Exhibit A

APR 14 1997

DEPARTMENT OF HEALTH AND HUMAN SERVICES — Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
9200 Corporate Blvd.
Rockville, Maryland 20850

APRIL 09, 1997

HERBERT J. NEVYAS, M.D.
DELAWARE VALLEY LASER SURGERY INSTITUTE
TWO BALA PLAZA
333 EAST CITY AVENUE
BALA CYNWYD, PA 19004
ATTN: HERBERT J. NEVYAS, M.D.

Dear Sponsor:

The information you have submitted, as required by the Food and Drug Administration (FDA) investigational device exemptions (IDE) regulation, has been assigned the following document control number:

IDE Number: G970088
Dated: 18-MAR-97
Received: 08-APR-97
Device: NEVYAS EXCIMER LASER SYSTEM

FDA will notify you when the review of this submission has been completed or if any additional information is required. In accordance with Section 812.30 of the IDE regulation, you may begin your investigation 30 days after the date FDA received your submission, unless FDA notifies you that your investigation may not begin.

Any questions concerning this submission should be directed to the undersigned at (301) 594-2205. Any future correspondence regarding this submission should be identified with your IDE number and should be submitted, in triplicate, to :

Food and Drug Administration
Center for Devices and
Radiological Health
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

Sincerely,

FDA 0 0002

A. Ralph Rosenthal, M.D.
Director
Division of Ophthalmic Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

C D R H
Division of Ophthalmic Devices

9200 Corporate Boulevard
Rockville, MD 20850
FAX NO. 301 480-4201

Date: MAY 8, 1997 Time: 3:45 P EDT

To: CHRISTINE LOONEY FAX #: 610-668-1509

Organization: DELAWARE VALLEY LASER SURGERY INSTITUTE

From: EUGENIE T. BEERS

Department: DIAGNOSTIC & SURGICAL DEVICES

Subject: DISAPPROVAL OF IDE

No. of Pages: 10
(Including Cover Sheet)

Comments:

☐ As Requested ☐ FYI ☐ Read and Destroy

☐ Response Needed ☐ Signature ☐ Circulate

☐ For Correction ☐ Investigate ☐ File

Division Director	301 594-2205
Diagnostic and Surgical Devices Branch	301 594-2018
Vitreoretinal and Extraocular Devices Branch	301 594-1744
Intraocular and Corneal Implants Branch	301 594-2053
Mail Code: HFZ 460	

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

MAY - 8 1997

Herbert J. Nevyas, M.D.
Nevyas Eye Associates
Delaware Valley Laser Surgery Institute
333 City Line Avenue
Bala Cynwyd, PA 19004

Re: G970088
Sullivan Excimer Laser System (Nevyas Model)
Indications for Use: LASIK for Myopia (-0.5 to -22 Diopters with up to -7 D Astigmatism)
Dated: March 18, 1997
Received: April 8, 1997

Dear Dr. Nevyas:

The Food and Drug Administration (FDA) has reviewed your investigational device exemptions (IDE) application. We regret to inform you that your application is disapproved and you may not begin your investigation. Our disapproval is based on the deficiencies listed below. Because your excimer laser system, which you have told us is being used to treat patients, has neither an approved application for premarket approval (PMA) under section 515(a) of the Federal Food, Drug and Cosmetic Act (the Act), nor an IDE under section 520(g), your device is adulterated under section 501(f)(1)(B). This is to advise you that, consequently, any use of these devices to treat patients is a violation of the law.

Our disapproval of your IDE is based on the following deficiencies:

1. On page 22 you indicate that cadaver eyes were ablated with the laser and topography measurements were taken to verify uniformity of ablation. Since your submission contains no actual ablation profiles (other than the theoretical ablation patterns in Attachment 3.4.1.3.A-1) which show that the laser can actually function as designed, please provide the corneal topographies of the cadaver eyes, or provide corneal topographies from your previous clinical studies.

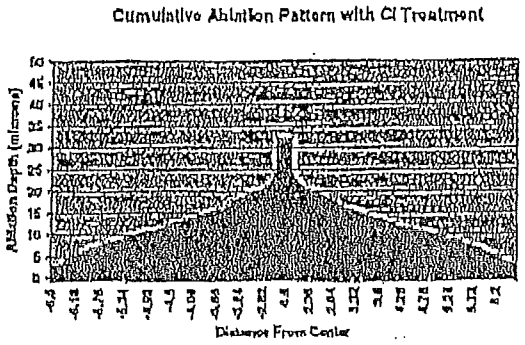
2. You have not provided a sufficiently detailed scientific and technical analysis of the following critical engineering aspects of your device. Please provide this information for each refractive indication being studied:

FDA 0 0004

a. Please provide a description of the pattern of ablation including detailed diagrams and explanations of the hardware and software components involved in generating the new surface (variable apertures, masks, annulae, crescents, diaphragms, multizones, multipasses, and scanning patterns).

b. Please provide cross-sectional views (profilometry) of the PMMA ablation for each indication (minimum and maximum), including astigmatism, and compare the theoretical versus the actual (achieved) plot. This profilometry should be for your particular device, rather than for a generic or similar laser. In addition, please provide the following information on your profilometry measurement: signal to noise ratio, accuracy of depth measurement, accuracy of transverse movement, and number of measurement points per surface.

c. The pattern depicted below is from page 153 of your submission and shows theoretically the cumulative effect of a -3.0 diopter ablation using your multizone, multipass ablation algorithm.



