SUMMARY MINUTES

MEDICAL DEVICES ADVISORY COMMITTEE

OPTHALMIC DEVICES PANEL

110TH MEETING

April 25, 2008

Gaithersburg Holiday Inn

Gaithersburg, Maryland

Opthalmic Devices Panel Meeting
April 25, 2008
Attendees:

Chairperson (Acting):
Jayne S. Weiss, M.D.
Kresge Eye Institute

Voting Members:
Neil M. Bressler, M.D.
Wilmer Eye Institute

Timothy B. Edrington, O.D.
Southern California College of Optometry

Dale K. Heuer, M.D.
Medical College of Wisconsin

Andrew J. Huang, M.D., M.P.H.

Washington University School of Medicine

Janine A. Smith, M.D.
National Eye Institute

Consultants (Deputized to vote):
Stephen D. McLeod, M.D.
University off California, San Francisco

David C. Musch, Ph.D., M.P.H.
University of Michigan

Consumer Representative:
Richard Bunner
Private Public Health Consultant

Industry Representative:
Barbara A. Niksch
Visiogen, Inc.

Patient Representative:
Barbara A. Cofer

Executive Secretary:
Karen F. Warburton, M.H.S.

FDA Representative:
Malvina Eydelman, M.D.

CALL TO ORDER

Chairman Weiss called the meeting to order at 8:29 a.m. **Ms. Warburton** read the conflict of interest (COI), appointment of temporary voting member, and acting chairperson statements. All members and consultants of the panel were in compliance with ethics and COI laws. COI waivers were issued to Dr. Heuer. Dr. Weiss was appointed temporary voting member and acting chairperson by an order signed April 21, 2008 by Dr. Schultz. The Panel members introduced themselves. The purpose of the meeting was to discuss post-market experience with LASIK (laser-assisted in situ keratomileusis) and phakic intraocular lenses.

OPEN PUBLIC HEARING

Chairperson Weiss said all written comments received would be made part of the meeting record, and she read the open public hearing statement, urging the speakers to disclose any interests.

Dr. Michael Patterson urged discontinuation of LASIK. He said the LASIK procedure on his left eye ruined his vision and quality of life (QOL) and that what doctors often call a good outcome is actually poor. He said he had numerous complications and that FDA's risk/benefit analysis did not fully evaluate the risks, including quality of vision and dry eye. He said that the LASIK procedure is unsafe, with a 5 percent failure rate. He accused LASIK surgeons of dishonesty and FDA of failing to ensure compliance. He accused the FDA of intentional negligence and noted that there were few adverse event reports, despite numerous customer complaints. He said there was bias in the LASIK QOL study, that ASCRS's involvement was a conflict of interest, and that the connection between LASIK and suicide was known to the FDA. He said LASIK patients commit suicide at four times the normal rate. He mentioned Dr. Richard Lindstrom as a surgeon with financial COI. He asked FDA to redo the risk/benefit analysis and make the risks known; regulate LASIK centers as Ambulatory Surgical Facilitiess; utilize physicians independent of the LASIK industry in the QOL study; place a moratorium on LASIK devices; evaluate potential dry eye treatments; and stop LASIK procedures. He said that LASIK surgeons should not sit on an FDA panel evaluating LASIK, mentioning Dr.

Huang by name.

Dean Andrew Kantis said LASIK ruined his vision and that he had spent $30,000 trying to restore his vision, finding no cure. He said that hundreds of patients had contacted him at his website, lifeafterlasik.com, expressing suicidal thoughts. He said that there had been backlash when he spoke out, including a lawsuit and harassment from his surgeon. He asked why his surgeon faces no disciplinary action despite numerous lawsuits. He said that the doctors cover for each other when giving second opinions and in regulatory bodies. He said that doctors lie about the healing period so that the statute of limitations will run out. He urged FDA to investigate flap and pupil size; mandate an updated pamphlet with all known side effects as well as the statute of limitations for malpractice; accurately define LASIK success to exclude patients with complications; review 21 CFR 803.17, which requires the reporting of adverse outcomes; and look into the emotional effect on doctors, patients, and family. He asked the media to investigate visionsite.net. He asked for the creation of a fund to assist hurt LASIK patients.

Glen Hagele spoke on behalf of **Barbara Berney and Dr. David Hartzog**, founders of the Vision Surgery Rehab Network (VSRN), which helps patients with complications from surgery that alters the eyes' refractive status. Refractive Surgery Syndrome (RSS) is a complex and chronic visual, psychological, and physiological condition. Symptoms include dry eye, which can cause pain and reduced vision. Vision has a substantial effect on perception. Since a person's reality is based on perceptions, LASIK alters reality in sometimes disturbing ways. Patients are frustrated by surgeons' denial of complaints, which aggravates the psychological aspects of RSS. Loss of visual quality reduces well-being, leading to depression and anxiety. How doctors manage LASIK problems affects stress levels and is critical to recovery. Patients whose rehab efforts fail to restore normal vision suffer a higher degree of RSS. The discrepancy between the surgeons' procedural view of success and the patients' perceptional view of success must be resolved, and QOL investigations must be impartial and include behavioral and perceptional specialists.

Gerard Dorrian spoke on his son, Colin. Colin had LASIK surgery in law school after becoming intolerant to contact lenses due to dry eyes. He was warned that the size of his pupils could affect the procedure but that there was less than one percent of a chance that his experience would be worse than contacts. After treatment, he experienced large starbursts, triple overlapping images, and ghosting off white objects. His eyes were too dry to tolerate contact lenses. He lost contrast sensitivity. He said everything looked ugly and confusing, and he fell into a deep depression. Six and a half years after the surgery, he killed himself.

