Page 2 - Herbert J. Nevyas, M.D.

We continue to be concerned that your ablation is likely to have multifocal properties, which means that some light will be out of focus even at the best focal plane. It is possible that your proposed mesopic contrast sensitivity study will help resolve some of these concerns. Also, any claims you may wish to assert regarding advantages of multifocality may not be supported by your change in accommodation study.

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administrati
9200 Corporate Boulevard
Rockville MD 20850

NOV 10 1999

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

Re: G970088/S17
Sullivan Excimer Laser System (Nevyas Model)
Indications for Use: LASIK (Laser-Assisted In Situ Keratomileusis) 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 retreatment to correct myopia and myopic astigmatism of eyes treated with this laser prior to IDE approval
Dated: October 8, 1999
Received: October 12, 1999
HCFA Category: A-2
Next Annual Report Due: August 7, 2000

Dear Dr. Nevyas:

The Food and Drug Administration (FDA) has reviewed the annual progress report to your investigational device exemptions (IDE) application and has determined that additional information is required. Please address the following questions and concerns:

1. Please separate IDE subjects from pre-IDE subjects in all of your tables, or report only on IDE subjects.

2. Please include an accountability table, similar to the one presented by you in last year's annual report, showing completed visits, missed visits, etc. for each visit time for all eyes. You should account for all eyes treated in the IDE.

This information must be submitted to FDA within 45 days from the date of this letter. It 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

FDA 0 0054

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.

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB 09 2001

JAN 30 2001

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 (Laser-Assisted In Situ Keratomileusis) to correct myopia of –0.5 to –15 Dipoters (D) with up to –7 D of astigmatism for protocol NEV-97-001 Myopia; and, LASIK retreatment to correct myopia and myopic astigmatism of eyes treated with this laser prior to IDE approval

Dear Dr. Nevyas:

The Food and Drug Administration (FDA) granted approval of your investigational device exemptions (IDE) application on August 7, 1997. As part of your responsibilities as sponsor of a significant risk device investigation, you are required to submit a progress report to FDA and to all reviewing institutional review boards (IRBs) on at least a yearly basis. We have not received a response to FDA's November 10, 1999 request for additional information regarding your August 1998 – August 1999 annual progress report (enclosed). In addition, please provide your annual progress report for the year August 1999 – August 2000.

Please submit your response to FDA's November 10, 1999 letter and your year 2000 annual progress report to FDA within 45 days from the date of this letter. The 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 the requested information within 45 days from the date of this letter, we may take steps to propose withdrawal of approval of your IDE application.

FDA 0 0056

If you have any questions, please contact Ms. Deborah Falls at (301) 594-2205.

Sincerely yours,

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

Enclosure
FDA's November 10, 1999 request for additional information regarding annual progress report

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

APR 13 2001

APR 10 2001

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

Re: G970088/S18
Sullivan Excimer Laser System (Nevyas Model)
Indications for Use: LASIK (Laser-Assisted In Situ Keratomileusis) 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 retreatment to correct myopia and myopic astigmatism of eyes treated with this laser prior to IDE approval
Dated: March 14, 2001
Received: March 16, 2001
Next Annual Report Due: August 7, 2001

Dear Dr. Nevyas:

The Food and Drug Administration (FDA) has reviewed the annual progress report to your investigational device exemptions (IDE) application and has determined that additional information is required.

Please address the following questions/concerns, as well as provide the information requested in the tables enclosed with this letter.

1. You have stated that, for the safety and efficacy analyses, the "N" used as the denominator when calculating percentages was the actual number of patients completing each visit. The "N" should be the number of eyes that completed the particular evaluation being analyzed at that visit. For example, if a subject, who had bilateral treatment, was available for analysis at the 1-month follow-up visit, but did not undergo manifest refraction, this subject's 2 eyes would not be included in the "N" (or the "n", numerator of the percentage calculation) for the BSCVA analysis. Please adjust the tables accordingly, if necessary.

2. The only protocol deviations reported were that "some" visits were completed outside the visit windows. Visits falling outside the visit window should not be included in the analyses at that particular visit, but should be analyzed separately. Please revise your tables accordingly including the accountability tables.

FDA 0 0058

3. Please provide stability analyses and indicate the point of stability for each indication (see enclosed tables).

4. You reported the percentage of eyes losing more than 2 lines of BSCVA. This should

5. Please provide narratives for the reported adverse events/complications to further elaborate these events and their outcomes.