As seen in the diagram, it appears that the central 2 mm of the ablation is flat (uncorrected), with steep slope (approximately infinite) for about 25% of the ablation depth (8 microns out of 32 microns), then continuing with more modest slope out to 6.6 mm. Please explain:

i. During vision with narrowed pupils at 2 mm diameter, is the refraction of the cornea the same as prior to surgery (since that area did not receive a modification of the curvature)?

ii. During vision with pupils greater than 2 mm diameter, will glare and halo be significantly increased?

iii. Please relate this theoretical pattern to your profilometry measurements and explain any differences.

iv. Please provide scientific documentation that a final aperture opening of 2 mm does not adversely affect the quality of the ablation profile and whether or not it could induce complications.

d. Please provide the etch rate and the precision of the etch rate for your laser.

e. The Spiricon beam analysis provided in Attachment 2.1.B-1 does not appear to be from your laser but, possibly, from a laser similar to yours. Please provide one of the following: (1) a detailed Spiricon beam analysis from your laser; (2) certification from Spiricon that the data presented are from your laser; (3) some other measurement of beam homogeneity performed on your laser; or, (4) appropriate manufacturing information demonstrating that your device is the same (in terms of all components comprising the laser and optics generating the beam, method of manufacture, and GMP compliance) as the device measured in the Spiricon beam analysis. The beam homogeneity measurements should be performed on the beam at the treatment plane at maximum diaphragm opening.

f. Please provide additional details regarding methods for obtaining and maintaining both temporal and spatial beam homogeneity.

g. Please provide the nomogram you will be using to produce the patterns of ablation.

3. Please explain the low effectiveness and safety outcomes achieved in your prior clinical studies and specify what steps you are taking to improve your results. Your refractive and visual outcomes were reported at one month as: MSRE for low myopes, < 57% were within 1D and < 35% were within 0.5D; less than 60% achieved BUCVA > 20/40; complication and adverse events occurred in > 2% of the cases.

4. Please indicate what Operating System your computer is using.

5. Please provide a beam path and narrative description (with diagrams) of the subsystem and components of the operating microscope subsystem, including geometry and eye illumination levels (provide microscope lamp specifications and whether or not illumination is changed for different indications).

6. On page 62 you indicate that the beam divergence is 4°. This seems quite large, since beam divergence for these types of refractive lasers is usually on the order of fractions of a degree. Please specify in milliradians what the beam divergence is following the last focussing lens and explain any large divergence (> 50 milliradians).

7. Please provide your agreement (or justification for not agreeing) that retreatments done to improve refractive outcome are NOT considered as treatment failures, whereas retreatments done to achieve resolution of an adverse event ARE considered as treatment failures.

8. Please clarify why you have omitted or modified the following inclusion criteria (Section 3.2.4.1):

   a. BSCVA should be 20/40 or better in both eyes.

   b. Contact lens wearers should:

      i. remove soft or gas permeable contact lenses two weeks prior to baseline measurements

      ii. remove hard contact lenses three weeks prior to baseline measurements, and have two central keratometry readings and two manifest refractions taken at least one week apart that do not differ by more than 0.50 diopter in either meridian; mires should be regular.

   c. Spherical or cylindrical portion of manifest refraction should progress 0.50 diopter or less during the year prior to the baseline exam.

   d. Subjects should be willing and capable of returning for follow-up examinations for the duration of the study.

   e. Videokeratography should be normal.

9. Please clarify why you have omitted or modified the following exclusion criteria (Section 3.2.4.2):

   a. Taking systemic medications likely to affect wound healing, such as corticosteroids or antimetabolites

   b. Immunocompromise (e.g., AIDS, autoimmune disease)

   c. Unstable central keratometry readings with irregular mires

   d. History of glaucoma or an intraocular pressure > 21 mm of Hg.

10. Your description of study procedures, examination conditions and techniques is not adequate. Please provide a detailed description of each procedure, test and instrument to be used in the study. Standard references may be used for generally accepted tests and instruments, but distances, luminances, and other settings should be provided.

11. On page 134 of your submission you have presented a sample of your Intraoperative Report Form. Operative reports should be completed for all treated subjects, and for those subjects on whom a procedure was attempted but not completed. In addition, the report should include the information on attempted spherical correction, attempted cylindrical correction, number of laser pulses, time for entire procedure, whether procedure was interrupted, drug treatment before, during and after the procedure, and which eye was treated first (and second). Report forms should be in a forced-choice format. Please revise your intraoperative report form or present justification for not conforming with the above recommendations.

12. Please provide a copy of your patient questionnaire.

13. You have indicated that cylinder will be evaluated based on desired versus achieved correction. However, since your study design involves a high degree of astigmatism (up to -7 D), please provide a plan to stratify your results also by astigmatic presentations. Also, for the astigmatic corrections, please report the proportion of eyes that achieve minimal residual astigmatism.

14. In your Informed Consent Document, page 197, please correct or justify the following:

    a. please provide a statement in one of the initial paragraphs that the study involves research;

    b. please provide a statement of the expected duration of the subject's participation;

    c. please delete the last sentence in the second paragraph on page 198, which begins, "However, this laser was developed by Dr. Nevyas...."; and,

    d. please correct the typographical errors on page 199 which mention Drs. Wong & Thorne.

15. All co-managing practitioners are considered investigators and must sign the investigator agreement prior to their participation. Please certify that all investigators (and co-managers) who will participate in the investigation have signed [illegible] Agreement.