Glenn Hagele spoke for **Sandy Keller,** who had LASIK in 1999 for myopia. She experiences serious complications and received a settlement for malpractice and improper referral. She met with the surgeon after taking Valium. She had dry eyes and corneal warpage. Her pupil size was 8 mm, but the ablation zone was 6 mm. The blade jammed her eye, and she developed Diffuse Lamellar Keratitis (DLK). Eight weeks postop, her vision was 6 diopters of hyperopia. A subsequent surgery further reduced the effective optical zone and caused myopia and multiple images. Although she had several contraindications for LASIK, her optometrist referred her to an inexperienced surgeon because he had a financial interest in the center and received $1100 for the referral. She filed a MAUDE report in 2001, but the disposition was that there was no record of her existence. Seven additional surgeries failed to restore her eyesight. She suffers from post-traumatic stress disorder and depression.

Dom Morgan said he is legally blind due to the improper use of an investigational laser. He had retinopathy of prematurity at birth and 20/50 vision before the procedure. The suction ring destroyed his retinas, and he was dropped from the clinical study. His data was not reported to the FDA, and he was sued when he went public. In 2003, he filed a petition on medical devices and refractive surgery. It was ignored. He has corresponded with hundreds of injured, depressed, and suicidal patients. He said FDA has been ineffective in enforcing the policies mandated for the industry and protecting the patients. He said FDA's receiving funding from the industry creates a conflict of interest and harms credibility. He submitted a letter from Dr. Steven Friedman to FDA's Office of Criminal Investigation summarizing his physician's actions and a letter from Dr. James Salz explaining why he was not a candidate for the procedure, as well as other documents and correspondence with the FDA. He directed the Panel to his webpage: lasikdecision.com. He urged the Panel to recommend an independent and unbiased study, survey injured patients, investigate doctors for criminal activity, and issue a moratorium on advertising.

David Shell spoke on his experience with LASIK. Prior to the procedure, he was farsighted. The procedure damaged his eyes, causing eye pain, double vision, difficulty reading, poor night vision, and clinical depression. He experiences starbursts, double vision, glare, fluctuating vision, floaters, and impaired vision in dim light. He showed pictures simulating the visual problems. He testified on dry eyes to the FDA in 2002. Dry eyes cause stinging pain, and he has found no effective treatment for it. He said LASIK has inherent problems: severed corneal nerves, weakened corneas, and high order aberrations. He urged an independent investigation, reclassification of dry eye and visual quality issues as complications, and that FDA look at safety and effectiveness again.

Glenn Hagele spoke for **Barry Elbasani**, a quadriplegic with limited arm mobility. Due to his disability, he was unable to put on or adjust his glasses or put in contact lenses. Mr. Hagele showed a video of a news story about Dr. Daniel Durrie, who gave free LASIK surgery for people whose arms are paralyzed.. After the surgery, Mr. Elbasani's vision was 20/10 and he gained added independence. He and Dr. Durrie founded Focus on Independence, which helps quadriplegics get LASIK from doctors who donate their time and expenses.

Glenn Hagele, Executive Director of the Council for Refractive Surgery Quality Assurance, said his Council provides surgeon certification, distributes objective information, and runs the website usaeyes.org. He said that LASIK patients measure success by QOL, so the Council uses that standard. Patient satisfaction is based on expectations. The Council developed the USAEyes CORE survey (Confidence Opinion Relative to Expectation). Patients from multiple centers and different types of surgery are mailed copies of the survey. In the preliminary data, 89 percent of patients are seldom or never wearing corrective lenses; 98 percent of patients say their quality of day vision is as expected or better, 91 percent for night vision. 96 percent report overall quality of vision was as expected or better. 99 percent reported QOL was as expected or better. 0.9 percent reported QOL worse than expected. 98 percent of the patients said they would recommend the surgery and 97 percent would do it again. He submitted the preliminary data to the Panel and suggested that FDA look at other endpoints in addition to QOL.

Dr. Diana Zuckerman, President of the National Research Center for Women and Families, said that there are problems with self-reports, which are subjective. She said that there are safe, effective, and inexpensive alternatives to LASIK: contact lenses and glasses. The risks must be weighed against the benefits. She noted that product labeling is important, since patients don't read the FDA website, which does not appear to be geared toward patients. She said the Panel should address eye pain, dry eye, the need for additional surgery, higher suicide rates, and informed consent.
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Dr. Lauranell Burch, speaking as a private citizen, said the task force to examine post-LASIK QOL issues is dominated by individuals with conflicts of interest. She mentioned specifically Dr. Kerry Solomon. She said a growing body of evidence indicates that LASIK is harmful and that even satisfied patients have reduced contrast sensitivity and are unaware of the damage incurred or the long-term effects, such as the risk of flap injury, weakened cornea, permanent pathologic changes to the cornea, altered patterns and density of corneal nerves, complications in future cataract surgery, invalidated intraocular pressure motion, and an increased rate of progressive corneal stromal cell density loss. She said patient satisfaction is not a substitute for objective testing and urged FDA to abandon the QOL study for a study on dry eye and visual quality and that approval be withdrawn pending the outcome of the study.

Matt Kotsovolos spoke on his experience with LASIK. Though his vision was corrected to 20/20, he has had debilitating eye pain since the surgery. He said the complication rates were misrepresented and that the procedure is marketed unethically. He said some complications are called symptoms and occur at rates of 20 percent. He cited a study that reported dry eyes in 20 percent of patients and worsened night vision in 15 percent. He emphasized that patient satisfaction is not an accurate measure of complications and that surveys are easily skewed. He raised the issue of LASIK-related depression and suicide and urged a moratorium on LASIK until a comprehensive study of the complications is completed. He asked that dry eyes and night vision disturbances be included in the labeling as complications. He said the FDA is controlled by the industry.

