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

Via Federal Express

MAY 23 2001

WARNING LETTER

Robert H. Osher, M.D.
Cincinnati Eye Institute
10494 Montgomery Road
Cincinnati, Ohio 45242

Dear Dr. Osher:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site and requests from you a prompt reply informing us of your corrective actions. You participated as a clinical investigator in the study entitled, "[REDACTED]" sponsored by [REDACTED] to investigate the [REDACTED] device. Data from the study conducted at your site was submitted to the FDA in support of the investigational device exemption (IDE) [REDACTED].

During the period of March 5 through March 19, 2001, you were visited by Gina M. Brackett, an investigator from the FDA's Cincinnati District Office. The purpose of Ms. Brackett's visit was to conduct an inspection to determine whether your activities and procedures as a clinical investigator for the [REDACTED] study complied with applicable regulations. This product is a device as that term is defined under Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

This inspection was conducted under a program designed to ensure that data and information contained in applications for Investigational Device Exemptions (IDE), Premarket Approval (PMA), 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.

We have completed our review of the inspection report submitted by the Cincinnati District Office. The report reveals significant violations of the requirements under Title 21, Code of Federal Regulations (21 CFR), Part 50 - Protection of Human Subjects; 21 CFR, Part 56 - Institutional Review Boards; and 21 CFR, Part 812 - Investigational Device Exemptions. These violations are listed on the Form FDA 483, "Inspectional Observations," which was presented to and discussed with you and [REDACTED] at the conclusion of the inspection. The violations noted on the Form FDA 483 and our subsequent review of the inspection report are summarized below. We acknowledge your letter of April 3, 2001, which addresses the items listed on the Form FDA 483.

1. Failure to follow the investigational plan and applicable FDA regulations (21 CFR 812.100 and 812.110(b)).

- You failed to follow the investigational plan that allowed you to enroll fifteen (15) study subjects into the study. For example, rather than enrolling 15 study subjects into the study as stated in the investigational plan, you enrolled 182 study subjects. The protocol was not amended to reflect the increase in study subject enrollment, and the IRB did not approve of the increased enrollment at your site.
- You failed to follow the investigational plan for the inclusion criteria age requirement for four study subjects. For example, two study subjects, numbers [REDACTED] and [REDACTED] were 16 years old at the time of surgery. You failed to obtain a waiver from the provisions stated in the investigational plan to enroll these ineligible study subjects into the study. In addition, you failed to obtain a waiver for study subject number [REDACTED]: the June 17, 1999, Data Report Form for Investigational Device Exemption (IDE) Study [REDACTED] for this study subject shows that this subject was 3 years old at the time that the form was completed. The fourth study subject, number [REDACTED], born on [REDACTED], did not have proper informed consent for the surgery performed on his right eye (O.D.).

We acknowledge from your response that you have amended the protocol to allow inclusion of minors under special circumstances and that you are obtaining FDA waivers in every instance of intended [REDACTED] implantation in minors. However, your response did not properly identify the last two study subjects (numbers [REDACTED] and [REDACTED] mentioned above and therefore, your explanation of why these study subjects should not be included as a violation is inadequate.

- You failed to follow the investigational plan to include the 23-25 month post-operative visit for the following ten study subjects: [REDACTED] and [REDACTED]. We acknowledge that the sponsor's representative, [REDACTED], sent to you on September 26, 1999, a facsimile stating in part, ". . . the study as originally constructed . . . called for patients to be followed for two (2) years. We have succeeded in getting an agreement from the FDA to accept one year!" We understand that you might interpret this statement to mean that you no longer had to complete the 23-25 month visit. However, whenever there is a substantive change to the investigational plan, a protocol amendment must be executed, the institutional review board (IRB) must review the amendment for approval, and the FDA must be notified. The fact that this process was not followed should have prompted you to inquire further regarding [REDACTED] communication.

2. Failure to provide to study subjects the basic elements of informed consent (21 CFR 50.25).

You failed to provide to study subjects the basic elements of informed consent before allowing the study subjects to participate in a clinical trial. For example, study subjects entered into the study prior to September 1997 signed a consent form that did not contain the following elements: a statement that the study involves research; an explanation of the purposes of the research and the expected duration of the subject's participation; a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the FDA may inspect the records; an explanation of whom to contact for answers to pertinent questions about the study; a statement that participation is voluntary and that refusal to participate or discontinuation of participation in the study will involve no penalty or loss of benefits to which the subject is otherwise entitled.

3. Failure to maintain accurate, complete, and current records relating to the investigation (21 CFR 812.140(a)(2)).

You failed to adequately maintain records of receipt, use or disposition of a device that relate to the names of all persons who received, used, or disposed of each device. For example, in your response letter of April 3, 2001, you state that nine [out of 286] [REDACTED] are not accounted for in the study records.

4. Failure to prepare and submit complete, accurate, and timely progress reports on the investigation (21 CFR 812.150(a)(3)).

You failed to prepare and submit to the IRB annual progress reports. For example, the study coordinator stated that the IRB does not require annual reports and therefore, you did not submit to the IRB annual progress reports. However, the regulations state that, "An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly."

In addition to the above listed violations, please note that *all* study subject adverse experiences occurring during the study, whether device-related or not, anticipated or unanticipated, must be recorded on the appropriate case report form.

The violations listed above are not intended to be an all-inclusive list of violations at your site. 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 clinical investigators.


Please advise this office, in writing, **within fifteen (15) working days of receipt of this letter**, of the specific steps that 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 may result in regulatory action, including disqualification, 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: Kathleen E. Swisher, J.D., R.N., Consumer Safety Officer.

A copy of this letter has been sent to our Cincinnati District Office, 6751 Steger Drive, Cincinnati, Ohio 45237. We request that a copy of your response be sent to that office as well.

Sincerely yours,

Charuallb, RPh, RAC

Larry Spears
Acting Director
Office of Compliance
Center for Devices and
Radiological Health

Enclosure

cc:

[REDACTED] (purged)
U.S. Representative [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED] (purged)
[REDACTED]
[REDACTED]

[REDACTED] (purged)
Chairperson
[REDACTED]
[REDACTED]
[REDACTED]

bcc:

HFA-224

HFC-210 (DCarroll)

HFC-230 (BIMO Coordinator) (FEI No. 3003264188)

HFR-CE400 (DD)

HFR-CE450 (DIB/GBrackett)

HFI-35 (FOI Purged copy)

HFM-650 (JSalewski)

HFZ-300 (LSpears)

HFZ-305 (Precedent File)

HFZ-306 (Warning Letter File)

HFZ-305 (OC Reading File)

HFZ-310 (CBraxton, DBM Read File, and CI File - **Robert H. Osher, M.D.**)

HFZ-312 (VSellman/KSwisher)

HFZ-330 (DOE II)

HFZ-460 (JGlover)

HFZ-403 (G960190)

Draft:KSwisher:05/08/2001

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Finalized:KSwisher:05/23/2001

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Call 5/23/01