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WARNING LETTER

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

Via Federal Express

Thomas L. Croley, M.D.
Chair, Institutional Review Board
Central Florida Eye Institute
3133 SW 32nd Avenue
Ocala, Florida 34474

Dear Dr. Croley:

This Warning Letter informs you of violations found during the Food and Drug Administration (FDA) inspection of the Central Florida Eye Institute Institutional Review Board (IRB). This letter also discusses your written response, dated March 23, 2004, and requests that you implement prompt corrective actions. Mr. Albert A. Salvador and Ms. Brunilda Torres, investigators from FDA's Florida District Office (FLA-DO) and Ms. Contress Braxton, Consumer Safety Officer, FDA's Center for Devices and Radiological Health (CDRH) conducted the inspection from March 8 through 12, 2004. The purpose of the inspection was to determine whether your activities and procedures as an IRB complied with Title 21, Code of Federal Regulations (21 CFR) Part 56-Institutional Review Boards, and Part 812-Investigational Device Exemptions. These regulations apply to certain clinical studies of products regulated by FDA.

Our review of the establishment inspection report submitted by the district office revealed serious violations of the above stated regulations. At the conclusion of the inspection, Mr. Salvador presented a Form FDA 483 "Inspectional Observations" to you and [REDACTED] Surgical Administrator. Deviations noted on the Form FDA 483 and our subsequent inspection report review are discussed below:

1. Failure to prepare, maintain, and follow written procedures. 21 CFR 56.108(a) and (b); and 56.115(a)(6)

FDA regulations require each IRB to prepare and maintain written procedures for the IRB as specified in 56.108(a) and (b) and 21 CFR 56.115(a)(6). Our inspectional review revealed that Central Florida Eye Institute IRB does not have an official IRB written procedure.

Examples of your failure to satisfy these requirements include but are not limited to the following:

- there is no documentation of any IRB handbook or bylaws in place; and
- there are no documents which define the authority, functions, operations, details, and other requirements of the board.

As part of its procedures for conducting initial review of research, the IRB should have procedures for determining whether each investigation presented for IRB approval involves a non-significant risk (NSR) or significant risk (SR) device. Except in limited circumstances, the SR/NSR determination must be made by the IRB before the sponsor may begin the investigation. (21 CFR 812.66)

During the close-out discussion and in your written response, it was stated that an application to an independent IRB was submitted to request the handling of all IRB-related issues. In your response to this letter, please include the status of your request for an independent institutional review board to begin oversight of the clinical investigational study being conducted at your institution.

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

Pursuant to 21 CFR 56.107(d) and (e), IRBs are required to include at least one member who is not otherwise affiliated with the institution and 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.

Examples of your failures to satisfy these requirements include but are not limited to the following:

- According to the IRB roster, the IRB consist of five voting members, all who are employed by or associated with the IRB clinical facility. This violates the IRB membership requirements of 21 CFR 56.107(d).
- During the review and approval of your study, you voted as a member of the IRB which is in direct violation of 21 CFR 56.107(e) because you are the study's principal investigator.

Your response included a copy of the IRB meeting minutes dated March 22, 2004. The meeting focused on the FDA inspectional findings and captured voting results from previous meetings. The minutes from this meeting confirm the IRB membership violations described above. Your response also indicates that you have taken steps to have this study reviewed by another

IRB. Please note that to the extent that your IRB continues to review studies in the future, it must comply with the membership requirements set forth in 21 CFR 56.107.

3. Failure to provide adequate continuing review of approved studies. 21 CFR 56.108(a) & 56.109(f)

Pursuant to 21 CFR 56.108(a) and 56.109(f), an IRB is required to conduct continuing review, at least once a year, of studies that it has approved. In our review of the inspection report, the IRB files for the [REDACTED] study revealed that source documents and records do not indicate that IRB continuing review occurred on at least an annual basis.

4. Failure to assure that documentation of and information given to the subjects as part of the informed consent is in accordance with 21 CFR 56.109(b) and (c); and 56.111(a)(4) and (5).

In order to approve a study, the IRB must determine that informed consent will be sought from each subject in accordance with 21 CFR Part 50. The IRB must require that information provided to subjects as part of informed consent contains the basic elements described in 21 CFR 50.25, and that this information is documented as described in 21 CFR 50.27. An example of your failure to satisfy these requirements includes but is not limited to the following:

The informed consent form did not contain all of the elements as required by 21 CFR 50.25. For example, the informed consent form lacked information on whom to contact regarding questions about the research.

5. Failure to prepare and maintain adequate documentation of IRB activities. 21 CFR 56.115(a)(2).

Pursuant to 21 CFR 56.115(a)(2), an IRB must prepare and maintain adequate documentation of minutes of IRB meetings. The minutes must be sufficiently detailed to show meeting attendance, IRB actions taken, and votes cast by IRB members.

The IRB minutes for your IRB failed to adequately document the IRB's activities. Examples of these failures include but are not limited to the following:

- The IRB minutes for the meetings held on February 20 and March 4, 2004 do not adequately document the votes on the actions taken, including the

number of members voting for, against, and abstaining. Your response indicates that the March 22, 2004 minutes document the actions taken, who voted and how.

- The IRB minutes failed to document that a determination was made whether the study involved significant or non-significant risk devices and the frequency with which continuing review will occur.

The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist at your institution. It is the IRB's responsibility to assure its adherence to applicable FDA regulations.

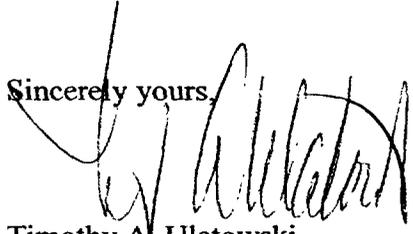
Within fifteen (15) working days, please provide written documentation of the additional specific steps that you have taken or will take to correct the violations noted. You should be aware that FDA considers the IRB's noncompliant actions to be serious violations of the law. Failure to respond to this letter and to take prompt action to correct these violations may result in further regulatory action, including initiation of procedures to disqualify the IRB.

Please address your response to the U.S. 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: Contress Braxton.

A copy of this letter has been sent to FDA's Florida District Office, 555 Winderley Place, Maitland, Florida 32751. We request that a copy of your response also be sent to that office.

If you have any questions, feel free to contact Ms. Contress Braxton at (301) 594-4723, ext. 138 or by email at cmb@cdrh.fda.gov.

Sincerely yours,



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