Beth Kotsovolos spoke on her experience as the wife of a LASIK patient. She said the complications, including dry eyes, pain, and depression, nearly destroyed her family. She asked the Panel to be objective and asked the media to hold FDA accountable. She asked FDA to investigate post-LASIK depression and suicidal ideation.

Dr. Kerry Solomon spoke for **Dr. Richard L. Lindstrom**, an attending surgeon at the Minnesota Eye Consultants, board member of TLC Vision, former president of the American Society of Cataract and Refractive Surgery (ASCRS), and consultant for AMO, Bausch & Lomb, and Alcon. He has performed numerous surgeries, including surgeries upon friends, family, and colleagues. He said 30 percent of LASIK surgeons undergo LASIK. He said ASCRS is the primary source of information on the field and that a decade of research reinforces the safety and efficacy of LASIK. He said the satisfaction rate for LASIK is higher than for any other procedure and that ASCRS continues to learn about patient satisfaction in order to improve it. The Joint LASIK Study Task Force is a collaboration to better understand the impact of LASIK on QOL. The Task Force includes ASCRS, the American Academy of Ophthalmology (AAO), the National Eye Institute (NEI), and FDA.

Dr. Eric Donnenfeld, spoke for the ASCRS. He is a consultant to AMO and Bausch & Lomb and was an FDA investigator for an excimer laser. He said that the majority of patients see better after the surgery than they did with glasses or contacts and that the lifetime risk of infection with contact lenses is over 100 times higher than with LASIK. The LASIK Task Force of the ASCRS reviewed the world's literature on dry eye and found that 35 percent of patients had dry eye after the procedure, but 32 percent had it before the procedure. Severe dry eye following LASIK is rare. New treatment options for dry eye are in the process of FDA evaluation. He introduced Nick Anderson, who received a corneal transplant at 9 years old whose vision was subsequently markedly improved when he received LASIK at 15.

Dr. Scott Barnes spoke for **Dr. Doyle Stulting**, who represented ASCRS. Dr. Stulting participated in a clinical trial of LASIK, was a former chairman of the Ophthalmic Devices Panel, and is a consultant to AMO. He said most patients achieve 20/20 vision or better and have less night driving difficulty after than before LASIK. Methods have been developed to correct abnormalities of the ocular system, address unique patient needs, and evaluate the eye in greater detail. Screening procedures have been instituted to identify the patients who might have sub-optimal results. At his center, an initial examination lasts two hours and includes an eye examination, wavefront measurements, detailed analysis of the cornea, measurement of the pupil, assessment of tear production, evaluation of the ocular surface, and a discussion with the patient. The Task Force will allow further refinement of the screening process. **Dr. Barnes** of the Warfighter Refractive Eye Surgery Program emphasized the importance of LASIK to the military.

Dr. Kerry Solomon, an eye surgeon at the University of South Carolina; an investigator in the LASIK study; and a consultant for AMO, Alcon, and Bausch & Lomb, spoke for ASCRS. He has reviewed the world's literature on patient satisfaction and found that 95.4 percent of patients are satisfied after LASIK. The review included all articles from LASIK's inception to 2008. Of 2,915 abstracts found, 309 were identified and entered into the database. Those articles were well-performed, peer-reviewed studies from major ophthalmic journals. The 95 percent satisfaction rate was consistent throughout the studies. The study creates a baseline of knowledge for identifying and reducing risks.

Todd J. Krouner, Esq. a plaintiff's malpractice attorney, said that most of his cases involve high-volume LASIK facilities that fail to properly screen for contraindications such as kerataconus. He urged FDA to encourage effective training; encourage reporting of adverse outcomes; commission an independent study on LASIK patient satisfaction; and report on the findings in a timely basis. He said the industry does not effectively police itself and that training levels vary widely. The screening process requires time and care. Adverse outcomes are under-reported. Voluntary reporting should be encouraged; mandatory reporting failures should be enforced. He said patient satisfaction should be measured by qualitative and quantitative measures. Visual acuity is only half of one's vision. He pointed out that even if the negative outcome rate is one only percent, that would be 10,000 patients per year suffering visual disability.

Dr. Peter McDonnell of Johns Hopkins University, who was involved in clinical and pre-clinical studies, said he has received federal research funding and has been an industry clinical investigator. He is a consultant for an excimer laser manufacturer. He spoke on behalf of the International Society of Refractive Surgeons of the American Academy of Ophthalmology (ISRS of AAO). He said LASIK is the most studied elective ophthalmic procedure, that it has benefited millions of patients, and that there have been incremental improvements to the procedure. Most complications can be treated without any vision loss, and side effects often resolve after 3 to 6 months. ISRS is dedicated to further improving the technology, techniques, and screening.

Dr. Jennifer Morse a psychiatrist, ASCRS consultant, and member of the Joint LASIK Study Task Force, said she had seen the benefits of LASIK in military and civilian populations. Psychological well-being is an important QOL issue. The literature on suicide and depression indicate that they occur due to multiple factors and are too complex to link to a single cause. There is no scientific evidence of any direct link between LASIK and depression or suicide. Studies from other elective surgeries have found associations between pre-operative psychological factors and patient perceptions of surgical outcome. Current data shows that QOL after LASIK is similar to patients who never had vision problems and that users of glasses or contacts have lower QOL scores than LASIK patients. She welcomed the knowledge the QOL study will provide, which will aid in pre- and post-LASIK counseling.

