DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

JUN 23 2014

Morris Waxler, PhD
President
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Re: Citizen Petition - Docket Number FDA-2011-P-0022

Dear Dr. Waxler,

This letter responds to the above referenced citizen petition that you submitted to the Food and Drug Administration (FDA or Agency) and that was filed on January 7, 2011. Your petition requests that the Commissioner of Food and Drugs: 1) withdraw premarket approval (PMA) for all laser-assisted *in situ* keratomileusis (LASIK) excimer lasers, and 2) issue a Public Health Advisory with a voluntary recall of these LASIK devices.[1]

In support of your petition, you cite data from several approved PMA applications, as well as published scientific literature, and you also offer your own analyses of the data. FDA has reviewed the information in your petition and is denying your petition for the reasons discussed below.

## I. Standard for PMA Withdrawal Has Not Been Met and a Public Health Advisory with a Voluntary Recall Is Not Warranted

Section 515(e)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 814.46(a) set forth the standards for withdrawing approval of a PMA application. These include[2] when FDA finds that:

- The device is unsafe or ineffective under the conditions of use prescribed, recommended, or suggested in the labeling of the device, section 515(e)(1)(A) of the FD&C Act;
- On the basis of new information before FDA with respect to the device, evaluated together with the evidence available when the application was approved, there is a failure to show reasonable assurance that the device is safe or effective under the conditions of use prescribed, recommended, or suggested in the labeling of the device, section 515(e)(1)(B) of the FD&C Act;

[1] The term "LASIK device(s)" as used in this response letter means laser-assisted *in situ* keratomileusis (LASIK) excimer lasers.

[2] Your petition does not make any claims or provide information regarding the other withdrawal standards included in section 515(e)(1) of the FD&C Act and 21 CFR 814.46(a), and so they are not discussed in our response.

- The PMA application contained or was accompanied by an untrue statement of a material fact, section 515(e)(1)(C) of the FD&C Act; or
- On the basis of new information before FDA, evaluated together with the evidence before FDA when the application was approved, that the labeling of the device, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Agency of such fact, section 515(e)(1)(F) of the FD&C Act.

As discussed below, the information presented to the Agency in your petition does not satisfy the statutory requirements for the Agency to withdraw approval of the PMA applications for LASIK excimer lasers. Further, in our continued assessment of the literature and medical device reports, we have not found any new safety concerns to lead us to believe that there is no longer a reasonable assurance that these devices are safe and effective under the conditions of use prescribed, recommended, or suggested in the labeling of the device.

Additionally, FDA does not believe that a public health advisory with a voluntary recall of LASIK devices is warranted. As discussed further below, after considering the information you provided in your petition, we have not found any new safety concerns associated with LASIK devices, the risks associated with each LASIK device are described in the patient labeling, and FDA's LASIK website provides information about the devices and the procedure, including a summary of the most common risks and links to the Summary of Safety and Effectiveness Data (SSED) and patient labeling for each approved LASIK device.

## II. Specific Arguments of the Petition and FDA Responses

### A. The Petition Alleges that PMA Applicants Withheld and Distorted Safety Data in Submissions to FDA

Section II.A.1 of your petition contends that LASIK device manufacturers and others made and are making false statements to FDA regarding the adverse event rates associated with these devices. You suggest that the actual adverse event rates are much higher than provided in the device labeling and persist for at least 12 months after surgery but you fail to provide information supporting the inaccuracy of any particular device labeling. You present several graphs purportedly representing data on post-LASIK vision changes but these graphs, which appear to be based on pooled data from different devices, are not a valid means of assessing the data on the post-LASIK vision changes given the variability in the inclusion and exclusion criteria, differences in follow-up assessments, and differences in measurements and assessment techniques.

