DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
US Food and Drug Administration Rm. 900 US Customhouse, 2nd and Chestnut Sts. Phila. PA 19106 (215) 597-4390	4/19,20, 23-30, [redacted] 5/1-4,7, 10/2001
	FEI NUMBER [redacted]

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO [redacted]

FIRM NAME	STREET ADDRESS
Medical Director	[redacted]
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
[redacted]	Sponsor/Clinical Investigator

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

The following observations refer to the Investigational Device Exemption (Protocol # [redacted]) for the indicated study, "[redacted] with an [redacted]er in the Surgical Treatment of Refractive errors: Myopia with and without Astigmatism"

1. There was no documentation to show that the CI notified the IRB about all amendments, changes or significant deviations to the protocol [per IRB requirements] prior to implementation.

   For example, the FDA granted your firm an increase in the number of subjects you could treat with your investigational device on Jan. 20, 1999. IRB Annual Review dated 7/29/00 does not indicate the IRB knew about population increase. The IRB did not approve the population increase until August 28, 2000, 20 months later

2. The firm is not complying with the Investigator Agreement which was signed and dated by the Clinical Investigator at the beginning of the Clinical Study.

3. There was a lapse of IRB approval for the protocol: [redacted]om 8/3/2000 until 8/29/2000 according to IRB lapse notices and the IRB annual re-approval letter.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
	[redacted]	[redacted]	May 10, 2001

[redacted]

SUMMARY OF FINDINGS:

The inspection of this Sponsor/Clinical investigator was conducted per assignment from CDRH, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II(HFZ-312)and in accordance with CP 7348.811. [redacted] is the Medical Director and founder of [redacted] where he performs laser eye surgery on patients. [redacted] has an excimer laser, [redacted] and is conducting a clinical study, Correction of Myopia with and without astigmatism Protocol [redacted] under an approved Investigational Device Exemption (IDE). [redacted] Sponsor/Clinical Investigator and [redacted] is the Co-Investigator.

An inspection conducted on 12/2/96 revealed the firm had assembled a single excimer laser and was using it to perform [redacted] eye surgery on at least 120 patients without an approved IDE.

A follow-up inspection on 6/30/97 of this facility revealed the firm continued to use the excimer laser to perform [redacted] eye surgery without an approved IDE, planned to use the excimer laser for new treatment procedures not included in the firms disapproved IDE and verification that the firm had received a disapproval letter from CDRH/ODE notifying them that use of the laser to treat patients was a violation of the law.

The previous inspection conducted 11/2/1998 revealed procedures being performed on IDE patients prior to approval date, missing date on a consent form, consent forms signed after surgery date and procedures done on IDE patients which are outside the IDE with an unidentified laser at an unauthorized location.

The current inspection revealed the firm has corrected the deficiencies noted in the inspection of 11/2/1998 however, the Clinical Investigator did not notify the IRB of all changes or deviations from the protocol. There was an unexplained lapse in IRB approval/coverage for the protocol [redacted] for approximately one month. The inspection is classified VAI. An FDA-483 was issued at the conclusion of the inspection.

HISTORY OF BUSINESS:

[redacted] is the founder, Chief of Staff as well as the most responsible individual of [redacted] There are six additional physicians and three other locations associated with the practice.

[redacted]

[redacted]

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All FDA correspondence should be addressed to [redacted] at the aforementioned [redacted] address. The firm operates Monday to Friday, 8:00am - 5:00pm.

PERSONS INTERVIEWED AND INDIVIDUAL RESPONSIBILITIES:

On 4/19/01 I presented my credentials and issued a FD-482 to [redacted] Clinical Coordinator. He is not the most responsible individual at the firm however, [redacted] who is the most responsible individual, was unavailable at the time. [redacted] is the founder and Medical Director of [redacted] stated [redacted] would be able to answer my questions and be present throughout most of the inspection.

OPERATIONS:

[redacted] is the Medical Director and founder of [redacted] where he performs laser eye surgery on patients. [redacted] has [redacted] laser and is conducting a clinical study, Correction of Myopia with and without astigmatism Protocol # [redacted] under an approved Investigational Device Exemption (IDE). [redacted] is a Sponsor/Clinical Investigator. [redacted] is the Co-Investigator and the only other physician who performs [redacted] surgical procedures with an excimer laser at the practice. The laser is identified as a [redacted] model [redacted] It was built in the fall of [redacted] a laser scientist and President of [redacted] provided [redacted] with the basic specifications for the laser and [redacted] then designed and built the laser indicating to [redacted] the components that were needed and where to order them. The laser beam generator is a [redacted] serial number [redacted] purchased from [redacted] The housing and electrical/gas delivery system [argon fluoride (ArF) as halogen source to produce the laser beam] was purchased from [redacted]. The other components were ordered from other various manufacturers.

Previously [redacted] of [redacted] performed all maintenance, repairs and calibrations on the [redacted] laser. Currently [redacted] a subsidiary of [redacted] performs all maintenance, repairs and calibrations on the [redacted] laser.