16. For your follow-up visit schedule, the text on page 20 of the protocol appears to be inconsistent with the chart on page 43 of the protocol. In addition, please justify your statement on page 20 that measurement of corneal topography will be at the discretion of the investigator.

On page 93 of your submission you give the name and address of your Institutional Review Board (IRB). You are advised that your IRB should be composed and conducted in accordance with 12 CFR Part 56 and that members of the IRB should conform to 21 CFR 56.107 (e): "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."

If you submit information correcting the deficiencies, we will reevaluate your application. The information should be identified as an IDE amendment referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

Alternatively, you may request a regulatory hearing regarding the disapproval of your IDE application. The enclosure "Procedures to Request a Regulatory Hearing" describes how to submit such a request. The procedures governing a regulatory hearing are described in the regulations at 21 CFR Part 16.

If you prefer not to request a regulatory hearing, you may nevertheless request that this decision be reviewed by the IDE Review Committee within the Office of Device Evaluation (ODE). The enclosure entitled, "IDE Review Committee and Procedures to Request Review" discusses the purpose and operation of the Committee as well as how to submit such a request to the Committee.

If you have any questions, please contact Everette T. Beers, Ph.D. at (301) 594-2018.

Sincerely yours,

A. Ralph Rosenthal, M.D.
Director
Division of Ophthalmic Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosures
(1) Procedures to Request a Regulatory Hearing
(2) IDE Review Committee and Procedures to Request Review

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 0 6 1997

JUL 29 1997

Herbert J. Nevyas, M.D.
Nevyas Eye Associates
Delaware Valley Laser Surgery Institute
333 City Line Avenue
Bala Cynwyd, PA 19004

Re: G970088/A1 and A3
Device name: Sullivan Excimer Laser System (Nevyas Model)
Dated: July 3 and 21, 1997
Received: July 8 and 22, 1997

Dear Dr. Nevyas:

On July 8 and 22, 1997, the United States Food and Drug Administration (FDA) received the amendments to your investigational device exemption (IDE) application that you submitted for your excimer laser system for use in refractive eye surgery. FDA has started to review this application. We have determined, however, that additional information is required in order to complete this review.

Excimer laser systems are Class III devices within the meaning of section 513(f) of the Federal Food, Drug, and Cosmetic Act (the Act). Accordingly, a physician may not use an excimer laser system to treat patients unless there is in effect an approved premarket approval application (PMA) or an approved IDE for that device.

FDA is aware that a number of physicians are using lasers for refractive surgery to treat patients even though there is no PMA or IDE in effect for their lasers. Based on the results of our investigations, we believe that you are currently using your laser to treat patients.

FDA 0 0013

Accordingly, on July 28, 1997, we called you to notify you that use of your excimer laser to treat patients would violate the Act and requested that, if you are presently using the laser to treat patients, you immediately cease doing so. To enable FDA to complete its review of your IDE application, we also requested that you provide the agency with the following additional information: a written statement that, as of the close of business on July 28, 1997, you are not using your excimer laser system to treat patients. Please complete the enclosed statement and transmit it to:

Morris Waxler, Ph.D.
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ401)
9200 Corporate Blvd.
Rockville, MD 20850

You may submit the statement by facsimile to (301) 480-4201, provided that you also send the original statement to the address above. This statement must be submitted within three (3) business days of the receipt of this letter.

You should be aware that FDA's regulations provide that an IDE application may be disapproved if "[t]here has been a failure to comply with any requirement of [21 C.F.R. Part 812] or the Act . . . ," 21 C.F.R. § 812.30(b)(1); thus, any previous use of an excimer laser system for which no PMA or IDE is in effect would be grounds for disapproval of an applicant's IDE. However, the agency, in an exercise of its enforcement discretion, does not intend to consider your previous use, if any, of such a device to be grounds for disapproval of your IDE. Nevertheless, FDA does intend to consider any use of your laser to treat patients after the close of business July 28, 1997 unless and until the agency approves an IDE for your device to be grounds for disapproval of your IDE. In addition, please note that failure to "respond to a request for additional information within the time prescribed by FDA" also would be grounds for disapproval of your IDE. 21 C.F.R. § 812.30(b)(3).

Furthermore, if you are, in fact, using an unapproved laser, failure to cease treating patients with the laser immediately also may result in regulatory action against you or the device by FDA without further notice. These actions include, but are not limited to, seizure, injunction, and civil money penalties.

We also want you to know that if FDA approves your IDE application, you would be able to use your laser to perform only specific procedures on a limited number of subjects to demonstrate the safety and effectiveness of your laser for those procedures. Studies conducted under such an IDE would be subject to all IDE regulations. See 21 C.F.R. Part 812. For example, you would be prohibited from promoting and commercializing the laser, and from representing that the device is safe and effective. The IDE process is designed to investigate the safety and effectiveness of devices either for research or for market authorization, and is not itself a means of market authorization for the commercial treatment of patients. Once studies under your IDE were complete, you would not be able to use your laser unless you were to seek a PMA and FDA were to approve it.

If you have any questions about this request, you may contact Everette T. Beers, Ph.D. at (301) 594-2018.

