DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

JUL 8

WARNING LETTER
Via Federal Express

David I. Geffen, O.D.
Gordon Binder Vision Institute
8910 University Center Lane, Suite 800
San Diego, California 92122

Dear Dr. Geffen:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site, discuss your May 13, 2003, response to the inspectional observations, and request a prompt reply to the remaining issues. The inspection took place during the period of March 20 through April 1, 2003, and was conducted by Mr. Thomas R. Beilke, an investigator from FDA's Los Angeles District Office. The purpose of the inspection was to determine if your activities as a clinical investigator in [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 (PMA) applications, and 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 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, and Part 50 - Protection of Human Subjects. 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 May 13, 2003, reply to the inspectional observations. The violations revealed during this inspection include the following:

1. Failure to obtain study approval from the reviewing institutional review board (IRB) prior to initiation of the study (21 CFR 812.110(a)).

The inspection revealed that the first subject entered the study at your site on [redacted], and the last subject completed the study on [redacted] During the inspection, you provided a copy of an IRB letter dated [redacted],

from your study files. This letter is addressed to [redacted], of [redacted], the consulting firm responsible for the conduct of this study. This letter to [redacted] instead of approving the study, states that "the investigators were not approved because the investigator list has not been finalized and no CV's were submitted." According to 21 CFR 812.110(a), an investigator shall not allow any subject to participate in an investigational study before obtaining IRB approval. There is not sufficient evidence to show that you obtained IRB approval of the study prior to initiating the investigation at your site.

Your response to observation 1A includes a copy of an IRB letter addressed to you, also dated [redacted]. This letter to you says that the IRB approves the protocol, but it does not state that the IRB approved the study to be conducted at your site.

Your response to observation 1A states that your records have been updated in this regard. Please clarify the nature of your update. For example, if it includes a specific approval letter from the IRB that is different from the two letters described above, please provide us with a copy.

2. Failure to ensure that the informed consent document used during the study was approved by the IRB (21 CFR 50.27(a)).

The [redacted] IRB letters, one addressed to you and the other addressed to [redacted] state that approval of the informed consent document was tabled pending revisions to several elements. During the inspection, [redacted] asked his secretary in his [redacted] office to send, by facsimile, copies of two different informed consent documents. Your response to observation 1C includes a copy of one of the two informed consent documents supplied during the inspection.

Neither of the two informed consent documents is dated, though both contain signatures represented to be those of IRB members. In light of the [redacted] IRB letters that specifically withhold the approval of the informed consent document, these two undated informed consent documents do not provide sufficient evidence that the IRB approved the informed consent documents used at your site prior to the time at which you used them for the specific subjects that you treated with the device. Investigators are required by 21 CFR 812.100 to ensure that informed consent is obtain in accordance with 21 CFR Part 50. As stated in 21 CFR 50.27(a), informed consent must be documented by use of a written consent form approved by the IRB.

3. Failure to use an informed consent document that contains all of the required elements (21 CFR 50.25).

The informed consent document used failed to include a description of all procedures to be conducted as part of the study, including [redacted] measurements, [redacted] measurements, and [redacted] testing.

According to 21 CFR 50.25(a)(1), a description of the procedures to be followed is a required basic element of the informed consent document.

Your response to observation 9 states that the informed consent document was approved by FDA and the IRB. FDA does review informed consent documents for completeness but does not approve them. It is the responsibility of the IRB and the clinical investigator to ensure that they are adequate. The regulatory requirement that an informed consent document contain a full description of all procedures to be performed during a study is intended to ensure that individuals are fully aware of what will be expected of them if they choose to participate in the study. If this information is available up front, individuals can choose not to participate rather than become a drop-out later in the study, when they decide that study requirements are too burdensome. Study drop-outs can have a serious affect on the validity of the study and, therefore, the sponsor's ability to use the results in support of a marketing application.