Additionally, Section II.A.2 of your petition alleges that LASIK device manufacturers "pressured" FDA to classify post-LASIK surgery glare, halos, dry eye, and night driving difficulties as "symptoms" as opposed to adverse events. You suggest that inclusion of

these symptoms as adverse events would result in a true adverse event rate of much higher than 1%. We acknowledge that the visual symptoms you mentioned may occur following LASIK surgery but FDA was not "pressured" to classify these as symptoms. Not all of these visual symptoms are clinically significant enough to warrant classification as an adverse event (for example, because they are reported as being mild).[3] Moreover, studies reported in the literature indicate that most post-LASIK surgery visual symptoms are not persistent.[4,5] You note that FDA encourages the reporting of visual symptoms and claim that this signifies that the Agency considers such symptoms to be "reportable events." FDA encourages physicians and patients to report these and other problems relating to LASIK devices, regardless of whether or not they constitute serious injuries or other events that must be reported by certain entities under 21 CFR Part 803. FDA encourages such reporting so that the Agency may continue to assess relevant safety information on LASIK devices as part of its postmarket surveillance program.

Importantly, whether visual symptoms were identified as adverse events or not, they were considered, along with other information in each PMA application, as FDA determined whether the standard for premarket approval was met for each LASIK device. In other words, the full spectrum and persistence of all post-LASIK visual symptoms observed in the clinical studies submitted in the PMA application were considered in FDA's evaluation of the overall benefit-risk profile of each LASIK device during the premarket review process. Such visual symptoms are disclosed as potential risks in the patient labeling for the LASIK devices and the SSED for each LASIK device provides detailed information about the visual symptoms observed in the clinical studies submitted in the PMA application. Further, the patient labeling for each LASIK device also includes a summary of the data on these visual symptoms observed in the clinical studies submitted in the PMA application.

You further allege in Section II.A.3 of your petition that LASIK device manufacturers withheld an average of about 30% of the clinical follow-up data (including instances of dry eyes, night vision problems, glare, and halos) from FDA. However, you did not provide information in your petition to support your allegation. You also allege that the high satisfaction rate reported by patients who undergo LASIK is suspect based on various hypotheses that are not supported with any data or information.

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[3] The guidance entitled, "Checklist of Information Usually Submitted in an Investigational Device Exemptions (IDE) Application for Refractive Surgery Lasers," identifies some potential adverse events for LASIK devices and other refractive surgery lasers (e.g., adverse events include late onset of, or continuing, haze 6 months or more after LASIK surgery with loss of two lines (10 letters) or more of best spectacle corrected visual acuity). See http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080250.pdf.

[4] Toda I, Asano-Kato N, Komai-Hori Y, Tsubota K. Dry eye after Laser In Situ Keratomileusis. Am J Ophthalmol 2001;132:1–7.

[5] Pérez-Santonja JJ, Sakla HF, Alió JL. Contrast sensitivity after laser in situ keratomileusis. J Cataract Refract Surg. 1998 Feb;24(2):183-9.

Section II.A.4 of your petition presents information that you contend indicates that manufacturers distorted the effectiveness evidence to support the premarket approval of their LASIK devices. You also contend that the visual acuity of 43% of LASIK patients could be improved by wearing spectacles 6-12 months after surgery, and that the effectiveness rate for LASIK is 57%. You allege that LASIK device manufacturers and others influenced FDA to change the criteria for measuring effectiveness from the number of patients who do not need corrective lenses post-LASIK surgery to the percentage having uncorrected visual acuity of less than or equal to 20/40.[6] Despite your assertion to the contrary, FDA has never measured effectiveness by the percent of post-LASIK patients that would not need corrective lenses. Effectiveness for LASIK devices is generally evaluated by the proportion of eyes that achieve uncorrected visual acuity of 20/40 or better and refractive stability at 6 months or longer following surgery. None of the approved excimer lasers for LASIK surgery have an indication for use claiming to completely eliminate a specific type of refractive error. Perfect vision for all tasks under all conditions without the use of spectacles or contact lenses is not stated in any approved labeling as an intended outcome of LASIK surgery. Notably, the patient labeling for LASIK devices inform patients of the possible need for corrective lenses after surgery.