Sincerely,

Nancy C Brogdon for

A. Ralph Rosenthal, M.D.
Director
Division of Ophthalmic Devices
Office of Device Evaluation
Center of Devices and
Radiological Health

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Herbert J. Nevyas, M.D.
Nevyas Eye Associates
Delaware Valley Laser Surgery Institute
333 City Line Avenue
Bala Cynwyd, PA 19004

AUG 7 1997

Re: G970088/A1, A3 and A4
Sullivan Excimer Laser System (Nevyas Model)
Indications for Use: LASIK for Myopia (-0.5 to -6.75 Diopters with up to -7 D Astigmatism)
Dated: July 3, 21, and 29, 1997
Received: July 8 and 22, and August 1, 1997
HCFA Reimbursement Category: A2 (for procedures to request re-evaluation of this categorization decision, please see the appropriate enclosure)
Annual Report Due: August 7, 1998

Dear Dr. Nevyas:

The Food and Drug Administration (FDA) has reviewed the amendments to your investigational device exemptions (IDE) application. Your application is conditionally approved because you have not adequately addressed deficiency #2 cited in our May 8, 1997 disapproval letter. You may begin your investigation, using a revised informed consent document which corrects deficiency #1 (below), after you have obtained institutional review board (IRB) approval, and submitted certification of IRB approval to FDA. Also, we are in receipt of your certification (Amendment 4 received August 1, 1997) that you have not used the laser as of the close of business on July 28, 1997, and that you will not use the laser unless and until FDA approves the IDE application for your device. You are reminded that when the agency has approved (conditionally or otherwise) an IDE for a device, all treatments with that device after the date of FDA approval of the IDE are treatments under the IDE; consequently, the device may be used to treat only the number of subjects approved in the IDE and only for the indications approved in the IDE. Your investigation is limited to one institution and 100 subjects for Low Myopia (-0.5 to -6.75 D) plus Astigmatism (up to -7 D).

This approval is being granted on the condition that, within 45 days from the date of this letter, you submit information correcting the following deficiencies:

FDA 0 0016

1. Since your ablations are clearly non-spherical, as well as multifocal, you should provide a much stronger caution to your prospective subjects regarding the ability to see well in low light level situations. Please amend

with low illumination and low contrast as you see during the day; these situations may include, but are not limited to, nighttime, fog, dimly lit rooms. It is possible that you may not be able to drive at night. You should take precautions in situations where you may be at risk, because of your possible decreased visual acuity in the above situations. It is also possible that your eyes will become more tired than usual toward the end of the day."

Based on your patient questionnaires, you may be able to reassess this caution and provide to your patients some idea of the percentage of patients experiencing moderate to significant difficulty in seeing well in low light level situations. At PMA time, patient questionnaires can be reviewed by you and the agency for appropriate PMA labeling regarding the caution for low light level situations. In addition if you wish, you may conduct a substudy for contrast sensitivity and use this data as additional information for your PMA patient labeling or to reassess your IDE caution.

2. Because of concern about the non-spherical and multifocal properties of your ablations, please add the following to your patient questionnaire:

   a. a question regarding the patient's pre- and post-op ability to see well in low light level situations, such as in the dark, in dimly lit rooms or auditoriums, while driving at night, etc.; and,

   b. a question regarding how tired the patient's eyes become in the evening.

3. In addition to the times already specified in your protocol, your patient questionnaire should be administered at the one week, one month and six month visits.

4. Additional information is required regarding your PMMA ablations:

   a. Your PMMA ablations appear to be wider at the bottom than the algorithm predicts; for instance, most of the ablations are 2. FDA wide at the bottom, rather than 2.0 mm. Please explain what cau difference in width.

   b. Your PMMA ablations also appear to have a "hump" in the bottom of each ablation of about 10% to 20% of the maximum depth. Please explain what causes these "humps".

profiles near the area where the dark blue and light blue areas meet. Please explain what causes this "scalloped" appearance.

5. Since your ablation equations do not appear to follow Munnerlyn's equations for generating a spherical correction on the cornea, it is unclear how you have verified that your ablation pattern and depth for any particular correction will actually produce the desired effect, i.e., the required dioptric change. For instance, using your high myopia ablation algorithm to produce a -12 D correction, please demonstrate how you have verified that removing 98.75 microns of tissue in the manner specified (single zone, multipass) produces a -12 D correction. What difference would it make if one removes 90 microns or 110 microns? How have you verified the other ablation parameters for ablations in both the low myopia and high myopia algorithms?

6. Regarding the total tissue removed, there appears to be a disconnect between your theoretical ablation algorithms (Amendment 1, page 40) and the ablation parameters in Amendment 3. For instance, on page 40 of your Amendment 1, a -6.0 D ablation should remove 61.8 microns of tissue, while a -7.0 D ablation should remove 70.6 microns. On the other hand, on page 7 of Amendment 3 you show that a -6.75 D ablation has a maximum ablation depth of 77 microns (greater even than the -7.0 predicted in Amendment 1). Please explain these differences.

7. In response to Deficiency # 2.d. about etch rate, you indicated that the etch rate was 0.194 microns per pulse in PMMA and 0.25 microns per pulse in tissue.

   a. Our description of this deficiency probably was unclear. Please provide the etch rate *curve*, showing the laser energy per pulse versus the tissue (or PMMA) removed. Relate PMMA removed to tissue removed (this would be a ratio, for instance).

   b. The etch rate of 0.194 microns per pulse in PMMA and 0.25 microns per pulse in tissue produces a ratio of 1.29. However, when the tissue ablation on page 7 of Amendment 3 is divided by the PMMA ablation taken from the PMMA ablation profiles, this ratio appears to vary with the number of pulses delivered, ranging from 1.25 at an ablation of -1 D to 1.48 at an ablation of -6.75 D. Please explain this discre variation.

