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DEPARTMENT OF HEALTH & HUMAN SERVICES



Public Health Service

Food and Drug Administration
9200 Corporate Blvd.
Rockville MD 20850

JUN 26 2007

WARNING LETTER

Via Federal Express

David Bailey, President
Staar Surgical Company
1911 Walker Avenue
Monrovia, CA 91916-4846

Dear Mr. Bailey:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your firm from February 15 through March 14, 2007, by an investigator from the FDA Los Angeles District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study titled *Clinical Study Protocol – STAAR Surgical Implantable Toric Phakic ICL (TICL) for Myopic/Astigmatic Patients* under IDE # G010252, and in support of PMA P030016/S001, complied with applicable federal regulations. The ICL (implantable contact lens) used for the study is a device as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h). This letter also requests prompt corrective action to address the violations cited and discusses your April 5, 2007, written response to the noted violations.

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 submissions (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 scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 812 -- Investigational Device Exemptions, Part 50 -- Protection of Human Subjects, and Section 520(g) (21 U.S.C. 360j(g)) of the Act. At the close of the inspection, the FDA investigator presented an inspectional observations form FDA 483 for your review and discussed the observations listed on the form with you. The deviations noted on the FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

1. **Failure to submit an IDE application to FDA, ensure IRB review and approval are obtained, and ensure FDA approval of an IDE application prior to beginning an investigation [21 CFR 812.40 & 21 CFR 812.42].**

You failed to adhere to the above noted regulations. Specifically:

- a.) Staar Surgical sponsored and initiated a clinical research study with a significant risk device without submitting an IDE application to FDA. A study site in [redacted] which was listed as a participant in the TICL study being conducted under IDE G010252, conducted its study under a different protocol that was designed to achieve a different objective than the study approved under IDE G010252. The study protocol under IDE G010252, as approved by the FDA, was for a non-randomized, open-label study to assess the effectiveness of the device. The study at the site in [redacted] which listed [redacted] as the clinical investigator, was for a randomized study in which subjects were randomly assigned to receive either the TICL implant or PRK (photorefractive keratectomy) with [redacted]. The study objectives were to assess and compare clinical outcomes of subjects receiving the two treatments.

[redacted] claimed on his IRB submission that this study was “part of an IDE study sponsored by and with the consent of Staar Surgical” and claimed that it was being conducted under IDE G010252. Staar Surgical provided the devices for the study, which was approved by the IRB on 9/17/03. [redacted] subsequently implanted the TICL into [redacted]. The data for these procedures have been included in your PMA submission P030016/S001 to the FDA.

In your response letter, dated April 5, 2007, you stated that “this issue was identified by the STAAR clinical team during their visit February 16/17, 2006,” and that you are “in active discussion with our site monitor contractor to establish a very specific schedule of activities to be undertaken.” This response is not adequate, in that it does not address any corrective and preventive actions regarding initiation of a significant risk study without an IDE. Please provide documentation of a corrective action plan, specific to this issue.

- b.) At least [redacted] of the [redacted] clinical study sites did not obtain IRB approval for the correct version of the study protocol. [redacted]

[redacted] used Western IRB (WIRB) as their IRB of record. WIRB approved the protocol version dated [redacted] for [redacted] on [redacted] and for each of the other three study sites on [redacted]. The FDA approved a revised version of the protocol on [redacted], and Staar Surgical finalized the revisions in the protocol version dated [redacted]. Mr. Robert Lally, the Staar Surgical Vice President of Regulatory Affairs and Quality Assurance, provided a document to the FDA investigator that stated the study was “activated” under the [redacted] version of the protocol, (with the FDA-requested revisions). Mr. [redacted], Senior Clinical Research Associate, who was present during the inspection, also told the FDA investigator that WIRB confirmed with him that they never reviewed or approved the [redacted] version of the protocol for these [redacted] study sites. Each of

these 4 study sites enrolled several subjects under the [] (non-FDA approved) version of the protocol.