[redacted]
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[redacted] performs minor parts replacement and maintenance however, all major work is performed by [redacted] Maintenance records observed during the inspection do indicate that [redacted] is performing maintenance, repairs and calibrations.

The emission from the laser passes through a safety shutter, beam shaping optics, beam modulator, imaging optics and finally is reflected downward into the working region. The operation of the laser, shutter and beam shaping optics is controlled by a computer system. According to [redacted] consultant, validation of the computer system is to be done by an outside firm and will be included with the submission

The desired lens correction information is entered into the computer which controls the laser beam size and delivered energy density during the ablation process. First a very thin corneal flap is created using an instrument called a microkeratome (diamond knife). When the eye is properly positioned, the operator uses a foot pedal to activate the laser and ablate the corneal tissue to achieve the desired lens correction. The corneal flap is then repositioned to heal.

[redacted] initial IDE submission was disapproved May 8, 1998. He was granted conditional approval on August 7, 1998. As [redacted] addressed various issues presented in letters from FDA CDRH/ODE he was granted more uses of the IDE laser. As of 11/2/98 his investigation is limited to **1 institution ([redacted]** and 225 subjects: 150 subjects (300 eyes) for low myopia (-0.5 to -6.75 diopters myopia plus up to -7 diopters astigmatism); 50 subjects (100 eyes) for high myopia (-7 to -15 diopters with up to -7 diopters astigmatism); and 25 subjects (50 eyes) for enhancements/retreatments of subjects treated prior to IDE approval (-0.5 to -15 diopters myopia with up to -7 diopters astigmatism).

According to a letter from the FDA to [redacted] dated 1/20/99 **EXHIBIT #1**, the investigation is still limited to one location, listed in bold above however, the population has grown to 1015 subjects (2030 eyes): 990 subjects (1980 eyes) for myopia (-0.5 to -15 D with up to -7 D astigmatism); and 25 subjects (50 eyes) for enhancements of subjects treated prior to IDE approval (-0.5 to -15 D myopia with up to -7D astigmatism).

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From the date the first patient was treated under the IDE, August 28, 1997, until 11/2/98 [redacted] has treated 154 subjects (276 eyes) for high and low myopia and 24 subjects (23 eyes) for myopic enhancements.
According to [redacted] refractive log **EXHIBIT #2**, from December 29, 1999 until April 20, 2001 590 patients, 1080 eyes, have been treated for high and low myopia and 162 patients, 241 eyes, for myopic enhancements.

[redacted] surgery is performed at the aforementioned main address and at the office located at [redacted]

OBJECTIONABLE CONDITIONS OR PRACTICES:

At the conclusion of the inspection an FD-483 was issued and a discussion with management held. [redacted] Clinical Investigator and [redacted] Clinical Coordinator attended the meeting.

The following observations refer to the Investigational Device Exemption (IDE) Protocol# [redacted] for the indicated study, " [redacted]) with an [redacted] Laser in the Surgical Treatment of Refractive errors: Myopia with and without Astigmatism"

1. **There was no documentation to show that the CI notified the IRB about all amendments, changes or significant deviations to the protocol [per IRB requirements] prior to implementation.**

   For example, the FDA granted your firm an increase in the number of subjects you could treat with your investigational device on Jan. 20, 1999. IRB Annual Review dated 7/29/00 does not indicate the IRB knew about population increase. The IRB did not approve the population increase until August 28, 2000, 20 months later.

[redacted] uses a national IRB, [redacted] Institutional Review Board [redacted] for his clinical research study.
EXHIBIT #1 is a letter from the FDA CDRH, Division of Ophthalmic Devices to [redacted] which among other things granted him an increase in the number of clinical research study subjects to 1,015.

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[redacted] Institutional Review Board sent [redacted] a notice dated August 1, 2000, **EXHIBIT #3,** to inform him that the revised protocol dated 7/8/98 in their possession indicated the low myopia population was limited to 400 subjects.

[redacted] reported in a biannual report that was sent to SAIRB the number of myopes had exceeded 400 patients however, he failed to mention that the patient population had been increased by the FDA in Jan. 1999. [redacted] drafted a letter to [redacted] **EXHIBIT #4** dated 8/16/2000 explaining the increase in patient population. SAIRB reviewed the information from [redacted] and responded by letter **EXHIBIT #5** dated August 30, 2000 reapproving [redacted] study for another year.

2. **The firm is not complying with the Investigator Agreement which was signed and dated by the Clinical Investigator at the beginning of the Clinical Study.**

EXHIBIT #6 is an Investor Agreement which was signed by [redacted] Sponsor/Clinical Investigator and [redacted] o-Investigator. The agreement indicates, among other things, the clinical investigators agree to promptly report to the IRB all changes in the research activity. The clinical investigators failed to report the increase in the number of study patients, granted by the FDA, to the IRB in a prompt manner.