6. Please provide a summary of contrast sensitivity results.

7. Please provide tables (similar to those requested for initial treatments) and narrative summarizing the results of the IDE substudy of enhancements for 25 subjects/50 eyes that had undergone treatment prior to implementation of the IDE, and of the data from enhancements performed for eyes enrolled under the IDE. Please provide separate analyses for the first enhancement, second enhancement, etc.

8. With regard to your future PMA submission, you have indicated that only subjects treated with the "new centration technique" will be included in the PMA, and that you have selected the eyes treated between 2/19/98 and 11/22/99 as the cohort to support the safety and effectiveness of the device. We would like to clarify that data from <u>all</u> subjects treated under the IDE should be included in the PMA. The main PMA cohort on which the decision of the safety and effectiveness of the device will mainly rest may be limited to <u>all</u> eyes treated with the new centration technique, but not to only those enrolled during a given period of time, as you appear to have suggested. Data from all eyes treated prior to the adaptation of the new centration technique may be analyzed separately from the main PMA cohort, but must be submitted as supportive evidence.

This information must be submitted to FDA within 45 days from the date of this letter. It 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.

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 and Ear, Nose and Throat Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure
Data Tables – October 26, 1998 Version

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administratio
9200 Corporate Boulevard
Rockville MD 20850

JUL 25 2001

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

Re: G970088/S20
Sullivan Excimer Laser System (Nevyas Model)
Dated: June 21, 2001
Received: June 25, 2001
Next Annual Report Due: August 7, 2001

Dear Dr. Nevyas:

The Food and Drug Administration (FDA) has reviewed the supplement to your investigational device exemptions (IDE) application proposing two new clinical protocols to evaluate the spherical ablation algorithm. We regret to inform you that your supplement is disapproved and you may not implement the change in your investigation. Our disapproval is based on the following deficiencies which, unless otherwise specified, relate to both protocols:

1. You have stated that subjects will be evaluated preoperatively and 1 day, 1 week, and 1, 3, and 6 months post-LASIK, and that a final exam will be conducted at least 3 months after the time when refractive stability is achieved. For new indications, where the time point of stability is not established, we recommend 24 months of follow-up. We consider all indications using the new, spherical ablation algorithm to be "new" indications. Please revise your protocol, case report forms, and consent form accordingly, or justify not doing so. Please add evaluations for each study eye at 9, 18, and 24 months postoperatively regardless of the individual subjects' postoperative refractive stability. You may request to modify your protocol if the preliminary data indicate earlier stability of the cohort. Please note that the point of stability may differ for different refractive indications, e.g., low spherical myopia only, high spherical myopia only, low myopia with astigmatism, high myopia with astigmatism, spherical hyperopia, and hyperopia with astigmatism.

2. You have identified target values at the "mean time of stability" and you have defined stability as "two manifest refraction spherical equivalent (MRSE) measurements taken at two consecutive visits that are at least 2 to 3 months apart that are within 1.0 D of each other". The FDA normally evaluates target values at the point of stability defined as the time point when 95% of the eyes have a change of $\leq$ 1D of MRSE between 2 refractions performed at least 3 months apart. Please revise your protocol in order to be consistent with the FDA's definitions.

3. You have not provided in your protocol the methodology for performing any of the clinical evaluations. For each clinical evaluation, please specify the testing procedures and instruments that will be used, including the lighting conditions and charts you will use to measure distance vision and near vision, etc.

4. You have indicated that pupil size measurements will be performed in dim lighting conditions, ~2 lux. However, this is closer to photopic than mesopic conditions (~0.1 lux) that are required for appropriate inclusion of subjects in the study. Please specify in your protocol how the pupil size measurement will be obtained, as requested above, and revise the lighting conditions under which this measurement will be obtained to assure that the measurement will be performed under mesopic conditions. We recommend dark adaptation for 10 minutes prior to the measurement and the use of an infrared pupillometer for consistency of the measurement.

5. Section 8.7 of each protocol states that the manufacturer's recommended settings are provided in Attachment D, and that the optical zone size (transition zone = 7.5 mm or 9.0 mm) will be selected by the investigator in accordance with the manufacturer's recommendations. Attachment D was not provided, however, and the previous statement implies that the optical zone size may be varied within each protocol. Please provide the optical zone and corresponding transition zone sizes for each of the indications - spherical myopia, myopic astigmatism, spherical hyperopia, and hyperopic astigmatism. Please note that we do not recommend varying the optical zone and transition zone according to an algorithm. However, if you choose to utilize varying optical zones, please provide adequate justification and the algorithm for determining zone size. In this case, you are reminded that outcomes must be stratified by optical zone and, possibly, transition zone.