In your response letter, you stated that a new procedure is being developed to cover annual renewals and supplemental approvals of revisions to protocols. Please provide us with a copy of this procedure once it is finalized, and please include an explanation and supporting documentation regarding training of appropriate staff on the new procedure.

2. Failure to secure the investigators' compliance with the investigational plan and applicable FDA regulations [21 CFR 812.46(a)].

Staar Surgical failed to ensure that all clinical investigators participating in the study adhered to the investigational plan and FDA regulations. Examples of this failure include:

- a.) The Patient Eligibility Checklist Case Report Form (CRF) provided to [] clinical site in [] listed a requirement for "direct and retro illumination photographs." The CRF also stated that "all answers must be YES to proceed" and "if the patient does not satisfy ALL the eligibility criteria above DO NOT PROCEED FURTHER." On all [] CRFs for the subjects' eyes implanted by [] the question for "direct and retro illumination photographs" was marked "N/A." Mr. [] told the FDA investigator that this study site had been given verbal approval to proceed without these photographs, and that the site did not have the necessary equipment to take these photographs.

Furthermore, in the [] Database maintained for this study, the responses that were marked "N/A" on the CRFs were entered as "1" (indicating a YES answer) or left blank in the data listing. The original validation for the database required that an entry marked as "2" (no photographs) or left blank would result in a message that "this patient might become disqualified." The database coding was changed on 10/27/04 to show no message when any entry was made, and to default to a "1" no matter what entry was made.

In your response, you noted that direct and retro-illumination photographs were not required in the study protocol, and the eligibility checklist CRF was inadvertently carried over from the previous study. FDA regulations consider an investigational plan to include the written protocol [21 CFR 812.25(b)]. The CRFs are considered part of the investigational plan. If the requirement for direct and retro-illumination photographs was not a requirement for the study, it should not have been included on the CRF and in the study database. Your response also stated that your IT department is developing a new procedure covering changes to validated databases. This is not an adequate response in that it does not address any corrective or preventative actions for the above stated violation. Please provide an explanation and supporting documentation regarding how Staar Surgical will ensure that all study documents correspond to the approved protocol, and how study site non-compliance issues will be addressed for future studies.

- b.) A study site under [redacted] in [redacted] used a non-IRB approved consent form for the pre-operative YAG Laser Iridotomy portion of the study, for [redacted] of the [redacted] subjects enrolled in the study at that site. The IRB had approved the consent form on 2/8/02. This violation occurred during the period of 9/17/02 through 11/30/05, which is after the IRB approved the consent form. Furthermore, Staar Surgical did not identify this violation until a monitoring visit conducted in August 2006, nearly four years after the date of the first violation.

In your response, you stated that “appropriate action was swiftly implemented to remediate the situation” following a site visit in August 2006. You also stated that you are “amending arrangements with our site monitoring contractor to avoid recurrence of similar omissions.” This response is not adequate in that it does not address any corrective or preventative actions for the violation. Please provide an explanation and supporting documentation regarding how Staar Surgical will ensure that study sites are using the correct IRB-approved consent forms for all enrolled subjects.

3. Failure to immediately conduct an evaluation of all unexpected adverse device effects [21 CFR 812.46(b)].

According to Staar Surgical’s procedure titled “Clinical Trials Adverse Event Reporting,” effective 8/30/2005, any unexpected adverse device effects are to be reported to the FDA within 10 working days of initial receipt of the report. Anticipated adverse events will be reported annually in the IDE annual report. The SOP also notes that a change in frequency or severity of anticipated adverse events will be evaluated by the Medical Reviewer to determine whether it becomes an unanticipated adverse event. At least three adverse device effects were reported during the study, which were not immediately investigated to determine if they were expected or unexpected. Specifically:

- a.) Subject [redacted] experienced subcapsular cataract in the left eye, as reported to Staar Surgical on 1/8/04. Subject [redacted] experienced retinal detachment requiring surgical treatment on 7/8/04. There was no documentation that these events were evaluated by your Medical Reviewer to determine if they met the 10-day reportability requirement.
- b.) Subject [redacted] experienced slight Iris Bombay, enlarged pupil, and darkened iris on 1/31/03. This event was not evaluated by the Medical Reviewer until 1/28/04, which is nearly a year after the event occurred.