Dr. Steve Schallhorn spoke for AAO. While in the Navy, he founded the DoD Refractive Surgery Program, and he is a consultant to AMO. AAO is committed to responding ethically and compassionately to patients' needs. He said that LASIK is safe and effective and that patient satisfaction is excellent. He said the next step is to focus on QOL. Current studies show an overall QOL improvement after LASIK, but the studies could not fully assess QOL in patients who were dissatisfied. He said the collaborative study will further evaluate underlying factors that impact satisfaction. Due to the low dissatisfaction rates, the study will enroll a large set of patients in order to capture the factors associated with dissatisfaction.

Dr. Terylyn F. Bankes was a physician counselor for several LASIK patient support groups. Group members had vision problems and various emotional responses. Many became obsessed with their vision and became estranged from family and friends. She said LASIK problems are well-known in the ophthalmologic community and that defending the practice is disgraceful. She asked FDA to protect the patients. She told of a patient, Kim Harringer, who had RK surgery 14 years ago, then LASIK in 2006 when her vision regressed. LASIK caused vision problems, which caused suicidal depression. Dr. Bankes said there is a lot of catching up to do with understanding and treating poor outcomes.

Dr. Michael Mullery said that the industry has known about the risk of depression and suicide since inception. Bad outcomes are not rare and can result in serious vision loss and blindness. He said allowing the industry to conduct the QOL study is a conflict of interest and is inconsistent with the scientific method and common sense. He cited the Grifffith University-World Health Organization study that compared suicides in hearing impaired and vision impaired populations. Vision loss was a greater risk factor for suicide, and vision loss was the main causal factor in those suicides, while the hearing loss suicides were linked to several causes. He said he had personally interviewed approximately 75 people with suicidal ideation as a result of LASIK. Since preexisting psychopathology was not the cause of suicidal ideation, screening would not solve the problem. He presented examples from his practice with suicidal and depressed LASIK patients. He said that research on this issue is lacking and urged a moratorium on the procedure until the risks are understood. He also urged that the labeling reflect the risks.

Courtney Henrichs said ASCRS provided her travel. In 2002, she broke her neck skiing and became a quadriplegic. In 2006, she had LASIK through the Focus on Independence Program. Prior to the accident, she had worn contact lenses. After the accident, she wore glasses, which she could not put on, clean, or adjust by herself. She said the surgery improved her independence and her quality of life.

Todd Krouner, Esq., spoke for his client, **Amanda Campbell**, whose husband committed suicide this year. Mr. Campbell's suicide note states that he was not a candidate for LASIK and that his adverse outcomes including dry eyes, pain, and distorted vision that made life unbearable. He had no known mental illness prior to the surgery. **Mr. Krouner** said FDA should investigate the association between suicide and depression. He urged FDA to be transparent in its work and respond to FOIA requests in a timely manner.

Dr. Roger Davis, a clinical psychologist, said he has communicated with 300 patients with LASIK complications, 100 of whom had suicidal ideation. In a study with the Surgical Eyes Foundation, most patients with suicidal ideation had been told by their surgeon that they were successes. The complication most strongly associated with suicidality was dry eye syndrome. With severe complications, patients develop RSS, which includes depression, suicidal ideation, and post-traumatic stress. Patients consider suicide after having exhausted the search for solutions, feeling like a victim of a corrupt industry, wishing to escape the complications and anxiety, wishing to validate their suffering, or out of guilt for having the surgery. No pre-existing psychopathology is necessary for patients to develop suicidality. Research has

shown psychological crisis after a catastrophic injury. He asked that the study address psychological issues such as deception and informed.consent. He said satisfaction surveys are inadequate for studying depression. He urged a moratorium on LASIK, since the QOL data should have been collected before approval.

Jo Ann Wills spoke for her husband, Keith, who had LASIK in 1997. Unknowingly, he was part of an IDE study. The doctor performed seven procedures, first under-correcting, then over-correcting. She said the doctor was deceitful. She said her husband had vision problems: starbursts, ghosting, and multiple images. She said FDA is not adequately policing the industry. She noted that nine of the Panel members wear glasses.

Dr. Edward Boshnick, an optometrist in private practice, said he devoted much of his practice to non-surgical treatment of patients with lost quality of vision due to ocular trauma, disease, and LASIK. Complications he had seen included loss of visual acuity. visual distortions, overcorrection and undercorrection, , dry eye, loss of contrast sensitivity, corneal ectasia, and depression. He said that LASIK presents a significant health crisis.

Rebecca Petris, founder of Laser My Eye, said she left her former career in finance due to LASIK complications. Since dry eye is such a common problem, she founded the Dry Eye Company, which runs informational websites and collects products that can help. She said that LASIK-related depression is caused not only by the failed procedure but also by the way the patients are treated afterward and problems that develop as a result of the complications and lack of solutions. She said that if the industry wanted to help it would partner with consumer groups to bring practical solutions.

Lt. Col. Scott Barnes, M.D., a cornea and refractive surgery specialist at Ft. Bragg, said that before becoming an eye surgeon he worked with Special Forces. The Army has created a program to correct the vision of Special Forces soldiers. The soldiers have found that LASIK greatly improves QOL and their ability to perform their duties. Vision is important in such operations, and the loss of glasses while parachuting can be disastrous. Additionally, if captured, a soldier's glasses are likely to be taken. He asked that the procedure not be made unavailable.

Joseph Schnell spoke on his experience after having LASIK in 2007. Though his doctor said he had a positive result and determined no significant problems in subsequent evaluations, Mr. Schnell regards his vision as inferior to what it was before the procedure. He experiences glare, halos, starbursts, astigmatism, poor dim light perception, double vision, increased floaters, dry eyes, and psychological problems, including anxiety and suicidal ideation. He said what are described as possible side effects are actually universal. He said informed consent was not handled properly.

