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

WARNING LETTER

AUG 28 2000

Alan B. Aker, M.D.  
Aker-Kasten Cataract and Laser Institute, Inc.  
1445 NW Boca Raton Boulevard  
Boca Raton, Florida 33432

Dear Dr. Aker:

During the period of February 1 through February 11, 2000, Ms. Michelle S. Dunaway, an investigator from the Food and Drug Administration's (FDA) Florida District Office visited you. The purpose of that visit was to conduct an inspection to determine whether your activities and procedures as a clinical investigator for the investigational study of the [REDACTED] [REDACTED] complied with applicable FDA regulations. This investigational study is sponsored by [REDACTED]. This product 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), or 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 the scientific investigation.

Our review of the inspection report submitted by the Florida District Office revealed deviations from Title 21, Code of Federal Regulations (21 CFR) – Part 812 – Investigational Device Exemptions and Part 50 – Protection of Human Subjects. At the conclusion of the inspection, Ms. Dunaway presented to and discussed with you the observations listed on the Form FDA-483 "Inspectional Observations." [REDACTED] and [REDACTED] were also present during this final discussion.

We acknowledge receipt of your letter dated March 7, 2000, in response to the items listed on the Form FDA-483. 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. Deviations noted include:

**Failure to conduct an investigation in accordance with the investigational plan and signed investigator's agreement [21 CFR 812.100 and 812.110(b)].**

You failed to conduct the investigation in accordance with the signed agreement with the sponsor and the investigational plan. Examples are as follows:

- The actual treatment pulse energy delivered to the corneal tissue of subjects [REDACTED], [REDACTED], and [REDACTED] exceeded the energy level specified in the protocol.
- A subject not meeting the inclusion criteria as specified in the protocol was allowed to participate in the study. The criteria states that a contact lens wearer must not have used soft or gas-permeable contact lens for at least two weeks and must not have used hard contact lenses for at least three weeks prior to having [REDACTED] performed on their eye(s). Subject [REDACTED] removed the OD contact lens on 3/2/98 and [REDACTED] was performed on this eye on 3/5/98. This does not meet the two- or three-week criteria outlined in the protocol.

In addition, the following procedures were not performed for the following subjects as required by the protocol:

Patient [REDACTED]

- contrast sensitivity not performed during the one-month and twenty-four month visits;
- slit lamp photography not performed during the pre-op, one-day, one-week, and twenty-four month visits;
- pachymetry not performed during the twelve-month visit;
- vascularization not completed during the twelve-month visit;
- best spectacle corrected near visual acuity not completed during the twenty-four month and one-month visits for the "fellow" eye; and
- patient questionnaire not completed during the twelve-month visit.

Patient [REDACTED]

- contrast sensitivity during the twelve-month visit for the primary eye;
- slit lamp photography during the twelve- and twenty-four month visits;
- best spectacle corrected distance vision and subjective manifest refraction were not completed during the one-day visit;
- best spectacle corrected near vision and additional lens power were not completed during the three-month, nine-month, and twelve-month visits;
- dilated pupil diameter, corneal topography, and ultrasound pachymetry were not completed during the twelve-month visit; and
- dilated pupil diameter was not obtained during the twenty-four month visit.

As a clinical investigator, you are required to conduct an investigation in accordance with the signed agreement, the investigational plan, and applicable FDA regulations for protecting the rights, safety, and welfare of subjects under your care.

**Failure to maintain accurate, complete, and current records [21 CFR 812.140(a)(3)].**

You failed to maintain accurate, complete, and current records relating to your participation in an investigational study. For example, case report forms (CRF) for the following subjects did not accurately reflect supporting source data:

Patient [REDACTED]

- finding of “collateral vessel mild drusen” and “fine drusen” as noted on the source document for the one-year and two-year visits were not recorded on the associated CRFs; and
- pachymetry performed during the twenty-four month visit was not recorded on the associated CRF.

Patient [REDACTED]

- uncorrected distance vision (low light), cycloplegic refraction and keratometry information regarding the “OD eye” were incorrectly recorded on the CRF for the eighteen-month visit;
- patient comments of blurred vision and tearing were not reported on the CRF for the twenty-four month visit; and
- patient’s reports of “vertical blurriness” and “vision blurred” were not reported on the CRFs for the one-week and one-month fellow-eye visits.

Patient [REDACTED]

- findings of “fine drusen” on 6/10/98, “conj. Hyperemia\*\*\*mild infiltrates” on 4/22/99 and “mild NS\*\*\*cortical” on 12/6/99 as noted in the source documents were not recorded on the associated CRFs;
- patient comment of “fluctuating VA” as noted in source documentation was not reported on the CRF for the one-month re-treated eye visit; and
- patient complaint of dry eye noted in source documentation was not reported on the CRF for the six-month re-treated eye visit.

Patient [REDACTED]

- patient comment of “cloudy on + off” as noted on the one-week source document was not noted on the associated CRF;
- finding of “mild hyperemia” as noted on the one-day visit source document was not noted on the associated CRF; and
- patient’s use of “Celluvisc OD BID” as noted on the one-month fellow eye visit source document was not noted on the corresponding CRF.