In addition, during the FDA inspection, your Medical Reviewer, [redacted] reported that he discarded all documentation regarding his evaluation of adverse events. Your Adverse Event procedure also states that “the Clinical Department will trend anticipated adverse events, as appropriate. If there is an increase in the frequency or severity of an event, the information will be forwarded to the Medical Reviewer.” [redacted] told Mr. Lally during the FDA inspection that he did not know how Staar Surgical established the expected frequency and severity of anticipated adverse events, and Mr. Lally could not provide documentation that trending of adverse events occurred.

In your response, you stated that your adverse event reporting procedure “is being revised to enhance controls along the lines discussed.” Please provide us with a copy of this procedure once it is finalized, and please include an explanation and supporting documentation regarding training of appropriate staff on the new procedure.

4. Failure to submit required reports and information to the FDA for an investigation being conducted under an IDE, including reports of prior investigations. [21 CFR 812.27]

Staar Surgical failed to adhere to the above noted regulations. Specifically, during the FDA inspection, Mr. Lally told the FDA investigator that a similar study had been conducted with [] subjects in [] prior to conduct of this study. The protocol was titled [] IDE # [] The Implantable Toric Contact Lens for Patients with Myopia and Astigmatism, version May 11, 1999.” Information regarding this study was not provided to FDA in the IDE submission, and Mr. Lally could not provide any information regarding the outcome of this study.

In your response, you stated that you have asked the Staar Surgical team in the Swiss facility to notify you of any records related to the conduct of the pilot study in [] Please provide us with this information once it is received.

In addition to the violation above, you notified FDA of an IDE change on October 8, 2002, in which you added [] as one of the clinical investigators for the IDE study. In this notification letter, you stated, “No other changes are being made to the Toric Implantable Contact Lens (TICL) Clinical Investigational Plan approved by the agency on January 3, 2002.” This statement appears to be false since, as previously mentioned, the study conducted by Dr. [] differed significantly from the study approved under the IDE. Dr. [] provided a memo to Staar Surgical, dated February 17, 2006, in which he stated “early in the discussion of plans to include [] as a clinical site, we decided we wanted to expand our participation to include randomization of study participants... We had discussion with [] by teleconference... we explained our plan to include randomization to procedure and [] provided enthusiastic agreement.”

The violations described above are not intended to be an all-inclusive list of problems that may exist with your clinical study. It is your responsibility as a study sponsor to ensure compliance with the Act and applicable regulations.

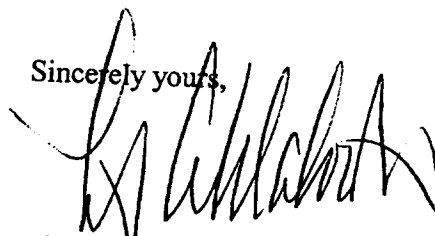
Within **fifteen (15) working days** of receiving this letter, please provide written documentation of the additional actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are the study sponsor. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. Please send your response to:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Bioresearch Monitoring, HFZ-311
9200 Corporate Boulevard, Rockville, Maryland 20850
Attention: Ms. Doreen Kezer, MSN, Chief, Special Investigations Branch.

A copy of this letter has been sent to FDA's Los Angeles District Office, 19701 Fairchild, Irvine, CA 92612. We request that a copy of your response also be sent to that office.

If you have any questions, please contact Ms. Doreen Kezer at 240-276-0125 or at Doreen.Kezer@fda.hhs.gov.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Timothy A. Ulatowski". The signature is fluid and cursive, with a large initial "T" and "U".

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