**B. The Petition Alleges that LASIK Creates "Sick" Corneas**

You contend that published scientific reports demonstrate that LASIK weakens normal corneas. You claim that the scientific literature describes: 1) permanent physiological changes (including corneal distortions and weakening of the corneas), and progressive pathology as a result of LASIK surgery, 2) adverse events resulting from LASIK surgery, including neuropathic dry eye, keratectasia, dislocated and amputated flaps, diffuse inflammation, and loss of contrast sensitivity in dim light, 3) unstable vision correction leading to regression and the need for additional eye care following LASIK surgery, and 4) similar damage caused by old and new LASIK excimer lasers. FDA responds to each of these concerns below.

*1. Physiological Changes*

In sections II.B.1, II.B.2, II.B.4 and II.B.6 of your petition, you provide information concerning physiological changes following LASIK surgery. Assuming the provided information establishes that such changes may occur, FDA believes that it is adverse medical events, and not physiological changes, that are important in determining whether LASIK devices are reasonably safe and effective. For example, even assuming that there is reduced density of corneal stromal keratocytes in post-LASIK patients, this may not

[6] You refer to the patient labeling for P930016 S10 as support for your claim. This patient labeling, however, does not support your claim. The patient labeling for P930016 S10 provides the results from the LASIK clinical studies which include the percentage of eyes having uncorrected visual acuity of less than or equal to 20/40. Moreover, the patient labeling clearly states the following under "Risks": "You may need reading glasses after laser surgery even if you did not wear them before. Your vision may not be perfect, and you may need to wear glasses or contact lenses for some activities even after laser vision correction."

lead to an adverse event. As you noted in your petition, the reported incidence of keratectasia in the cited literature ranges from 0.01% to 0.66%.

2. *Adverse Events*

In sections II.B.1, II.B.3, II.B.5, II.B.6, and II.B.7 of your petition, you discuss certain adverse events associated with LASIK devices including dislodged/amputated flaps, diffuse lamellar keratitis, neuropathic dry eye, keratectasia, corneal distortions, and loss of contrast sensitivity. FDA agrees that these adverse events described in your petition, as well as others observed in clinical studies submitted in the PMA applications, are potential risks associated with LASIK devices. For that reason, we require risk disclosure, including information about relevant adverse events, in the device labeling. For example, the patient labeling for LASIK devices either provide data on contrast sensitivity if evaluated in the clinical study or inform patients that they may have difficulty seeing in dim lighting, rain, snow, fog, or bright glare (see, e.g., patient labeling for P030008 approved on Oct. 10, 2003). FDA also provides general information about risks on FDA's public LASIK website (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/LASIK/default.htm). For example, we state on our LASIK website that "some patients do not see as well in situations of low contrast, such as at night or in fog, after treatment as compared to before treatment" (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/LASIK/ucm061354.htm). We also encourage consumers to report LASIK-related problems on our LASIK website (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/LASIK/ucm061479.htm).

Although it is important for consumers to understand the potential risks associated with LASIK devices, FDA does not believe the information contained in your petition changes the overall benefit-risk profile of approved LASIK devices. The rate of the adverse events reported in the literature cited in your petition appears to be consistent with the information provided in the PMA applications for the LASIK devices. The information in your petition does not support withdrawal of the approvals of the PMA applications for the LASIK devices or their recall.

3. *The Petition Alleges Vision Correction is Unstable Leading to Regression and Need for Additional Eye Care*

In section II.B.8 of your petition, you claim that several years after LASIK surgery, a large percentage of patients are unhappy with their vision and that losses in visual acuity and other vision deterioration significantly increase over time. Although studies of LASIK patients have shown some regression of the treatment effect, these studies are often on a small number of patients and do not account for the progression of the

underlying myopia.[7,8,9] There is not sufficient valid scientific evidence to support your claim that LASIK surgery, alone, accounts for the observed changes in refractive error over long periods of time. In fact, there is evidence that indicates that other factors contribute to these symptoms.[10,11] The papers that you submitted for review show that those with high myopia regressed significantly more than those without and younger subjects showed more regression, a pattern well-established in the progression of myopia.[12] In the articles you submitted for review that involved patient questionnaires, all the patients reported that they would have LASIK surgery again, contradicting your assertion that the majority of patients are unhappy with their vision.[13] The approved LASIK devices have demonstrated adequate stability of correction prior to approval, as detailed in the SSEDs, which are available on the FDA website.