Patient [REDACTED]

- patient's use of "Patanol" and "EES" as noted on the 3/24/98 source document was not noted on the corresponding CRF; and
- interim visit CRFs for this subject were not completed for the 3/24/98 and 3/31/98 visits.

Patient [REDACTED]

Patient comment of "burning" during the one-week fellow eye visit was not reported on the corresponding CRF.

In addition to the above, the source data for the following patients contained incomplete information and there was no documentation to show that attempts were made to contact subjects after they missed scheduled visits:

Patient [REDACTED]

- absence of corneal neovascularization reported on the one-day CRF was not supported by source data;
- one-week post-operative questionnaire CRF included the comment, "better vision," that was not supported by source data; and
- one-year CRF includes information on pupil diameter that was not supported by source data.

Patient [REDACTED]

- the source document dated 4/27/98 notes the patient will "discontinue contact lens wear before appointment," but the source documents do not contain information regarding what type of contact lenses the patient was prescribed and when the patient began wearing the lenses after [REDACTED] treatment; and
- there was no documentation to show that attempts were made to contact the subject after he missed his one-year and eighteen-month re-treat visits and one-year fellow eye visit.

Patient [REDACTED]

- source documents did not contain information regarding when the patient began wearing the contact lenses after [REDACTED] treatment; and
- there was no documentation to show that attempts were made to contact the patient after he missed his eighteen-month visit on 3/23/99.

Patient [REDACTED]

However, source documents indicate the patient “removed the OD contact lens on 3/2/98 and [REDACTED] was performed on this eye on 3/5/98.” The inclusion criteria CRF for the right eye, completed on 3/3/98, indicates “N/A” for the question, “Has the patient refrained from wearing hard contact lenses for three weeks or refrained from wearing soft contact lenses for two weeks?”

Patient [REDACTED]

There was no documentation to show that this patient had a stable history of pretreatment hyperopia over the previous six months prior to study enrollment and [REDACTED] treatment.

**Failure to submit progress reports in accordance with 21 CFR 812.150(a)(3).**

You failed to submit required progress reports to the sponsor, monitor, and reviewing IRB for the following investigations and periods:

- [REDACTED] between initial approval on 4/22/97 and the progress report dated 7/1/99;
- [REDACTED], between initial approval on 8/18/97 and the progress report dated 7/1/99;
- [REDACTED]; between initial approval on 12/2/97 and the progress report dated 6/30/99; and
- [REDACTED] between initial approval on 7/21/97 and the progress report dated 7/1/99.

**Failure to obtain an adequate informed consent (21 CFR Part 50.20).**

You failed to provide study subject [REDACTED] with an adequate informed consent before allowing the subject to participate in an investigational study, i.e., the subject signed an obsolete consent form rather than the revised version approved by the IRB on 2/25/98. In addition, the subject did not date the informed consent.

As a clinical investigator, it is your responsibility to ensure that informed consent is obtained from a study subject before the subject is allowed to participate in the investigational study. This gives the subject sufficient opportunity to consider whether or not to participate in the study and minimizes the possibility of coercion or undue influence.

**Failure to obtain IRB approval as required by 21 CFR 812.110(a).**

You failed to obtain IRB approval of the study before allowing subject [REDACTED] to participate: Subject [REDACTED] signed and dated the consent form for [REDACTED] on 8/4/97, but the IRB did not approve the study until 8/18/97.

The above deviations are not intended to be an all-inclusive list of deficiencies that may exist in your clinical study. As a clinical investigator, it is your responsibility to ensure that investigations that you participate in are conducted in accordance with applicable FDA regulations. To assist you, we have enclosed a copy of the FDA Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators.

According to your March 7 letter of response to the FDA-483, the failure to accurately record findings and conduct the study in accordance with the investigational plan was an oversight. You indicated that you will make a more “conscientious” effort to ensure that correct documentation is located on both the source documentation and the CRF. Also, you stated that you will treat any future subjects based on the spherical equivalent rather than the sphere alone to abide by the protocol including assuring that all protocol required exam components are completed.

Your response states that you were utilizing an internal IRB and progress reports were verbally submitted to the IRB and that the IRB is now “defunct.” Therefore, you are now using a commercial IRB. For your information, investigators are required to submit complete, accurate, and timely progress reports to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than once a year.

**Within fifteen (15) working days of receipt of this letter please send written documentation of any additional specific steps you have taken to correct these violations and other violations known to you, and to prevent the recurrence of similar violations in current or future studies. Failure to respond can result in further regulatory action, including disqualification, without additional notice.**

You should direct 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), 2094 Gaither Road, Rockville, Maryland 20850, attention: Ms. Pamela Reynolds.

A copy of this letter has been sent to our Florida District Office, 555 Winderley Place, Suite 200, Maitland, Florida 32751. We request that a copy of your response be sent to that office as well.

Sincerely yours,



for

Steven M. Niedelman  
Acting Director  
Office of Compliance  
Center for Devices and  
Radiological Health

Enclosure