6. The refractive inclusion criteria for Protocol NEV-01-002 (Myopia/Myopic Astigmatism) indicate that the uncorrected refractive error must consist of spherical myopia (-0.5 D to -16.0 D) or myopic astigmatism (-0.50 D to -16.0 D MRSE; cylinder -0.5 D to -6.0 D) for inclusion in the study. You also noted that the minimum allowable cylinder treatment is -0.5 D and that eyes with cylinder between 0.0 D and < 0.5 D may be enrolled in the study, but the cylinder cannot be treated. The refractive inclusion criteria for Protocol NEV-97-003 (Hyperopia/Hyperopic Astigmatism) indicate that the uncorrected refractive error consists of spherical hyperopia (+0.50 to +6.00D) or hyperopic astigmatism (+0.50 to +6.00 D MRSE; cylinder +0.50 to +4.00 D) for inclusion in the study. You also noted that the minimum allowable cylinder treatment is 0.5 D and that eyes with cylinder between 0.0 D and < 0.5 D may be enrolled in the study, but the cylinder cannot be treated. It has been FDA's experience that there is more variability in refractive outcomes with lower corrections. Therefore, please justify the lower limits of your refractive inclusion criteria by providing a scientific argument for why you think you will be able to accurately treat and measure the outcomes at the lower limits of the refractive ranges you have chosen. Otherwise, please use 0.75 D as your lower unit for sphere and cylinder.

7. Your protocol states that subjects must have a best spectacle corrected visual acuity (BSCVA) of at least 20/40 in each eye in order to be enrolled in the study. Please be advised that while we find this criteria acceptable for subjects with high myopia ($\geq$ 7 D MRSE), in order for subjects with low myopia (< 7 D MRSE) to be enrolled, we recommend a BSCVA of at least 20/25 in each eye. Please revise your protocol accordingly, or justify not doing so.

8. Please add an inclusion criterion for uncorrected visual acuity (UCVA), e.g., UCVA of worse than 20/40.

9. Protocol NEV-01-002 (Myopia/Myopic Astigmatism) states that subjects must have a stable manifest refraction defined as $\leq$ 0.5D change in sphere or cylinder during the year prior to the screening examination for inclusion in the study. Please revise your protocol to indicate that this inclusion criterion applies to subjects with high myopia, ($\geq$ 7 D MRSE). Please add that subjects with low myopia (MRSE < 7 D) must have a stable correction ($\pm$ 0.5 D), as determined by MRSE, for a minimum of 12 months prior to surgery.

10. Similarly, Protocol NEV-97-003 (Hyperopia/Hyperopic Astigmatism) states that subjects must have a stable manifest refraction defined as $\leq$ 0.5D change in sphere or cylinder during the year prior to the screening examination for inclusion in the study. Please revise your protocol to indicate that subjects must have a stable correction ($\pm$ 0.5 D), as determined by MRSE, for a minimum of 12 months prior to surgery.

11. Section 7.2 of your protocol states that subjects wearing hard contact lenses must have 2 refractions and central K readings taken at least 1 week apart that are within 0.5 D for both sphere and cylinder before undergoing LASIK. Please revise this inclusion criterion so that it applies not just to hard contact lens wearers, but all contact lens wearers, and so that it is consistent with the revised inclusion criterion regarding stability referred to above.

12. Your protocol states that subjects who have pupils (measured in dim illumination) that are too large compared to the intended optic zone should be excluded from the study. Please revise your protocol to indicate that subjects with mesopic pupil measurements $\geq$ the planned optic zone should be excluded from the study.

13. Please add axial length measurement to the baseline eye examination.

14. The postop Day 1 (1 to 3 days postop) and Week 1 (5 to 12 days postop) visit windows you have proposed are too long. We recommend the following visit windows - Day 1 (24-36 hours) and Week 1 (5-9 days). Please revise Appendix B accordingly, or justify not doing so.

15. Section 8.4, "Follow-Up Visits", is inconsistent with Appendix A: Study Flow Chart and the Notes for the Examination Schedule. For example, Section 8.4 of Protocol

NEV-01-002 (Myopia/Myopic Astigmatism) states that UCVA at near will be performed at Month 3 and the Final Exam. However, the Study Flow Chart in Appendix A indicates that UCVA at near should only be performed at the screening visit. As another example, Section 8.4 of Protocol NEV-97-003 (Hyperopia/Hyperopic Astigmatism) states that UCVA at near will be performed at Month 3 and the Final Exam. However, the Study Flow Chart in Appendix A indicates that UCVA at near should be performed at the screening visit and at Month 3. Please resolve all discrepancies between the text in Section 8.4, the Study Flow Chart, and the footnotes under Notes for the Examination Schedule.