Section II.B.9 of your petition claims that there is a need for additional eye care as a result of the adverse events described elsewhere in your petition, and the potential for undiagnosed glaucoma and poor outcomes from cataract surgery in LASIK patients. FDA is aware that changes in corneal thickness from LASIK surgery may affect intraocular measurements as well as future cataract surgery.[14,15] However, the diagnosis of glaucoma is largely based on the evaluation of the optic nerve and visual fields, not solely on intraocular pressure measurements. To improve outcomes following future cataract surgery, FDA has partnered with the American Academy of Ophthalmology (AAO) to develop a patient card detailing the patient's preoperative corneal measurements, which are important in determining the power of the implanted intraocular lens (http://one.aao.org/patient-safety-statement/kcard).

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[7] Zalentein WN, Tervo TMT, Holopainen JM, Seven-year follow-up of LASIK for myopia. J Refract Surg. 2009; 25:312-318.

[8] Rosman M, Alió JL, Ortiz D, Pérez-Santonja JJ. Refractive stability of LASIK with the VISX 20/20 excimer laser vs ZB5M phakic IOL implantation in patients with high myopia (>-10.00 D): A 10-year retrospective study. J Refract Surg. 2010 Jul 23:1-8.

[9] Dirani M, Couper T, Yau J, Ang EK, Islam FM, Snibson GR, Vajpayee RB, Baird PN. Long-term refractive outcomes and stability after excimer laser surgery for myopia. J Cataract Refract Surg. 2010 Oct;36(10):1709-17.

[10] Kato N, Toda I, Hori-Komai Y, Sakai C, Tsubota K. Five-year outcome of LASIK for myopia. Ophthalmology. 2008 May;115(5):839-844.

[11] Alió JL, Muftuoglu O, Ortiz D, Pérez-Santonja JJ, Artola A, Ayala MJ, Garcia MJ, de Luna GC. Ten-year follow-up of laser in situ keratomileusis for myopia of up to -10 diopters. Am J Ophthalmol. 2008 Jan;145(1):46-54.

[12] MA Bullimore, LA Jones, ML Moeschberger, et al. A retrospective study of myopia progression in adult contact lens wearers. IOVS 2002, 43: 2110-2113; WN Zalentein, TMT Tervo, JM Holopainen. Seven-year follow-up of LASIK for myopia. J Refractive Surgery 2009, 25: 312-8; M Rosman, JL Alio, D Ortiz, et al. Refractive stability of LASIK with the VISX 20/20 excimer laser vs ZB5m phakic iol implantation i patients with high myopia (>10.00D): a 10-year retospective study. J Refractive Surgery 2011, 27: 279-86.

[13] Zalentein WN, Tervo TMT, Holopainen JM, MD. Seven-year follow-up of LASIK for myopia. J Refract Surg. 2009; 25:312-318.

[14] Emara, B., Probst, L. E., Tingey, D. P., Kennedy, D. W., Willms, L. J., & Machat, J. (1998). Correlation of intraocular pressure and central corneal thickness in normal myopic eyes and after laser in situ keratomileusis. Journal of Cataract & Refractive Surgery, 24(10), 1320-1325.

[15] Argento C, Cosentino MJ, Badoza D. Intraocular lens power calculation after refractive surgery. J Cataract Refract Surg. 2003 Jul;29(7):1346-51.