3. **There was a lapse of IRB approval for the protocol: [redacted] from 8/3/2000 until 8/29/2000 according to IRB lapse notices and the IRB annual re-approval letter.**

EXHIBIT #7 is a reapproval letter from [redacted] dated 8/4/99 for [redacted] study with an expiration date of 8/3/00. [redacted] wrote [redacted] on August 1, 2000, **EXHIBIT #3** indicating they had not received an update in the form of a report from him concerning the study. The letter also stated the IRB approval will lapse on 8/3/00. [redacted] wrote [redacted] for a second time on 8/7/2000 **EXHIBIT #8** indicating they still had not received any updates concerning the study. The letter also stated [redacted] should cease enrollment on low myopia surgeries and if he chose to amend the protocol to request permission to do more low myopia surgeries he could not begin scheduling the surgeries until the amendment was approved by the IRB. The laser refractive study log **EXHIBIT #2 pgs.12&13** show [redacted] continued performing myopia surgeries throughout the month of August 2000.

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Finally, the letter stated IRB approval lapsed 8/3/00.

On 8/16/2000 [redacted] drafted a letter to [redacted] indicating the FDA had granted him an increase in the study patient population **EXHIBIT #4.** [redacted] sent [redacted] a letter dated August 30, 2000 reapproving the study effective the same date for another year **EXHIBIT #5.**

I explained to [redacted] that he did not have IRB coverage from 8/3/2000 and until 8/29/00. [redacted] stated his consultant, [redacted] was ill for several months and she normally took care of report submittals and updates which is why the firm was tardy with reporting updates. I indicated to [redacted] that either he or his consultant should have a back-up plan for such emergencies which could happen at any time. He stated a back-up plan would be drafted and implemented as soon as possible.

VOLUNTARY CORRECTIONS:

1. Simultaneous [redacted] was performed on [redacted] and [redacted] on 8/28/97 which was prior to the actual approval date.

According to [redacted], he was not aware that [redacted] was not approved and could not be performed. He stated this observation represents a misunderstanding between the FDA and him.

[redacted] stated he had been doing this procedure previously and no one had told him the procedure couldn't be performed as of 8/28/97. There were no violations of this type observed during the current inspection.

2. [redacted] received Myopic [redacted] on 9/25/97 OD (right eye) prior to the date approval was given to perform enhancements.

[redacted], Co-Investigator performed this procedure and stated her father, [redacted] told her it was okay to perform myopic [redacted] Both investigators indicated they did not know it was not approved. [redacted] stated he thought it was okay and remembers getting verbal approval from someone at FDA in Rockville Md. I indicated to [redacted] that in the future he should obtain documentation for all approvals given. There were no violations of this type observed during the current inspection.

[redacted]

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3. **Consent form for [redacted] was not signed. There was no way to determining whether consent was obtained before or after [redacted] surgery to the right eye on 12/4/97, due to lack of a date next to patients' signature.**

Same as above 4/97

[redacted] assured me this was merely a mistake and that all patients read and sign consent forms before surgery. He stated he would remind his staff to be more careful when filling out consent forms. There were no incidences of this type observed during the current inspection.

4. **Consent forms for [redacted] and [redacted] were signed and dated (2/20/98) one day after Myopic [redacted] surgery to the right eye was performed (2/19/98).**

✓ Same

[redacted] stated it may appear that patients signed the consent forms one day after surgery however, this is certainly not the case and is not the way things are normally done. He indicated this was a mistake made by someone on his staff. There were no incidences of this type observed during the current inspection.

5. **[redacted] had [redacted] for Myopia on 8/13/98. However, the patient information and consent form which was approved for use by the IRB on 7/17/98, was not present in the patient file or made available upon request.**

✓ Same

[redacted] indicated this was a mistake and they would have to be more careful in the future. The person who is responsible was new and not aware of the IRB approved consent form to be used. There were no incidences of this type observed during the current inspection.

6. **[redacted] and [redacted] had [redacted] performed which is a condition not indicated in the Protocol [redacted] Additionally, the procedures were performed with a laser that is not indicated in the study and the surgery was performed at a location that**

Same

[redacted]
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is not identified in the protocol.

During the examination of patient records there were no non-indicated procedures performed on IDE patients with a laser that was not indicated in the study at a location which was not identified in the Protocol [redacted]

7. There was no documentation to show that the CI notified the IRB about all amendments, changes or significant deviations to the protocol [per IRB requirements]

Same as prev 483

This observation was carried forth to the current listing of objectionable conditions or practices. **See FDA-483 observation #1 listed above on page #4 of this report.**

Questions from Compliance Program CP 7348.811:

Authority and administration:

1. [redacted] of [redacted] visits the clinical site to monitor the clinical research according to the monitor's log examined during the inspection.

2. [redacted] is the principal investigator and [redacted] is the Co-Investigator, they retain control and knowledge of the study.

3. The study was not discontinued before completion and is currently ongoing.

4. A review of file records revealed pre-surgical eye tests for study patients are performed at [redacted]

Protocol:

1. Protocol for study is included as **EXHIBIT #9.**

2. There were no major changes to the protocol with reference to subject selection, frequency of subject observations, dosage, route of administration, frequency of dosage and blinding procedures, however there was an increase in the number of subjects.