16. You have listed late onset of haze beyond 6 months with loss of 2 lines (10 letters) or more BSCVA as one adverse event, and haze beyond 6 months with loss of $\geq$ 2 lines of BSCVA as another adverse event. Please delete the first version of this haze adverse event from your protocol.

17. You have listed a decrease in BSCVA of more than 10 letters not due to irregular astigmatism as shown by hard contact lens refraction at 6 months or later as a possible adverse event. You have also listed a decrease in BSCVA of $\geq$ 2 lines at 3 months or later as another possible adverse event. Please delete the first version of this decreased BSCVA adverse event from your protocol.

18. Please add a statement to your consent form indicating that there are lasers approved for LASIK for the treatment of myopia with and without astigmatism and hyperopia with and without astigmatism.

19. As part of the discussion of alternatives in your consent form, please discuss intra-corneal rings for the treatment of myopia and thermal keratoplasty for the treatment of hyperopia.

20. The Voluntary Participation section of the consent form states that the study doctor can stop the subject's participation at any time if the subject fails to follow directions for participating in the study, or if it is discovered that the subject does not meet the study requirements. Since this is a device investigation, non-compliance with the study procedures is not an acceptable reason for the subject's discontinuation. In addition, if it is discovered after surgery that a subject did not meet the study requirements, a protocol violation should be noted, but the subject should not be discontinued from the study. Please revise the consent form to clarify these points.

21. The Conclusion section of the consent form states, "There is always a possibility of one or more late complications that were not known or anticipated at the time of this writing (1997)." It also states, "LASIK is investigational surgery and as such, it has not yet been completely and exhaustively studied by the FDA and medical researchers in this country." Please update the consent form as necessary in keeping with current knowledge including the additions previously mentioned. Please revise the second statement to improve its accuracy: LASIK is no longer investigational, it has never

been studied by the FDA, and the FDA does not regulate LASIK, only the devices used for the procedure.

22. Question 8 of the Informed Consent Quiz states, "TRUE OR FALSE: There is a good chance that my eyes will regress to the refractive error as before the surgery," and the Correct Answers and Explanation states, "FALSE There is practically no chance that your vision will regress completely." Since this is the subject of your IDE study, please remove this question from your consent form.

23. Please submit the intra-operative/day of surgery case report form for review.

24. Please be advised that until preliminary safety, efficacy, and stability are demonstrated in a sufficient number of eyes, we cannot allow fellow eye treatment or re-treatment. In addition, subject enrollment should occur in stages in an IDE study for a new technology, new refractive laser device, or a new indication. FDA will evaluate the subject data from each stage prior to expansion of the study. You may request a protocol modification to include fellow eye treatment, re-treatment, and an increase in the number of subjects by submitting data demonstrating satisfactory stability, safety and efficacy. Please revise your protocol and informed consent document accordingly. We recommend for the early subjects to be contact-lens tolerant in the fellow eye. These subjects should be advised that six or more months may elapse before fellow-eye treatment is allowed.

25. Please confirm that subjects with mixed astigmatism will not be enrolled into either protocol.

26. Please verify that there will only be 2 investigators involved in this study.

27. Please provide your agreement that all co-managing doctors that collect data on the study subjects will be considered sub-investigators, and, therefore, they will need to follow the same SOP's under the protocol and sign the investigator's agreement prior to their participation in the study.

28. There are discrepancies in the way you refer to the protocols throughout the submission. For example, in the Introduction you refer to the new protocols as NEV-97-002 (Myopia/Myopic Astigmatism) and NEV-97-003 (Hyperopia/Hyperopic Astigmatism). However, the myopia protocol itself has been labeled with the protocol number NEV-01-002. To avoid confusion, please make all necessary revisions in any future submission to correct such discrepancies.

Please respond to the following engineering concerns:

29. In Section 2.2 (Page 8-9), the total cumulative number of pulses (shown in Figure 2.2-1) for each area in a selected 1.33 mm zone does not match your narrative. Based on your description, the pulses are delivered to a diamond shaped area (not a slot area). It

appears that area of square 8 receives the total 4 pulses at each axis; area 7 receives 3 (4 - 1) pulses; area 6 receives 2 (4 - 2) pulses; and area 5 receives 1 (4 - 3) pulse. However, in Figure 2.2-1, you marked that areas (8 - 5) along the axis 0° receive all of 4 pulses at axis of 0° and areas (8 - 5) along the axis 90° receive all of 4 pulses at axis of 90°. Please explain this discrepancy.

