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Via Federal Express

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

WARNING LETTER

Amos J. Willis, M.D.
Willis Eye Associates
Rappahannock Eye Center
10 White Oak Road
Fredericksburg, Virginia 22405

Dear Dr. Willis:

During the period of April 23 through May 8, 1998, Mr. Gerald Mierle, an investigator from the Food and Drug Administration's (FDA) Baltimore District Office conducted an inspection at your facility. The purpose of the inspection was to determine whether your activities and procedures as a clinical investigator and sponsor for the [REDACTED] complied with applicable FDA regulations. Excimer lasers 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 revealed serious deviations from Title 21, Code of Federal Regulations, (21CFR), Part 812 - Investigational Device Exemptions and Part 50 - Protection of Human Subjects and Section 520(g) of the Act. The deviations noted during the inspection were listed on form FDA-483, "Inspectional Observations," which was presented to and discussed with you at the conclusion of the inspection. The following deficiencies were found:

- You failed to investigate the failure of the [REDACTED] when operating in MS Access. The system locks up at random and it is unknown whether the software which controls the [REDACTED] during [REDACTED] which operates off of MS Excel, could be similarly affected. Disruption of the [REDACTED] or an incorrect [REDACTED] pattern could result from such an occurrence. According to an Office of Device Evaluation (ODE) medical reviewer of [REDACTED] investigational studies, it is not known if there is any irreparable damage to [REDACTED] when and if [REDACTED] are interrupted in the course of a prescribed [REDACTED] pattern. However, irregular [REDACTED] leave the patient with a refractive error that is uncorrectable by any means to date.

As a sponsor, you are responsible for conducting an evaluation of any unanticipated adverse device effects. If it is determined that an

unanticipated adverse device effect presents an unreasonable risk to subjects, you must terminate the investigation not later than 5 days after making this determination and not later than 15 days after the effect was noticed [21CFR 812.46(b)(1) and (2)]. In addition, you are required to report the results of your evaluation to the FDA and to the reviewing IRB within 10 working days after the effect. Thereafter, you must submit such additional reports concerning the effect as FDA requests [21CFR 812.150(b)(1)]. Also, as an investigator, you are responsible for ensuring the safety and welfare of the subjects under your care [21CFR 812.100].

- No security password is used on the computer for entering of data or when sending data to the study monitor over the internet. Subject medical records are, therefore, easily accessible. 21CFR 812.100 states that an investigator is responsible for ensuring the rights and welfare of subjects, which includes security of their records.
- No documentation exists on who enters preoperative [REDACTED] measurements onto the [REDACTED] panel for the [REDACTED] Worksheet or a review of the worksheet prior to the [REDACTED] procedure. The protocol requires independent verification by at least two people. 21CFR 812.110(b) requires an investigator to conduct an investigation according to the investigational plan.
- Protocol [REDACTED] was used in the retreatment of study subjects without Institutional Review Board (IRB) approval. According to 21CFR 812.110(a), an investigator may not allow any subject to participate in an investigational study before obtaining IRB and FDA approval.
- An unapproved informed consent was used for approximately 80 study subjects between 10/8/97 and 2/19/98. Moreover, the informed consent for Amendment [REDACTED] was signed by 20 subjects who underwent the [REDACTED] procedure prior to IRB approval of the document. According to 21CFR 812.100, an investigator is responsible for ensuring that informed consent is obtained in accordance with 21CFR Part 50. 21CFR 50.27(a) requires that informed consent be documented by the use of a written consent form approved by the IRB.
- Comparison of the on-site data with monthly reports submitted to FDA revealed a number of transcription errors. 21CFR 812.150(a)(7) and 21CFR 812.150(b)(10) require a study investigator and sponsor respectively to provide, upon request by a reviewing IRB or FDA, accurate, complete, and current information about any aspect of the investigation.

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

The inspection report notes that, during the inspection, a policy was initiated for writing on the form the name of the person entering the data and the person

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verifying the data, as a means of documenting data entries. It is also noted that you stated that you would inquire as to procedures for instituting a password protection procedure for data being uploaded via the internet to the study monitor. Moreover, more than 75% of study subjects who initially signed an incorrect informed consent had signed a correct, approved copy of informed consent, at a follow-up visit, by the completion of the inspection.

Please advise this office, in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct remaining deficiencies and ensure they will not be repeated. Your failure to respond may result in further regulatory action without notice. Please send your response 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.

A copy of this letter has been forwarded to our Baltimore District Office, 900 Madison Avenue, Baltimore, Maryland 21201. We request that a copy of your response be sent to that office.

If you have any questions or concerns, please contact Jean Toth-Allen at (301) 594-4723, ext. 141.

Sincerely yours,



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