Chairperson Weiss opened the floor to questions from the Panel. **Ms. Cofer** asked about the metaanalysis and whether or not the studies were representative of standard of care. **Dr. Donnenfeld** said that well-trained surgeons can achieve results better than those in the metaanalysis, since most of the results were obtained on old technology. However, there will always be some doctors who are better than others. Complications and satisfaction do not necessarily have a one to one relationship, so complication rates cannot be derived from satisfaction rates. The studies in the metaanalysis varied widely in follow-up time. **Ms. Cofer** further asked about dry eyes and night vision in the studies. Dr. Donnenfeld said the percentage of patients reporting dry eye before the surgery was similar to the number reporting it after. **Chairperson Weiss** asked about the rate of severe effects. **Dr. Schallhorn** said the percentage of complications being discussed were very rare, under one percent. **Mr. Bunner** asked about informed consent and second opinions. **Chairperson Weiss** said that would vary by practitioner. . . .

FDA PRESENTATION

Donna Bea Tillman, Ph.D., opened the FDA presentation. The meeting's purpose was to gain information from the public and to hear discussion among the Panel members relating to LASIK and phakic intraocular lens (PIOL). She gave an overview of the medical device review program. CDRH's mission is to balance risk and benefit in medical devices, getting devices to market quickly while ensuring safety and effectiveness. FDA does consumer outreach to inform the public and help make appropriate decisions. Because devices span a wide spectrum of risk, there is a spectrum of regulatory approaches to reviewing a device and three device classes, Class I being the lowest, Class III being the highest and requiring pre-market approval. LASIK and PIOL devices are Class III and were both approved

by PMA to the level of a reasonable assurance of safety and effectiveness as defined by 21 CFR 860.7.

Labeling plays a role in ensuring that physicians and patients have access to appropriate information on safety and appropriate use. The physician labeling includes indications, contraindications, warnings, precautions, and a summary of the clinical study. Patient labeling includes a description of the procedure, risks and benefits, and questions to ask the doctor. FDA does not regulate the practice of medicine.

After approval, there is continued monitoring of device performance, including post-approval studies (PAS), mandatory adverse event reporting, annual reports from the manufacturers, and interaction with the clinical and scientific communities, and monitoring of the literature. Manufacturers make device modifications, and post-approval data can facilitate updated labeling. Devices are constantly evolving, and FDA has an active role throughout the life cycle of the product.

Kwame Ulmer, M.S., presented on LASIK's regulatory background. Conventional LASIK was first approved in 1998. The treatment was based on manifest refraction and input by the surgeon. Subsequent developments include wide beam lasers, small spot tracking lasers, eye trackers, transition zones from optical zone to cornea surface, larger optical zones, Wavefront-guided lasers, eye torsional control, and iris registration. LASIK systems have been approved for myopic astigmatism and hyperopic astigmatism.

To approve the devices, FDA requires a complete and detailed device description, reviews engineering tests, evaluates the software, and evaluates patient alignment. Maintainance procedures are reviewed.

Labeling ensures that risks and benefits are communicated to the doctor and patient. The contraindications, warnings, and precautions are identical in the patient and physician labeling. Physician labeling includes a detailed device description and a summary of the clinical trial, while patient labeling uses plainer language and includes basic concepts of vision and refraction as well as a glossary.

One example of a contraindication is keratoconus; patients with keratoconus should not have LASIK surgery. Warnings are the second highest level of risk communication. Patients with dry eyes or severe allergies are warned that LASIK may be riskier for them. Precautions include conditions that should be discussed with the doctor. Precautions include unstable eyes or a history of corneal disease or injury.

FDA also encourages, via the labeling, that doctors check for undiagnosed dry eye and measure pupil size in dim light.

The LASIK website was launched in 2000 and is frequently updated. There has been an average of 650,000 visits per year. LASIK related injuries is the top search term on the FDA website. The site includes a checklist for patients to see if they are good candidates and outlines of risks and expectations. Patients are informed of the contraindications, warnings, and precautions. The site explains what symptoms to expect over six months and notes that long term data is not available. FDA does not recommend specific doctors but provides items to consider when selecting a physician.

Gene Hilmantel, O.D., M.S., gave an overview of the American National Standards Institute (ANSI) laser standard. FDA is evaluating standard Z80.11, which concerns laser systems for corneal reshaping, for recognition. There are two broad categories of standards: horizontal standards that address basic principles applicable to many product lines and vertical standards, which are specific to one kind of device. Standards address terminology, test methods, acceptable levels of performance, and examples of clinical protocols. For ophthalmic vertical standards, there are two organizations: ANSI and the International Organization for Standardization (ISO). ANSI is the sole US representative to ISO. Use of standards ensures consistency and predictability, reduces data reporting requirements, and results in reduced review time. The FDA Modernization Act allows FDA to recognize voluntary consensus standards and requires FDA to publish a list of recognized standards. FDA recognizes 30 ophthalmic standards.

ANSI Z80.11 for laser systems for corneal reshaping was published in 2007. The pre-clinical section of the standard outlines laser safety requirements. The clinical section outlines a consensus of an adequate clinical study for refractive lasers, calling for staged enrollment and 300 eyes in the study to detect adverse events with an expected rate of 1 percent or greater. The standard outlines a methodology to determine when refractive stability is attained and calls for effectiveness analyses that assess the predictability of the refractive change and uncorrected visual acuity (UCVA). The recommended safety analyses include assessment of the percentage of eyes that lose 2 lines or more of best spectacle corrected visual acuity (BSCVA), percentage of eyes with BSCVA worse than 20/40, percentage of eyes with an increase in refractive astigmatism greater than 2 diopters, and the rates of adverse events.