31. With respect to the profiles of your ablated PMMA samples:

a. The PMMA ablations for the spherical myopia (Fig 1-3), appear to have a "hump" in the bottom. Please explain the causes and discuss the potential impact of this "hump" on safety and effectiveness. In addition, your PMMA ablation curves did not include theoretical curves. Please provide plots of PMMA ablations versus the theoretical curves.

b. The PMMA ablations for the astigmatism (Fig 7-15) appear to be notably asymmetric. In particular, the asymmetry seems to be about 25% of the ablation depth in the maximal astigmatism as shown in Fig 9. Also, since you stated that (in Table 3-2) the signal to noise ratio was too low to obtain meaningful data at –0.5 D cylinder, you should improve the quality of the laser beam to enhance the signal to noise ratio. This might improve the quality of your astigmatic ablations. After improving the quality of your laser beam, please provide PMMA ablations for the astigmatism profiles to include sections through both axes, and plot these ablations versus the theoretical curves.

32. With respect to the software, please provide the following information:

a. Software Description: description and flowchart of the software lifecycle of the device, a flow diagram and narrative about the function of the software and about how the software interacts with the hardware.

b. Software Requirements Specifications (SRS): the Software Requirements Specification document, which clearly documented their functional, performance, interface, design and development requirements.

c. Validation (including verification and testing): an acceptable description of the systematic process of life cycle activities, including analysis, evaluation, assurance and testing of the software, and supporting documentation. This included a description of the activities and protocols at the unit, integration and system level, including pass/fail criteria, test reports, summaries and tests results.

d. Certification: if the software design, development and maintenance system have been certified to an international or national standard, specify to which standard and provide the name of the organization that performed the certification.

e. Revision Level History: the revision history log, documenting all major changes to the software during its development cycle and a description of the version numbers and dates.

The deficiencies identified above represent the issues that we believe need to be resolved before your IDE application can be approved. In developing the deficiencies, we carefully considered the relevant statutory criteria for Agency decision-making as well as the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at: http://www.fda.gov/cdrh/modact/leastburdensome.html

If you submit information correcting the deficiencies, FDA will reevaluate the proposed change in the investigational plan. Please submit revised versions of the protocols, consent form, and any revised case report forms indicating deletions with strikethroughs and additions with underlines.

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

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.

Please take into consideration the following issues related to any future PMA submissions when revising your protocol:

33. The protocol indicates that the subject questionnaire will be administered 3 and 6 months postoperatively and at the final exam with optional administration at the other visits. Please be advised that subject questionnaire data are expected at the point of stability. We recommend you remove the option for administration of the questionnaire "at other visits" and consider adding this as a mandatory evaluation to other follow-up visits, if there is the possibility that the cohort (or a subgroup) may reach stability after 6 months.

34. Please be advised that for possible future pre-market approval, although 300 eyes total are needed to support overall safety, data from approximately 125 eyes are needed to support each indication for which approval is being sought. Therefore, if you intend to seek approval for each indication you have proposed in the submission, you will need data from ~125 eyes in each of the following groups - the low spherical myopia only group, the high spherical myopia only group, the low myopia with astigmatism group, the high myopia with astigmatism group, the spherical hyperopia only group, and the hyperopia with astigmatism group.

35. Please be aware that if a subject moves and is, therefore, no longer followed in the study, the subject is considered lost-to-follow-up for purposes of reporting accountability.

If you have any questions, please contact Alfred Montgomery DVM at (301) 594-2080.

Sincerely yours,

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

Enclosure
(1) Procedures to Request a Regulatory Hearing

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

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

AUG 16 2001

Re: G970088/S22
Nevyas Excimer Laser
Dated: July 20, 2001
Received: July 23, 2001
Annual Report Due: August 7, 2001 (overdue)

Dear Dr. Nevyas:

The Food and Drug Administration (FDA) has reviewed the supplement to your investigational device exemptions (IDE) application proposing the validation for Appollo Software. We regret to inform you that your supplement is disapproved and you may not implement the change in your investigation. Our disapproval is based on the following deficiencies:

1. An important function of the software in the device is to control the beam delivery hardware (iris size, slot movement, synchronizing iris/slot with laser pulses, etc.) in the creation of an ablation pattern. This area, however, is not discussed at all in the Software Requirement Specifications document. Please provide a step-by-step description, from the very first pulse to the last pulse, of how the ablation pattern(s) to be used in this study is(are) to be created by the device. This description should include specific values for the starting size for the iris, starting position for slot, the amount to incremental change for iris or slot, etc.