*4. The Petition Alleges Similar Damage Caused by Old and New LASIK Excimer Lasers*

Section II.B.10 of your petition states that newer LASIK technologies have the same risks as older technology and have not resolved problems inherent in LASIK surgery. You also assert that in some cases, newer LASIK technology results in poorer outcomes or increased risk. As explained above, there are risks associated with LASIK devices that are described in the device labeling. However, there are also benefits provided by these devices and studies reported in the literature indicate that most LASIK patients are satisfied with the outcome.[16] FDA believes that the valid scientific evidence submitted in the PMA applications supports the conclusion that each of the currently approved LASIK devices is reasonably safe and effective when used in accordance with the approved labeling.

## III. Conclusion

FDA has reviewed your petition, including the published literature cited in your petition and other information you referenced, and other relevant data and information available to the Agency. This information in its totality does not provide a basis for withdrawal of the approved PMA applications for LASIK excimer lasers or the issuance of a Public Health Advisory with a voluntary recall of the devices. For the reasons discussed above, the Agency denies your request that we: 1) withdraw the PMAs for all LASIK devices; and, 2) issue a Public Health Advisory with a voluntary recall of LASIK devices.

However, FDA will continue to monitor postmarket data related to LASIK devices and the promotional claims made about these devices. FDA will also continue to provide updated information on its LASIK website about actions taken with regard to LASIK devices. Examples of such actions include:

- FDA assembled a task force comprised of members of the American Society of Cataract and Refractive Surgeons and the AAO to assess the need to further study the range of patients' visual symptoms following LASIK surgery and how such visual symptoms affect the day-to-day function of patients (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/LASIK/ucm190291.htm). As a result of these discussions, FDA launched the LASIK Quality of Life Collaboration Project with the Department of Defense (DoD) and the National Eye Institute (NEI) to help measure validated patient-reported outcomes, following LASIK surgery, and explore factors that may affect these outcomes. Of note, this project was developed and is being conducted with ongoing advisory input from LASIK patients. The information from this study will help measure patient outcomes following LASIK surgery as

[16] Solomon KD, Fernández de Castro LE, Sandoval HP, Biber JM, Groat B, Neff KD, Ying MS, French JW, Donnenfeld ED, Lindstrom RL. LASIK World Literature Review: Quality of Life and Patient Satisfaction. Ophthalmology 2009;116: 691–701.

well as explore factors that may affect these outcomes. Please visit the LASIK website to view study progress and updates (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/LASIK/ucm190291.htm).

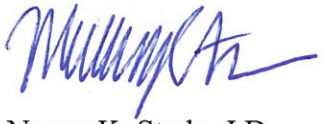
- FDA has emphasized the mandatory reporting requirements to LASIK providers. In October 2009, for example, FDA issued warning letters to 17 LASIK ambulatory surgical centers after inspections revealed inadequate adverse event reporting systems at all of the centers. Moreover, FDA has made clear that if a patient has persistent, visual symptoms, then these symptoms should be reported and FDA will conduct an evaluation of those symptoms (http://www.eyeworld.org/article-fda-interest-in-lasik-continues--ascrs-webinar-clears-confusion-about-medical-device-reporting-and-lasik).

- As mentioned above in section II.B.3, to improve outcomes following future cataract surgery, FDA has partnered with the AAO to develop a patient card detailing the patient's preoperative corneal measurements, which are important in determining the power of the implanted intraocular lens (http://one.aao.org/patient-safety-statement/kcard).

FDA's LASIK website also provides updated general background and risk information for the public, including information on the most common risks associated with LASIK devices (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/LASIK/ucm061354.htm), as well as a list of FDA-approved LASIK lasers and links to the approved patient labeling for each device (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/LASIK/ucm192109.htm). We note that we are continuing to improve the quality of information on our LASIK website, and intend to take some of your suggestions into consideration as we make modifications to the website. We have already incorporated your recommendation to remove the figure cited on page 4 of your petition from our website as it may not have been clear that this figure generally reflects the experience of the majority of LASIK patients.

If you have any questions in this regard, please contact Mr. John Maiers by e-mail at john.maiers@fda.hhs.gov or 301-796-0343.

Sincerely yours,



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