The standard recommends a validated questionnaire to measure subjective outcomes. There should be

questions regarding glare, halos, double vision, night driving, and use of spectacles or contact lenses. The scaling system for the ratings should be specified, and the ratings should be used to assess the incidence of clinically significant symptoms and any postoperative change in symptoms compared to preoperative status. Postoperative satisfaction and use of distance correction should also be incorporated in the questionnaire.

The standard also calls for a contrast sensitivity sub-study when features of the laser raise concerns about vision loss or to justify reductions in precautionary labeling. The ANSI standard created a basic structure for pre-clinical and clinical studies and includes comprehensive evaluation of numerous safety and effectiveness standards.

Quynh Hoang, M.S., spoke on FDA's postmarket review, which FDA conducted in 2006 in response to complaints from patients. CDRH convened an action team that compared postmarket data (AE reports, literature, recall information, and comments on the FDA web page) to premarket data (PMAs, trial protocols and results). The literature survey included 15 articles studying QOL. The action team concluded that the postmarket literature was not comparable to the pre-market data, since the scoring methods differed and the patient-reported outcomes were covered by a very small number of articles. Both pre- and postmarket surveys showed a high level of satisfaction, and the postmarket literature did not suggest widespread problems. The surveys do not adequately evaluate the effects of rare and severe events. The action team recommended that FDA consider further evaluation of post-LASIK QOL in a clinical setting. CDRH is carrying out that recommendation.

Eva Rorer, M.D., spoke on the LASIK QOL Assessment. Patient-reported outcome (PRO) measures and PRO QOL. A PRO measure comes from the patient without interpretation by the physician or anyone else. It adds an evaluation measure independent of clinical success. Health-related (HR) QOL represents the patient's perception of the impact of a health condition and treatment. PRO categories include symptoms, functioning, and perceptions. Measurement of PRO must be standardized. Questions must be evaluated for their ability to measure. The use of existing instruments is desirable for comparability. A questionnaire should be validated for content validity, criterion validity, construct validity, internal consistency, and test-retest reliability. The questionnaire must be tested in different populations to assess generalizability. Due to the cost and complexity, there are few validated LASIK QOL questionnaires. The first was published in 2000. PRO are assessed during device clinical trials but are not generally used as primary endpoints. PRO data is considered during application review, is incorporated in labeling, and may be used as primary endpoints in post-market studies.

Based on the PMI Action Team's recommendation, FDA considered a large prospective study to evaluate LASIK outcomes. FDA solicited cooperation with NEI, ASCRS, and AAO to form the joint LASIK Study Task Force, and the Task Force members have committed resources toward a multi-center clinical trial investigating QOL after LASIK. The objectives are to measure levels of satisfaction after LASIK, changes in HR-QOL after LASIK, and factors associated with the level of satisfaction after LASIK. The protocol is not yet finalized, and the group is assessing the appropriate instrument, which will be validated and easy to use in clinical practice as well as premarket and postmarket studies. FDA has an integral role in the study design and execution and will objectively evaluate the information collected. Consumer representation will be included.

FDA initiated a collaborative study with NEI to facilitate use of HR-QOL instruments in device trials. The study will add to the body of knowledge in the field of PROs and validate computer administration of ophthalmic HR-QOL instruments. Outcomes of all studies will be made public and could lead to modification of the FDA website, revised labeling, and modified educational outreach.

Bernard P. Lepri, O.D., M.S., M.Ed., spoke on FDA's adverse event data collection. The best known program is MedWatch, which monitors for safety information and adverse events post-approval. Reports come from manufacturers, user facilities, healthcare professionals, patients, and consumers. There are two main categories of device reporting: mandatory and voluntary. Mandatory reporting is required of medical device manufacturers and user facilities. Voluntary reporting is by healthcare professionals and consumers.

MedSun is a subset of mandatory user facility reporting that allows interactive two-way collaboration between FDA and MedSun participants. MedSun is a network of highly trained reporters who recognize and report device problems. It is designed to identify, understand, and solve problems and provides regular feedback by newsletters, conference, webcasts, and alerts. MedSun reports are encrypted, stored securely, and accessible only to staff with security clearances.

SightNet was made as a subset of MedSun in 2007 to provide a real-world view of ophthalmic medical

device use in a variety of settings. The goal is to amplify signals of potential device problems to aid in timely intervention and risk mitigation. Participants collaborate with FDA and other facilities to understand potential safety issues. Participant sites designate at least one reporter per site and agree to actively participate for at least a year. Reports are confidential. Problems that are reported include problems with labeling, packaging, manufacturing, software, function, and interaction with other devices, as well as human factors and problems with off-label use. FDA aims to collect reports on all ophthalmic medical devices in use and on a wide variety of adverse events. For LASIK, FDA is looking to collect data on adverse events such as infectious keratitis, endemic cases of DLK, abnormal trends in post-op topography, significant losses of BCVA, glare, halos, starbursts, and distortions as well as device failures.

PANEL QUESTIONS FOR FDA

Dr. Heuer asked about existing validated dry eye instruments. **Dr. Eydelman** said they were incorporated into the NEI-FDA pilot. **Ms. Niksch** asked about the QOL study protocol and whether there would be psychodynamic profiling questions. Dr. Eydelman said the protocol was not finalized. There is discussion of incorporating several domains of previously validated questionnaires to provide the best questionnaire possible. The questionnaire will be administered pre- and post-surgery. **Ms. Cofer** asked how it is enforced that the patients actually get the labeling. **Dr. Eydelman** said that FDA regulates manufacturers, not physicians. However, the patient labeling is part of the approval package and is downloadable, so it is available. **Dr. Musch** asked if the ANSI standard should indicate the time post-operative that QOL should be measured. **Dr. Eydelman** said the times are specified in the ANSI standards. The Panel was provided with a synopsis of the standard, not the actual standard. **Dr. Musch** questioned the statement that refractive change is not statistically different from zero and that the 95 percent confidence interval does not include zero. **Dr. Hilmantel** said there was a mistake on the slide. **Dr. Musch** asked how contrast sensitivity would be measured. **Dr. Hilmantel** said it is described in detail in the standard. **Dr. Musch** asked what would be compared among QOL trials. **Dr. Rorer** said that would be known when the protocol is finalized. **Dr. Musch** recommended the Centers for Epidemiologic Studies depression instrument as an existing validated instrument for depression.