2. The provided Hazard Analysis and Test Data appear to be limited to the user-interface function of the software. Given all the functions of the software, please identify those that are either safety critical or safety-related (see the Checklist of Information Usually Submitted in an IDE for Refractive Surgery Lasers, section 3.4.1.3 D, available at http://www.fda.gov/cdrh/ode/2093.html), and discuss how those safety functions were validated.

3. The Revision History Log is only up to version 3.22. Please update it to include all revisions up to version 3.66, which appears to be the latest version for the software.

4. The software allows the user to set 10 preferences such as fluence count & size; nitrogen on/off delay(s); laser frequency; wipe alert options, etc., and for manual positioning of the aperture doors and angle, and selection of iris size. Please specify which, among the selectable options in software, are selected for the study.

5. The naming convention for the software is confusing and inconsistent with the typical software practice. Typically, the higher software version would include everything in the lower version, as well as some additional features. Therefore, if Apollo version 3.66 were installed in the machine, there should be no need to install Apollo version 3.5. If 3.5 and 3.66 contain two distinct and separate routines, then different names should be given to them and their versions should each be 1.0.

The deficiencies identified above represent the issues that we believe need to be resolved before your IDE application can be approved. In developing the deficiencies, we carefully considered the relevant statutory criteria for Agency decision-making as well as the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at: http://www.fda.gov/cdrh/modact/leastburdensome.html

If you submit information correcting the deficiencies, FDA will reevaluate the proposed change in the investigational plan. 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

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.

If you have any questions, please contact Alfred Montgomery, DVM at (301) 594-2080.

Sincerely yours,

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

Enclosure:
Procedures to Request a Regulatory Hearing

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

APR 26 2002

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

Re: G970088/S25
Sullivan Excimer Laser System (Nevyas Model)
Indications for Use: LASIK (Laser-Assisted In Situ Keratomileusis) 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 retreatment to correct myopia and myopic astigmatism of eyes treated with this laser prior to IDE approval
Dated: March 26, 2002
Received: March 27, 2002
Next Annual Report Due: August 7, 2002

Dear Dr. Nevyas:

The Food and Drug Administration (FDA) has reviewed the additional information for your annual progress report to your investigational device exemptions (IDE) application and has determined that additional information is required.

Please address the following questions and concerns with regard to this submission:

1. You must still provide responses to deficiencies 1, 2, 3, and 5 from our letter of February 6, 2002.

2. You did not provide the requested information in your response to deficiency 4.

   a. For the eye with the central, corneal infiltrate noted at the 1-month visit, please report the eye's preoperative BSCVA, how the infiltrate was managed (i.e., cultures, antibiotics administered, etc.), when the infiltrate resolved, and the final BSCVA.

   b. In addition, you stated, "The observation was omitted from the 2001 Annual Report because the adverse event listing is 'corneal infiltrate or ulcer at 1 month or later' and the observation actually occurred earlier than 1 month postoperatively (although the infiltrate was noted at the 1-month visit, 25 days postoperatively)." We would like to point out that the FDA interprets "1 month or later" to mean within the 1-month visit window or later. This is true as well for all other time point references made in the protocol. Please keep this in mind when preparing all other future submissions to the FDA.

3. Although you have reported the number of eyes with unintended over-corrections > 2 D at each time point starting at 3 months in response to deficiency 6, it is not clear whether these reports represent different eyes at each visit or whether some of the reports are for the same eye. Please clarify.

4. In response to deficiency 8, you have indicated how you will verify your current accountability for visits that have already past. After your internal audit is complete and you have more insight as to the reasons for any problems with accountability, please directly address the original issue outlined in previous deficiency 8: please describe how you intend to improve subject follow-up and data reporting during the rest of the course of your IDE study.

Please note: In response to a question you asked previously by telephone, eyes that have been enhanced are considered discontinued at the point of enhancement (retreatment). These are then treated the same as the monovision subjects; that is, they are accounted for and analyzed separately. You should not enter subjects into the study that you know you are going to undercorrect or enhance.

This information must be submitted to FDA within 45 days from the date of this letter. It 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.

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 and Ear, Nose and Throat Devices
Office of Device Evaluation
Center for Devices and Radiological Health

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

IDE: G970088

To Dr. Waxler:

On July 28, 1997, FDA requested additional information regarding my investigational device exemption (IDE) application for a Sullivan excimer laser system (which I refer to in my IDE application as Nevyas Excimer Laser and hereafter refer to as "the laser") for use in refractive eye surgery. This letter responds to FDA's request for additional information.

