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Via Federal Express

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

WARNING LETTER

Jon L. Siems, M.D.
Siems Advanced Lasik Center
Investigational Review Board
1000 South Rampart Boulevard, Suite 10
Las Vegas, NV 89128

Dear Dr. Siems:

This Warning Letter informs you of violations found during the Food and Drug Administration (FDA) inspection of the Siems Advanced Lasik Center Institutional Review Board (IRB). Mr. Anthony E. Keller, an investigator from the FDA's San Francisco District Office, conducted the inspection from November 13 through 26, 2003. The purpose of the inspection was to determine whether IRB procedures complied with Title 21, Code of Federal Regulations (21 CFR), Part 50 – Protection of Human Subjects, Part 56 – Institutional Review Boards, and Part 812 – Investigational Device Exemptions.

Based on our records, your IRB has reviewed one clinical study, [REDACTED] sponsored by [REDACTED]. Our review of the inspection report submitted by the district office revealed serious violations from pertinent regulations. At the conclusion of the inspection, Mr. Keller discussed the violations with you and presented a copy of the Form FDA 483, "Inspectional Observations," for your review. The violations are discussed below:

Failure to function and operate in compliance with FDA regulations regarding IRB membership. (21 CFR 56.107)

FDA regulations state that no IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. 21 CFR 56.107(e). According to your IRB roster, your IRB consists of five members. Two of these members had a conflicting interest with respect to the only research protocol reviewed by the Board. You participated as a member of the IRB during its review of this study and signed an approval sheet for the study, yet you were also the clinical investigator for the study. [REDACTED] also participated in the IRB (as IRB Secretary) during its review and voted to approve the study, yet she was designated to work in the capacity of a research nurse for this study by performing study-related examinations and entering data in medical records.

Failure to conduct initial and continuing review of the clinical study in accordance with FDA regulations and IRB procedures. (21 CFR 56.103, 56.108, & 56.109)

Under FDA regulations, an IRB is required to review and approve research activities and subject informed consent documentation before a study is initiated. 56 CFR 56.103 & 56.109. Continuing review by the IRB is required by 21 CFR 56.109(f). The IRB is also required to prepare, maintain, and follow written procedures for conducting initial and continuing review. 21 CFR 56.108(a) & 56.115(a)(6).

According to the minutes of your initial IRB meeting, the Board decided to meet quarterly while subjects were actively being accepted into the study, as authorized by your IRB procedures, for the purpose of reviewing adverse events, clinical endpoints, follow-up compliance, and "contemporary data." This initial meeting, which was the IRB's only meeting, was held prior to the initiation of the study on December 11, 2002. Subjects continued to be enrolled, however, through May 2003. As of the November 2003 inspection, there had been no follow-up IRB meetings beyond the initial meeting. The Board therefore failed to carry out its plan for conducting continuing review of the research on a quarterly basis.

Failure to prepare and maintain adequate documentation of IRB activities, including a list of IRB members. (21 CFR 56.115(a)(5))

Under FDA regulations, an IRB must prepare and maintain adequate documentation of a list of IRB members identified by: name; earned degrees; representative capacity; indications of experience, such as board certifications and licenses, sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution. 21 CFR 56.115(a)(5).

The membership list for your IRB does not include [REDACTED] although he participated in the Board's review of and voting for the study. In addition, the membership list fails to identify each member's earned degrees, representative capacity, indications of experience, or other criteria sufficient to describe the member's anticipated contributions to the IRB deliberations.

In addition to the above, we noted additional issues raising concern about your IRB's ability to function and operate in compliance with FDA regulations. For example, the FDA Field Investigator interviewed [REDACTED], IRB Chairman. [REDACTED] stated that he did not know the other IRB members and that he believed Dr. Siems to be the person most responsible for the IRB's functions. The FDA Field Investigator also interviewed [REDACTED] who stated that he never read the protocol that he voted to approve, but instead that Dr. Siems explained the study during the IRB meeting.

Your IRB was previously inspected in December 2002, at which time numerous deficiencies were identified. In a letter from you dated December 12, 2002, you replied to the inspectional observations identifying the corrective actions you planned to take to resolve the deficiencies. In our acknowledgement letter dated March 21, 2003, we also

referred you to a number of FDA guidance documents and we specifically identified applicable regulations regarding human subject protection, investigational review boards, and investigational device exemptions to which your IRB must adhere. Despite the previous inspection and the information provided by FDA, it appears that your Board continues to violate its responsibilities and fails to function and operate in compliance with FDA regulations.

IRBs are responsible for their functions and operations with respect to review and approval of relevant FDA-regulated research and for the protection of the rights and welfare of human subjects in research. We are concerned that your IRB activities and operations are not adequate to satisfy the IRB's responsibilities specified in FDA regulations. For this reason, in accordance with 21 CFR 56.120(b)(1) and (2), effective immediately:

- FDA will withhold approval of new studies subject to 21 CFR Part 56 that are reviewed by your IRB.
- No new subjects are to be admitted to ongoing studies subject to 21 CFR Part 56 that are under review by your IRB.

On the basis of your response to the violations identified, we may schedule a reinspection of your IRB to confirm the adequacy of your corrective actions. If non-compliance with FDA regulations continues, further regulatory action may be justified, including initiation of procedures to disqualify your IRB.

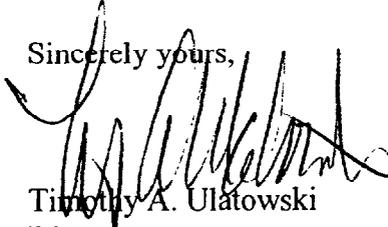
Please advise this office, in writing, **within fifteen (15) working days of receipt of this letter** of the specific steps you have taken to protect human research subjects at Siems Advanced Lasik Center, to correct all other violations known to you, and to prevent the recurrence of similar violations in current or future studies. Failure to respond can result in regulatory action without further 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)
2098 Gaither Road
Rockville, Maryland 20850
Attention: Mr. G. Levering Keely, BSN, MPA,
Consumer Safety Officer.

A copy of this letter has been sent to our San Francisco District Office, 1431 Harbor Bay Parkway, Alameda, CA 94502. We request that a copy of your response be sent to that office as well.

Sincerely yours,



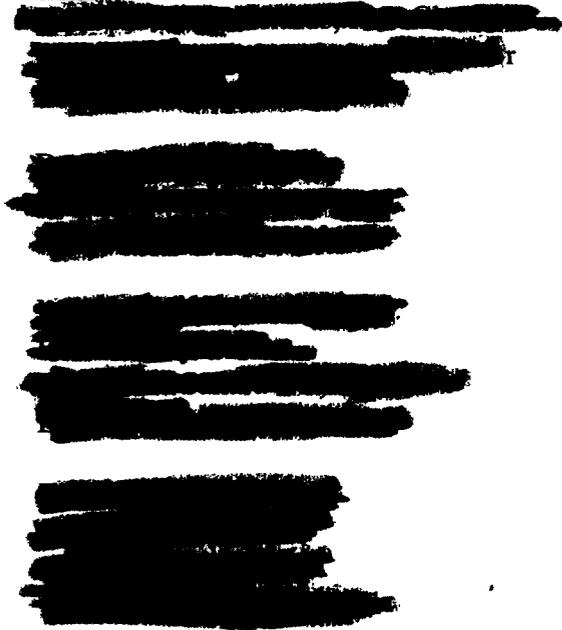
Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

cc:

Sponsor/Purged Copy to:



IRB Members Purged Copy to:



FDA OHRP Copy to:

Kristina Borrer, Ph.D.
Office for Human Research Protections
Department of Health and Human Services
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852