Dr. Heuer said that epithelial ingrowth requiring reoperation should be considered an important adverse event for reporting. **Mr. Bunner** asked how baseline history for a change in refractive state would be evaluated. **Dr. Eydelman** said the recommendation was to establish the refraction either by history, comparison to the prescription. **Chairperson Weiss** said that a surgeon can tell by the patient's glasses whether or not there has been a significant change.

Dr. Huang asked if the public has access to SightNet data. **Dr. Lepri** said reports and recommendations are available online, but the information is anonymous. **Dr. Eydelman** added that the FDA analyzes and summarizes the data before it is released. **Chairperson Weiss** asked if there was any way to verify that what is happening is being reported. **Dr. Lepri** said there is no check but that MedSun's being a voluntary system suggests that the participants will comply. **Dr. Eydelman** said a cross-check could be run against the mandatory reporting. **Ms. Cofer** asked if the ANSI standard would supercede the guidance document. **Dr. Eydelman** said that would be considered if the standard is accepted. **Ms. Cofer** said that some terms in the ANSI standard, especially regarding symptoms, are very confusing. **Dr. Eydelman** said that the patient labeling has a glossary but that the Panel can suggest modifications. **Ms. Niksch** asked if there would be industry representation in the QOL assessment. **Dr. Eydelman** said there was no such intent at this time. **Dr. Heuer** asked about centers not subject to mandatory reporting. **Dr. Eydelman** said most LASIK is done in ambulatory surgical centers, and serious adverse event reporting is mandatory. **Dr. Musch** asked about the organizations' financial support of the QOL study. **Dr. Eydelman** said that precautions were being taken to prevent conflicts of interest.

GUEST SPEAKER

Commander David J. Tanzer, M.D., Program Director of the US Navy Refractive Surgery Program, spoke on what refractive surgery means to the military. He said he had no financial conflicts of interest and spoke for himself. The military has demanding visual requirements for aviators, Special Forces operatives, and infantry. Modern weapons systems use sophisticated optical devices, and all personnel are trained in chemical and biological protective gear. Contact lenses cannot be worn by personnel deployed to Iraq, Afghanistan, or Korea. Approximately 30 percent of military personnel needs glasses or contact lenses. DoD has performed 45 studies in order to independently validate the safety and effectiveness LASIK as applies to the military.

In a study in naval aviators that randomized 480 aviators over 4 different eximer lasers showed that 94

percent of the eyes treated attained uncorrected 20/20 or better. The majority of eyes showed no change in BCVA or a gain in lines. There were few complications; 0.5 percent experiences a haze that was treated with topical steroids. 100 percent of patients treated to date have returned to flight status.

In the laser comparative trial, 90 percent of all eyes treated were 20/20 or better uncorrected at one month. Most patients show no change or a gain in lines of BCVA at six months. In the keratome comparison trial using the wavefront-guided laser, the majority of patients had excellent uncorrected visual acuity at one month. At 3 months, the majority of patients have a gain or no change in lines of corrected visual acuity. The overall satisfaction rate for LASIK was 98.1 percent. A night driving simulator test demonstrated that 15 percent of patients were improved at detecting a target after surgery, 25 percent at identifying the target. A flap stability study showed the flap to be stable to a level of force equivalent to a high altitude low opening jump.

The LASIK procedure in naval aviators showed 100 percent of eyes treated at 20/20. 100 percent of patients said they would recommend the procedure. DoD currently has 20 centers for refractive surgery and has performed on over 224,000 eyes. The average age of the patient is 34, and 82 percent of patients are male. Refractive errors range from plus 6 diopters of hyperopia to minus 13 diopters of myopia. Laser vision correction is approved for all aspects of military service and for astronauts. However, the procedure has risks and is voluntary. There has been one DoD medical disability retirement related to laser vision correction. The patient achieved 20/20 but had vision complaints. The procedure has been successful and has shown operational benefits in the military. Satisfaction has been high.

Dr. McLeod asked about patient selection. **Dr. Tanzer** said the preoperative process is exhaustive, including testing, and patients come pre-screened by optometrists. After all the testing, there is an extensive informed consent process. He said that pupil size does not predict post-operative quality of vision. **Dr. Weiss** asked how many patients are screened out. **Dr. Tanzer** said approximately 10 percent of patients are screened out at the centers but he did not know what percentage of patients were screened out by the referring optometrists.. **Ms. Cofer** asked about contrast sensitivity testing. **Dr. Tanzer** said the night driving simulator simulated headlight glare from a rearview mirror. **Dr. Edrington** asked what reasons are used to exclude a patient. **Dr. Tanzer** listed cornea physiology, irregular topographies, thin corneas, and refractive instability.

FDA QUESTIONS AND PANEL DISCUSSION

1) **Please discuss any recommendations you may have for modifications to patient labeling of excimer lasers for LASIK.**

Panel Consensus was that the labeling should include mention of the post-operative difficulty of checking intraocular pressure; the difficulty of implant measurement for cataract surgery after LASIK; illustrations of visual symptoms like halo and starburst; strong wording concerning patients with keratoconus, pellucid marginal degeneration, and other ectatic disorders; and a distinction between patients with collagen vascular disease and patients with collagen vascular disease and dry eyes. There was discussion on addressing psychological issues, but the Panel was unsure how to do so. There was discussion on hormonal replacement therapy affecting dry eyes.