Since the close of business on July 28, 1997, neither I nor anyone else has used the laser. I certify that, unless and until FDA approves the IDE application for that device, neither I nor anyone else will use the laser to treat patients. I have notified all of my employees, as well as anyone with access to the laser, that the laser may not and will not be used until there is an approved IDE in effect for that laser.

I declare that to the best of my knowledge the foregoing is true and correct.

Executed on 9/6, 1997.

Sincerely,

FDA C 0083

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB 6 2002

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

Re: G970088/S24
Sullivan Excimer Laser System (Nevyas Model)
Indications for Use: LASIK (Laser-Assisted In Situ Keratomileusis) 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 retreatment to correct myopia and myopic astigmatism of eyes treated with this laser prior to IDE approval
Dated: January 5, 2002
Received: January 8, 2002
Next Annual Report Due: August 7, 2002

Dear Dr. Nevyas:

The Food and Drug Administration (FDA) has reviewed the annual progress report to your investigational device exemptions (IDE) application and has determined that additional information is required.

Please address the following questions and concerns with regard to this submission, which also applied to the previous, delinquent, annual report as outlined in FDA's letter of April 10, 2001, and for which we never received a response:

1. When reporting protocol deviations, you indicated that some subjects had study visits that were late. For each time point, please clarify how many eyes had visits that fell outside of the visit window. Please clarify how far outside of the visit window each of these visits fell. Visits falling outside the visit window should not be included in the analyses at that particular visit, but should be analyzed separately. Please revise your tables accordingly including the accountability tables.

2. For each eye that experienced a loss of 2 or more lines of BSCVA at 6 months or later postoperatively and for each eye that had BSCVA worse than 20/40 at 6 months or later, please provide a dataline listing and an explanation for the vision loss or vision. Please include a narrative for each case discussing any other visual or non-visual symptoms, the management, and the outcome. Please group this information according to the 4 indications for treatment in this protocol.

3. Please provide narratives to further elaborate on each case reported as a complication, including the management and outcome, for eyes not included in the narratives above. Please group this information according to the 4 indications for treatment.

4. The adverse event previously reported in the last annual report, 1 case of a corneal infiltrate or ulcer at 1 month postoperatively, was not included in the tabulation of adverse events in this report. Please elaborate on this adverse event including the subject's preoperative visual status, management, and outcome.

5. Please provide tables (similar to those requested for initial treatments) and narrative summarizing the results of the IDE substudy of enhancements for 25 subjects/50 eyes that had undergone treatment prior to implementation of the IDE, and of the data from enhancements performed for eyes enrolled under the IDE. Please provide separate analyses for the first enhancement, second enhancement, etc.

Please address the following additional deficiencies related to the annual report:

6. Please report the rate of unintended overcorrections > 2 D at 3 months or later, a key safety variable.

7. Although page 38 of this annual report indicates that 188 eyes were enrolled in the contrast sensitivity substudy, Substudy NEV-98-002, page 4 states that a total of 184 eyes of 113 subjects have been enrolled in this substudy – 92 low myopia subjects and 21 high myopia subjects. Please resolve this apparent discrepancy.

8. Accountability is extremely poor. Please describe how you intend to improve accountability by assuring proper follow-up of subjects according to your protocol during your ongoing IDE study. Please be advised that aside from being a serious PMA concern, continued, improper follow-up of subjects may be reason for withdrawal of approval of an IDE study by the FDA.

9. You indicated to FDA, through your consultant Dr. Fant, that you are no longer enrolling subjects. However, it appears that you enrolled subjects up to at least December 19, 2001. As you have been advised previously, you are required to submit monthly accountability reports for each subject treated; these reports should include the investigator, the patient identifier, the eye treated, the date treated and the treatment performed.
   a. Please provide these monthly reports beginning with patients treated in January, 2002.
   b. The last monthly report we have on file is for January 1998. Please provide an accountability table for all eyes treated since January 20, 1998, in the format described in a., above.
   c. If you have ceased enrollment, please submit a request to FDA to cease enrollment. If this is the case, you still need to provide the information requested in b. above up to the date of cessation of enrollment.

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

1. Please note that, based on the stability analyses you have provided in this submission, we do not agree that the time point of stability is at 12 months postoperatively as you have indicated, and, in fact, may be earlier for some of the indications. However, the eyes treated for high myopic astigmatism (high astigmatic group) appear to remain unstable throughout the follow-up period. If PMA approval were requested for all of these indications in one submission, a decision regarding approval would be significantly affected by the inability to confirm stability at the same time point for each of the indications under consideration.