4. Failure to conduct the study in accordance with the investigational plan (21 CFR 812.100 and 812.110(b)).

Investigational findings revealed you departed from the investigational plan in that testing required by the study protocol, for example, [redacted] measurements and [redacted] was not always performed at the times specified by the protocol. Several subjects did not receive the morning and afternoon visits required at either the 6- or 9- month follow-up visit. In addition, a number of study subjects were seen for follow-up outside of the timeframes proscribed by the protocol. Investigators are required by 21 CFR 812.100 and 812.110(b) to conduct an investigation in accordance with the investigational plan.

Your responses to observations 2 through 6 address these findings for each specific case identified. In a number of cases you state that the testing was inadvertently omitted. In several others you state that the subject either was discontinued from the study or was seen outside of the prescribed times. The types of test results found to be omitted for a number of these subjects are still important for determining safety parameters, even though this information could not be pooled with subjects who complete the study and are compliant with the protocol, the information is important.

5. Failure to submit timely progress reports to the IRB (21 CFR 812.150(a)(3)).

You did not provide, either during the inspection or in your response, any documents to show that you had submitted the required progress reports to the IRB. The [redacted] letter from the IRB, a copy of which was included with the inspection report, indicates that you submitted a summary report on [redacted] However, if you assumed study approval was granted by the [redacted] letter from the IRB, the first progress report was due no later than [redacted] Investigators are required by 21 CFR 812.150(a)(3) to submit progress reports to the

IRB at regular intervals but no less than yearly, and a final report to the IRB within three months after termination or completion of the investigation.

Progress reports are used by an IRB for their continuing review, to determine if reapproval of the study at the site is appropriate. Your response notes that, for future studies, you will be cognizant of the responsibility of an IRB to provide continuing review. We recommend that investigators be pro-active in ensuring the submission of timely reports and verification of continuing approval from the reviewing IRB.

6. Failure to properly maintain records (21 CFR 812.140(a)).

Investigators are required under 21 CFR 812.140(a) to maintain accurate, complete, and current records relating to the investigator's participation in an investigation. You failed to properly maintain the following records:

(a) Failure to maintain accurate, complete, and current correspondence with the IRB, including required reports (21 CFR 812.140(a)(1)).

You were unable to provide, during the inspection or in your response, accurate, complete, and current records of your correspondence with the IRB. For example, an IRB letter addressed to you and dated [redacted] indicates that the IRB "received your periodical report," but you did not maintain a record of your report.

(b) Failure to maintain accurate, complete, and current device accountability records (21 CFR 812.140(a)(2)).

An inspectional comparison of subject source documents revealed that incorrect information regarding the disposition of investigational lenses was included for at least two study subjects.

Your responses to observations 2 through 6 discuss the effect of inaccurate information in terms of the subject's record of lens use. Accurate accountability records are necessary as investigational devices cannot be used outside of approved studies. Both the sponsor and clinical investigator, therefore, have a regulatory responsibility to ensure accurate, complete, and current records of the receipt, use, and disposal of all investigational devices.

(c) Failure to accurately record all relevant medical history (21 CFR 812.140(a)(3)(ii)).

Past history of contact lens use is required information on the "Initial Visit Form" for this study. Several subjects were found to have incomplete information in this regard on their form.

Your response to observation 12 states that the files for these subjects have been appropriately annotated.

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. We had previously written to you on [redacted] to notify you of similar noncompliance in another study, including lack of IRB approval of informed consent and lack of inventory records to show the number of lenses received from and returned to the sponsor.

Please inform us, within 15 working days of receipt of this letter, of specific corrective actions you have taken or plan to take to ensure that the deviations noted are not repeated in this study or future studies. Also, please include the clarification requested in discussion of the first violation above. 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. Failure to respond and to implement corrective actions could result in enforcement action without further notice or the initiation of investigator disqualification procedures.

A copy of this letter has been sent to FDA, Los Angeles District Office, 19900 MacArthur Boulevard, Suite 300, Irvine, California 92612. We request that a copy of your response also be sent to that office. If you have any questions, feel free to contact Dr. Toth-Allen at (301) 594-4723, ext. 141.

Sincerely yours,

for Michael E Marcarelli

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