8. You have not adequately addressed Deficiency #5 in our letter of May 8, 1997 regarding the beam path for the operating microscope and subsystems. Please provide a ray trace which also shows how the microscope is positioned in referen e to the subject's eye, the aiming laser, the treatment laser, the fixation lights, etc.

9. Although you indicate that the COMPex 201 laser engine has a divergence of 3 milliradians/meter, please provide the divergence for your laser system after the last focusing lens.

10. In your description of the operative procedure, please specify the thickness of the corneal flap that is cut and reflected prior to ablation.

11. Please correct your protocol, page 19, to reflect that soft contact lenses will be lef out for at least 3 days prior to examination and surgery.

12. Please provide additional *technical* information regarding the methods of obtainir g and maintaining both temporal and spatial beam homogeneity.

This information should be identified as an IDE supplement referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

If you do not provide this information within 45 days from the date of this letter, we may take steps to propose withdrawal of approval of your IDE application.

We acknowledge your request to conduct a study at one site with approximately 990 eyes f r each of two investigators. We believe that adequate safety information has been provided t allow the initiation of your study at one site with 100 subjects; however, issues remain whi h must be resolved prior to the expansion of your study for marketing approval. Prior to your request for expansion beyond 100 subjects, you should submit the results of this initial pha e after 50% of the subjects have achieved at least 3 months of follow-up. FDA 0 0019

We would like to point out that FDA approval of your IDE application does not imply th t this investigation will develop sufficient safety and effectiveness data to assure FDA appro l of a premarket approval (PMA) application for this device. You may obtain the guideline or

the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (30) 443-6597.

We have enclosed the guidance document entitled "Sponsor's Responsibilities for a Significant Risk Device Investigation" to help you understand the functions and duties of a sponsor. Also enclosed is the guidance document "Investigators' Responsibilities for a Significant Risk Device Investigation" which you should provide to participating investigators.

If you have any questions, please contact Everette T. Beers, Ph.D. at (301) 594-2018.

Sincerely yours,

A. Ralph Rosenthal

A. Ralph Rosenthal, M.D.
Director
Division of Ophthalmic Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosures
(1) Procedures to Request Re-Evaluation of HCFA Reimbursement Categorization Determination
(2) Sponsor's Responsibilities for a Significant Risk Device Investigation
(3) Investigators' Responsibilities for a Significant Risk Device Investigation

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administratic
9200 Corporate Boulevard
Rockville MD 20850

OCT - 3 1997

Herbert J. Nevyas, M.D.
Nevyas Eye Associates
Delaware Valley Laser Surgery Institute
333 City Line Avenue
Bala Cynwyd, PA 19004

Re: G970088/S2, S3, and S4
Sullivan Excimer Laser System (Nevyas Model)
Indications for Use: LASIK to correct myopia of -0.5 to -15 Diopters (D) with up to -7 D of astigmatism for protocol NEV-97-001 Myopia; and, LASIK enhancement to correct myopia of eyes previously treated with this laser
Dated: August 28, September 10 and September 19, 1997
Received: September 9, 12, and 22, 1997
Annual Report Due: August 7, 1998

Dear Dr. Nevyas:

The Food and Drug Administration (FDA) has reviewed supplements 2, 3 and 4 to your investigational device exemptions (IDE) application. Supplement 2 requests a protocol deviation to treat two anisometropic patients (one eye at -10 D and one eye at -7.50 D); you were granted permission by telephone on September 9 to treat these two anisometropic patients. We acknowledge receipt of your institutional review board (IRB) approval (supplement 3). Supplement 4 responds to our conditional approval letter of August 7, 1997 and requests: an increase in treatment range from -6.75 D to -22 D; approval to study simultaneous bilateral treatment; and, approval to retreat approximately 125 patients previously treated with this laser prior to IDE approval.

FDA cannot approve your request to study LASIK in higher myopes up to -22 D because you have not provided adequate data to support safe use above -15 D. FDA will conditionally approve, however, a study at this time of LASIK in 25 subjects with myopia -7 D to -15 D with up to -7.00 D of astigmatism; please see the conditions of approval below. If you agree to conduct your investigation within the modified limit, you may implement that change at the institution enrolled in your investigation where you have obtained institutional review board (IRB) approval. If you do not agree to this modified limit, you should consider this letter as a disapproval of your request for an expansion of the investigation, and you have an opportunity to request a regulatory hearing as described in the enclosure "Procedures to Request a Regulatory Hearing."

FDA 0 0021

FDA cannot approve your request to study enhancements on up to 125 of your prior clinical

and the time point of stability of, the procedure. FDA will conditionally approve, however, a study at this time of LASIK enhancement in 25 subjects previously treated with your laser; please see the conditions of approval below. Requests for additional subjects for enhancements for prior clinical patients will be evaluated as additional data is submitted to support stability of the procedure. If you agree to conduct your investigation within the modified limit, you may implement that change at the institution enrolled in your investigation where you have obtained institutional review board (IRB) approval. If you do not agree to this modified limit, you should consider this letter as a disapproval of your request for an expansion of the investigation, and you have an opportunity to request a regulatory hearing as described in the enclosure "Procedures to Request a Regulatory Hearing."

We regret to inform you that your request to study simultaneous bilateral LASIK treatment is disapproved and you may not implement the expansion of your investigation. Our disapproval is based on the following deficiency:

> If you wish to study simultaneous bilateral LASIK surgery, you should propose a substudy comparing simultaneous with sequential treatment to establish the safety of the simultaneous procedure. Your substudy should contain satisfactory preliminary data on the safety, effectiveness and stability of the procedure on the primary eyes. In your substudy you should specify the time between surgeries for each eye and any criteria used to determine when to treat the fellow eye; time between surgeries and treatment criteria should be specified for both simultaneous and sequential procedures.

