrectly.

Your response attributes a number of inspectional findings to transcription errors. Moreover, a number of other issues are attributed to lack of documentation of what actually occurred. It is the responsibility of the investigator to assure that all records are complete and accurate.

While your response discusses most of the individual items cited in the form FDA-483, you included no mention of the corrective actions taken or planned. Please prepare and submit written standard operating procedures (SOPs) for the conduct of clinical investigations at your site and schedule training of all essential personnel as to their implementation. These SOPs should include directions for personnel responsible for the informed consent process that include the following: a method for assuring that the inclusion/exclusion criteria for the study are observed; that potential subjects are fully aware of what is expected of them and willing to commit to the study requirements; and that accurate and complete documentation of the process is maintained, as evidenced by dates and signatures on the IRB-approved informed consent document. You should also include procedures for verification of data entered on CRFs and specify responsible personnel. Your required interactions with the reviewing IRB should also be delineated, as well as methods of device accountability. This is not necessarily a complete listing of the contents of clinical study SOPs. Also, please submit a proposed schedule of personnel training.

Moreover, please interact with the sponsor regarding the meaning of the cataract grading values entered on your CRFs. Please send us a copy of the documentation of this interaction and any resulting actions taken by you and/or the sponsor.

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,

Charmaine Connor, RPh

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

Enclosures

cc:

[redacted] (purged copy)
Chairman and CEO
[redacted]

William Lloyd, M.D., Chair (purged copy)
The Institutional Review Board
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Colorado Springs, Colorado 80926