2. As previously stated in FDA's letter of April 10, 2001, you have indicated that only subjects treated with the "new centration technique" will be included in the PMA, and that you have selected the eyes treated between 2/19/98 and 11/22/99 as the cohort to support the safety and effectiveness of the device. We would like to clarify that data from all subjects treated under the IDE should be included in the PMA. The main PMA cohort on which the decision of the safety and effectiveness of the device will mainly rest may be limited to all eyes treated with the new centration technique, but not to only those enrolled during a given period of time, as you appear to have suggested. Data from all eyes treated prior to the adaptation of the new centration technique may be analyzed separately from the main PMA cohort, but must be submitted as supportive evidence.

3. As indicated above, your follow-up accountability is very low. Seventy-five to 80% of total eyes treated should have reached the point of stability and, of those, about 80% should have been seen and accounted for at the stability time point.

This information must be submitted to FDA within 45 days from the date of this letter. It 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.

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 and Ear, Nose and Throat Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Exhibit B

Nevyas Eye Associates / Delaware Valley Laser Surgery Institute
Ambulatory Surgery Center

rbert J. Nevyas, M.D.
taract, Refractive, and
orneal Surgery

oann Y. Nevyas, M.D.
'taract & Glaucoma Surgery
nd Therapy

.nita Nevyas-Wallace, M.D.
ataract, Refractive, and
orneal Surgery

a B. Wallace, M.D.
phthalmic Plastic &
econstructive Surgery

lward A. Deglin, M.D.
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.. Stein, M.D.
ucoma, Retinal Disease,
dical & Surgical Ophthalmology

in M. DeVaro, M.D.
diatric Ophthalmology
dor Motility &
ro-Ophthalmology

Delaware Valley Laser Surgery Institute
Institutional Review Board
2 Bala Plaza
Bala-Cynwyd, Pa. 19004

Dr. Herbert Nevyas
2 Bala Plaza
Bala-Cynwyd, Pa. 19004

Dear Dr. Nevyas,

On June 17, 1996 the Institutional Review Board of the Delaware Valley Laser Surgery Institute met and reviewed the following protocols submitted for Laser Assisted Intrastromal Keratomileusis:

myopia -1.00 to -24.00 without astigmatism and no previous eye surgery

The protocol was approved and is to be implemented as stated in the protocol itself. The protocol will expire on June 17, 1997 at which time it can be submitted for re-approval.

Sincerely,

Chairman,
Delaware Valley Laser Surgery Institute
Institutional Review Board

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EXHIBIT
H. Nevyas-1
5-6-05 TA

Nevyas Eye Associates / Delaware Valley Laser Surgery Institute
Ambulatory Surgery Center

Herbert J. Nevyas, M.D.
Cataract, Refractive, and Corneal Surgery

Joann Y. Nevyas, M.D.
Cataract & Glaucoma Surgery and Therapy

Anita Nevyas-Wallace, M.D.
Cataract, Refractive, and Corneal Surgery

Ira B. Wallace, M.D.
Ophthalmic Plastic & Reconstructive Surgery

Edward A. Deglin, M.D.
Vitreo-retinal Disease & Surgery

[illegible]ell E. Stein, M.D.
Glaucoma, Retinal Disease, Medical & Surgical Ophthalmology

John M. DeVaro, M.D.
Pediatric Ophthalmology Ocular Motility & Neuro-Ophthalmology

Delaware Valley Laser Surgery Institute
Institutional Review Board
2 Bala Plaza
Bala-Cynwyd, Pa. 19004

Dr. Herbert Nevyas
2 Bala Plaza
Bala-Cynwyd, Pa. 19004

Dear Dr. Nevyas,

On July 12, 1996 the Institutional Review Board of the Delaware Valley Laser Surgery Institute met and reviewed the following protocols submitted for Laser Assisted Intrastromal Keratomileusis:

1. Hyperopia +0.75 diopter to +10.00diopters with less than -1.00 diopters of astigmatism

2. Astigmatism -1.00 diopters to -12.00 diopters

3. Astigmatism -1.00 diopters to -12.00 diopters, history of previous eye surgery

4. myopia -1.00 diopters to -24.00 diopters with less than -1.00 diopter astigmatism , history of previous eye surgery

The protocol was approved and is to be implemented as stated in the protocol itself. The protocol will expire on July 12, 1997 at which time it can be submitted for re-approval.

Sincerely,

Chairman,
Delaware Valley Laser Surgery Institute
Institutional Review Board

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