If you submit information correcting the deficiency, FDA will reevaluate the proposed expansion of the investigation. Alternatively, you may request a regulatory hearing regarding the disapproval of your IDE supplement. The enclosure "Procedures to Request a Regulatory Hearing" describes how to submit such a request. The procedures governing a regulatory hearing are described in the regulations at 21 CFR Part 16.

Also, FDA acknowledges the telephone conversation between you and Dr. Beers of the FDA on August 25, 1997 in which you were granted permission to perform simultaneous bilateral surgery on two subjects because of pressing personal needs of the subjects.

Your response to FDA conditional approval letter of August 7, 1997, remains conditionally approved because you adequately addressed only deficiencies 1, 2, 3, 4, 6, 7a, 8, 9, 10, and 11. You may continue your investigation at the institution where you have obtained IRB approval and submitted certification of IRB approval to FDA. Your investigation is limited to 1 institution and 150 total subjects: 100 subjects for low myopia (from -0.5 to -6.75 D); 25 subjects for high myopia (from -7.00 to -15 D), and 25 subjects for enhancements of prior

This approval is being granted on the condition that, within 45 days from the date of this letter; you submit information correcting the following deficiencies.

1. Your device does not have a fail-safe mechanism for automatically shutting down your laser in the event of inappropriate energy output from the laser. Please submit an engineering plan and time-table for retrofitting your device with an adequate fail-safe mechanism. This mechanism should include a safe means to complete the treatment.

2. You agree to submit monthly reports of the subjects treated with your investigational laser identifying them by a unique subject identifier, date treated, and indication for treatment.

3. You agree that you will not perform retreatment procedures for subjects initially treated under this IDE. Retreatment (enhancement) for subjects initially treated under this IDE is appropriate only after your preliminary data demonstrate safety and indicate the time point of stability of the procedure. You may begin retreatment procedures only after FDA has approved your retreatment study plan and data to support stability.

This information should be identified as an IDE supplement referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

If you do not provide this information within 45 days from the date of this letter, we may take steps to propose withdrawal of approval of your IDE application.

We acknowledge your request to conduct a study at one site with approximately 990 eyes for each of two investigators. We believe that adequate safety information has been provided to allow the initiation of your study at one site with 150 subjects; however, issues remain which must be resolved prior to the expansion of your study for marketing approval. Prior to your request for expansion beyond 150 subjects, you should submit the results of this initial phase after 50% of the subjects have achieved at least 3 months of follow-up.

Prior to your request for expansion beyond 150 subjects, you should submit adequate responses to the following deficiencies. Incremental expansions beyond 150 subjects may be

Calibration:

5. Your description of the beam calibration is inadequate. Specifically, you should provide:

   a. description of the method, technical specifications of any substrates used, validation procedures for the tests, and passing criteria for energy (fluence), homogeneity, beam alignment, and any other calibration procedures;

   b. information on how instrument measurement precision was determined, and a calibration schedule;

   c. a diagram of the measurement set up (i.e., for opening the "beam shaping aperture") and test firing;

   d. the technical specifications of the Chiron substrate used for measurements so that the number of pulses and the irradiance level(s) that provide for breakthrough and complete removal for the substrate material can be verified;

   e. a statistical analysis used for the determination of energy stability;

   f. a technical description of the transparent substrate used for beam homogeneity determination and a description of how the scientific accuracy and validity of the test was determined;

   g. descriptions of any differences between the output beam measurement and homogeneity tests using a substrate of known thickness and ablation characteristics; and,

   h. a description of how the device software determines the energy output needed during the calibration process.

Laser Characteristics:

6. The energy output of your aiming lasers, each at 1 mW, is high relative to the other aiming lasers that we have encountered. Please determine the exposure hazard per CFR 1040.10 and specify the maximum exposure time.

7. Does your laser system have the capabilities to treat other refractive conditions that are not described in this application and which are not disabled for this clinical trial? If the answer is "yes", then please indicate the steps taken to ensure that the device will not be used outside the approved protocol(s).

8. The electrical safety information provided applies only to the Lambda Physik excimer laser, not the complete device as required by FDA. Also, the standards cited are German standards which to date have not been accepted by FDA. You are reminded that you should provide electrical certification for the *entire system*, including the laser, motors, other electrical devices which connect to the laser, electrically operated chairs, etc. Please provide certification that the device conforms to a recognized national or international electrical safety standard for medical devices (e.g., Underwriters Laboratories, UL544 76, UL-2601 for Medical Equipment Systems; Canadian Standards Association, C22.2 No.125-M1984; British Standards Institute, BS 5724; International Electrotechnical Commission, IEC 601-1; Japanese Industrial Standard, JIS T1001; or, equivalent).

9. Although you provided the ray trace for the microscope section, the ray trace diagram in tab 3.4.1.3.B-2 (original IDE) does not show how the optics along the delivery path condition the beam, and the beam imaging module is not adequately depicted or described in the submission. Please provide more detailed information on both of these items and address the comments below:

   a. The optic diagram (3.4.2.2.A.4 on page 78) needs a ray trace to show how all the components function to condition the beam from the raw beam output to projection onto the corneal surface.

   b. The beam imaging module has not been adequately described. Please describe the components of the beam imaging module, their specifications, a diagram with ray trace diagram to illustrate the optical design, and the manner in which the intended functions are attained.

10. Please provide the following information about your laser system:

   a. please specify the cavity type for your laser: stable or non-stable; and,

   b. please specify the stability of the pulse through the gas lifetime and indicate how this was determined.

Ablation Algorithms and Profilometry:

11. You stated in supplement 4 that the etch rate curve is being generated; therefore, this remains a deficiency. Please provide the etch rate *curve*, showing the laser energy per pulse versus the PMMA removed, for energy levels above and below your treatment energy level. Provide the expected etch rate in tissue

Relate the amount of PMMA removed per pulse to the amount of tissue removed per pulse (this would be a ratio, for instance).

12. The formulation of the equation for the device ablation algorithm in Section 3.4.1.3.A "Ablation Patterns" is inadequate. Your description of the theoretical ablation algorithm appears to be internally inconsistent and lacks mathematical clarity. Please address the following:

    a. Why were 2 definitions provided for the same mathematical quantity c1(), and c2() as "curvatures" of the uncorrected and corrected cornea respectively, and simultaneously as "distances from an arc to a chord"? This information appears incorrect for the following reasons:

    Curvature is a mathematically defined quantity. It is defined as the angular velocity of the tangent to the curve as the tangent traverses and therefore describes the given curve. In the rectangular coordinate (as provided in your submission) an angle phi is defined as the angle between the tangent and the curve, and this angle phi is the arc-tangent of the first derivative of the spatial coordinates of the curve with "x" as the independent variable. In fact, the diagram you submitted illustrates "2 intersecting curves, labeled by the sponsor as c1(), and c2(), which represent a 2 dimensional cross section of the uncorrected and corrected cornea." It is illogical for them to be described as anything else. There cannot be 2 intersecting curves and "distances to an arc to a chord" at the same time as you described.

    The final equation [now labeled as (4)] does not appear to be one which can be related to ablation of the cornea because it is an equation which contains only spatial coordinates and no dependence on D (the dioptric power), or n (the index of refraction of the cornea). The statement that d(y) represents the depth at any spherical coordinate Y appears logically inconsistent because the equation is formulated in rectangular coordinates, and the equation has no Y dependence. In order to derive the ablation equation, one has to use the geometry of the 2 intersecting curves to set up an equation for the depth between the 2 curves as a function of Y where Y is defined as the lateral distance from optical axis of the cornea. At this point one has to get the dependence of D, and n into the geometrical equation by making appropriate substitutions from the equation for the power of a lens which is an independent equation. The result of these operations is a very complicated expression which is simplified by applying the binomial expansion to it. At this point a further simplification is made by finding the depth of cut on the corneal optical axis. This means let Y=0. The resulting simple equation is for t(on axis depth)= optical zone diameter squared times dioptric change divided by eight times the difference between the indices of refraction of the cornea and air. This is the so-called Munnerlyn equation.

b. You should supply scientific references applicable to the derived equation, and include all mathematical steps leading to the equation. You have not furnished the requested scientific references, nor the intermediate mathematical steps. Please provide this information.

c. You should provide an explanation of the reasons that D (power in diopters), and n (index of refraction of the cornea) do not appear in the ablation equation, and why the coordinate Y is undefined; no information has been provided explaining why the ablation equation has no D, or n dependence. As discussed previously, the explanation that Y is any spherical coordinate on the y axis is logically inconsistent.

d. You should identify the ablation axes for c1() and c2().

e. Please indicate how the derived equation is integrated into the device software to provide calculations that are required for the targeted corrections.

13. The theoretical fits to the profilometric data are based on 8th order polynomials. It is not clear what theory this procedure is based on and is apparently in qualitative disagreement with the data in the central 2 mm and outside the ablation zone. The appropriate theoretical fits should be to circular contours, since the ablations are supposed to approximate Munnerlyn's equations. Typically, one determines the theoretical mathematical ablation curve (i.e., the theoretical curve), employs hardware and software to approximate the mathematical curve (i.e., the programmed ablation curve), then measures the resultant ablation curve (i.e., the actual ablation curve in PMMA, for instance). It is not clear what is the theoretical curve to which you are trying to match your ablation curves (programmed and actual).

a. Please provide additional explanation regarding the theoretical ablation curves (mathematical equations) which you are trying to approximate with your hardware and software.

b. Please discuss how the programmed pattern described on pages 57-61 (Original IDE) and summarized in attachment 2.A-3 (Amendment 1, dated July 3, 1997) approximates the theoretical pattern described on pages 56-57 (Original IDE); plots of the programmed patterns versus the theoretical patterns would be helpful in this discussion.

Multifocality:

14. Your ablation patterns for correcting myopia and astigmatism do not appear to be spherical and cylindrical, respectively, and, therefore, cannot provide a single dioptric

correction of refractive error. The intended (theoretical) myopic ablation is flat (i.e., constant depth) over the central 2 mm, and decreases in depth in five linear segments of decreasing slope, with the five annular segments extending from diameters of 2 to 3 mm, 3 to 3.9 mm, 3.9 to 4.8 mm, 4.8 to 5.7 mm and 5.7 to 6.6 mm. The actual ablation is not flat in the central 2 mm, but shows a pronounced "central island" so that the ablation depth is up to 20% less at the center than at 2 mm diameter. The central 2 mm thus receives a hyperopic instead of a myopic correction. Outside the central 2 mm, the ablation produces a cornea with constantly changing curvature, i.e., constantly changing dioptric power. The amount of correction varies from overcorrection near 2 mm to undercorrection near 6.6 mm. Although the smoothing effect of the overlying corneal flap may modify this shape to some extent, it seems likely that the smoothing effects will be limited to distances no more than a few tenths of a mm from discontinuities in the ablation pattern. The predicted result of this type of ablation is a multifocal cornea, in which different portions of the cornea simultaneously focus portions of the "retinal" image at different positions in front of, on, or behind the retina. This multifocal property raises a number of safety and effectiveness issues that you will need to address:

a. An eye with a multifocal cornea generally will not have a well-defined best distance refraction. Uncorrected visual acuity as a function of distance may be nearly constant over an extended range, or it may be complex, with multiple peaks and troughs. Characterizing the refractive state may be difficult, requiring visual acuity assessments over a range of refractive corrections. Please provide a detailed description of the procedures you will use for measuring manifest refractions for postoperative subjects to take into account these concerns.

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b. To document the clinical effects of this multifocal ablation, please propose substudies for mesopic contrast sensitivity (or low contrast acuity) with and without glare. The background luminance of the contrast sensitivity test should be reduced to less than 3 cd/m^2 (about 0.2 cd/m^2 preferred) and the ambient illumination should be even lower. The test targets may be either grating contrast sensitivity charts or low contrast letter acuity charts. In order to limit pupil constriction and maintain uniform glare conditions across the test chart, the glare source should be an array of two or more small spots symmetrically positioned around the chart. The glare source should be bright enough to significantly reduce the contrast sensitivity of young adult subjects with normal corneas and normal vision. If the above conditions cannot be implemented, the Brightness Acuity Test (BAT) may be used as an alternative glare source if the subject's pupil is dilated and the above brightness criterion is met. Control data may be obtained either from the preop LASIK subjects or (preferably) from a sample of normal subjects with the same age, gender and refractive error distributions as the postoperative test subjects.

differences with 80% power (e.g., if the standard deviation is 0.3 log unit, about 80 subjects would be needed to meet this target). Postoperative testing should be conducted after visual function has stabilized.

c. If contrast sensitivity testing shows decreased sensitivity under mesopic conditions, it may be possible that better results could be obtained using a different spectacle correction. Knowing the dioptric powers of your ablation could help in choosing appropriate spectacle correction, or provide a basis for adjusting your algorithm. As an aid to documenting the degree of multifocal performance predicted for corneas treated with your ablation algorithms, please provide graphs of either dioptric power or radius of curvature as a function of distance from the center of the ablation for representative myopic, elliptical and astigmatic ablation profiles.

d. Please obtain preoperative and postoperative (after achieving refractive stability) corneal topographic measurements, and provide difference maps and difference profiles showing the change in the contour of the corneal surface resulting from your LASIK procedure for a subset of your subjects treated under this IDE.

e. Please provide data to support your statement (page 8 of supplement 4) that lensometer measurement of the PMMA ablation profile verified the desired dioptric correction. Please provide data to show whether or not lensometer measurement shows more than one possible dioptric reading for the same ablation.

Homogeneity:

15. Your beam appears to be inhomogeneous with varying hot spots and cool spots across the treatment area of the beam. Although you stated in supplement 4 that you are exploring options for adding a beam homogenizer onto your laser, the question regarding homogeneity remains a deficiency. In addition, since calibration is a part of maintaining beam homogeneity, you should address the questions above regarding beam calibration. Please provide additional technical details regarding your methods of obtaining (i.e., conditioning optics) and maintaining (e.g., calibration and maintenance) temporal and spatial beam homogeneity, including the range (tolerances) of acceptable values for homogeneity and data to support your findings.

You should also give serious consideration to the following items which are considered essential for the analysis of your data for the purposes of determining safety and effectiveness for a future PMA application:

Software:

16. Your description of your software is inadequate. Please address the following:

a. Hazards Analysis: Please submit a more detailed Hazard Analysis which provides a description of the hazards presented by this device to the subject, the causes of these hazards, and the methods used to eliminate or mitigate them. This analysis should specifically identify the system hazards, and the components whose failure could cause those hazards and which are controlled by or interact with software. The analysis should identify this controlling or interacting software, and describe in greater detail how errors in this software are controlled or mitigated throughout the software development process.

b. Functional Requirements and System Specifications: Please provide a much more detailed description of the system and software requirements and specifications, including safety critical functions implemented because of the ongoing hazards analysis, and any applicable algorithms.

c. Software Design and Development: Please submit your written procedures, or at a minimum a very detailed description of your procedures, for designing and developing the software to be used in the device, from concept to delivery to the customer.

d. Verification, Validation, and Testing: Please submit a more detailed description of the software verification, validation, and testing process, including but not limited to the techniques and methods used at the module, integration and system level, the testing strategies and methodologies, and the test acceptance and completion criteria. Include examples and documentation of testing results.

e. Revision Control: Please submit the written procedures, or at a minimum, a very detailed description of the procedures, for your revision control process.

Advisory:

Although we requested the patient questionnaire be administered at times in addition to the ones you had originally proposed, we now believe that the subjects may become acclimated to the questionnaire, if it is presented too frequently. Therefore, you may revert to the times originally proposed in your IDE.

If you have any questions, please contact Everette T. Beers, Ph.D. at (301) 594-2018.

Sincerely yours,

Nancy C. Brogdon for

A. Ralph Rosenthal, M.D.
Director
Division of Ophthalmic Devices
Office of Device Evaluation
Center for Devices and Radiological Health

~~Enclosure: "Procedures to Request a Regulatory Hearing"~~