2) **Please discuss any recommendations you may have for modifications to FDA's LASIK website.**

Panel consensus was to recommend more information on what is meant by “risk-taker;” photographs of what the visual disabilities look like; statistics on the frequency of adverse events, side effects, and complications; a link to the patient labeling; an emphasis that reading glasses will be needed in middle age; an area on retreatment; clarification on contact lens removal and refractive stability; and a link to a valid dry eye instrument, if there is such an instrument. The Panel recommended rewriting the "When is LASIK not for me" portion of the website to make it more coherent. The Panel recommended revising the mention of steroid and the question about the pupils (to correspond to new data). Autoimmune disease should be distinguished from autoimmune disease with dry eyes. There should be a better example of potential problems that can occur with a microkeratome.

Any updates from the manufacturers should be included. The download speed should be improved and the language simplified. The button "Questions for your doctor" should be on the LASIK site as well as the intraocular site.

3) **FDA is currently evaluating the ANSI Z80.11 Laser Systems for Corneal Reshaping Standard for recognition. Please discuss whether you recommend that the FDA recognize the standard in its entirety, in part, or with specific additions.**

The Panel had questions on topography and collection of data on adverse events. Dr. Eydelman said that the standard says topography should be performed on all study subjects, so the Panel had minimal issues with the standard. There was a question as to whether there would be forced choices to get statistics on post-operative problems like glare, halo, and dry eyes.

4) **The training packet for SightNet participants currently emphasizes evaluation for and reporting of the following LASIK-related adverse events and complications: infectious keratitis; endemic cases of diffuse lamellar keratitis (DLK); abnormal trends in post-operative topography; significant losses of best corrected visual acuity (BCVA); glare, halos, starbursts and distortions; and device failures. Please discuss any recommendations you may have for revision of this list of adverse events and complications for which reporting is emphasized.**

The Panel recommended that, when possible, intraoperative complications, such as flap complications, be distinguished from post-operative complications, such as epithelial ingrowth. Reports should include not only significant losses of BCVA, but also significant visual side effects, such as glares, halos, or starbursts.

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Chairperson Weiss thanked the speakers for their testimony. She said both perspectives on LASIK reported at the meeting are true; the majority of patients do well after LASIK, but the post-market assessments do not adequately characterize rare, severe effects or complications. FDA will be working with NEI, AAO, and ASCRS to get better statistics. There were many issues associated with unsatisfactory results after LASIK which are not under the purview of the FDA> which were also discussed. Issues of inappropriately aggressive advertising may fall under FTC regulations. Though it is not an FDA issue, a surgical procedure should not be sold as a commodity. Issues of inadequate informed consent may fall under medical malpractice. She said the FDA and the other organizations will help make things better for future patients.

OPEN PUBLIC HEARING

Chairperson Weiss opened the public hearing session session for post-market experience with Phakic Intraocular Lens (PIOL) and repeated public hearing statement.

Dr. Scott Barnes spoke for **Dr. Doyle Stulting**, on behalf of ASCRS. Dr. Stulting is a consultant for AMO. PIOL are rigid plastic artificial lenses implanted to correct severe nearsightedness in patients who are poor LASIK candidates. They were first approved in the US in 2004 and have been used in Europe since 1991. Satisfaction with the lenses has been excellent, with 99 percent satisfaction. Half of the patients saw better without glasses after implantation than with before. These patients are severely nearsighted, and the device meets a true unmet need. He said the technology is life-altering for those patients and that there is 17 years of data outside the US demonstrating safety.

FDA PRESENTATION

Kesia Alexander, Ph.D., spoke on FDA's PIOL safety initiatives. Two PIOL PMAs have been approved. Ophtec's

Artisan IOL was approved in 2004 for patients with minus five to minus 20 diopters of myopia. The second was in 2005, STAAR's Visian Implantable Collimer Lens, which was approved for patients with minus three to minus 15 diopter of myopia. Both companies are performing post-market studies.

The patient labeling gives an overview of how the device works, risks and benefits associated with the device, alternative treatments, and other aspects the patient should consider. The devices are contraindicated in patients under 21, who have anterior chamber of depth (ACD) outside the approved range, who have abnormal iris, who are pregnant or nursing, or who do not meet the minimum endothelial cell density (ECD). Patients are informed on the limitations and urged to ask questions of the physician. The contraindications, warnings, and precautions are based on data from the PMAs.

The PIOL website advises the public on whether or not they are candidates for the treatment, risks and benefits, what to know before having the surgery, and questions to ask the physician before undergoing the procedure. The risks include vision loss, retinal detachments, and visual symptoms. Long-term data on the devices is not available. The website also gives the patient an overview of what to expect during and following surgery and when to contact their doctor.

Don Cologero, M.S., reported on ophthalmic standards for PIOL. The two published standards are ISO 11979-10, which is recognized by FDA entirely with no additions, and ANSIZ80.13, which is being reviewed for recognition. Modifications recommended by the Panel will be presented to ANSI at the time of revision. The standards contain both pre-clinical and clinical requirements. In the pre-clinical requirements the optical, mechanical, biocompatibility, sterility, shelf life, and transport stability testing for PIOL are the same as the requirements for the monofocal IOLs, except for the clearance analysis requirement. This is analysis of the location of the PIOL surface with respect to ocular tissue to ensure the minimum anatomical dimensions acceptable for the PIOL design and the range of powers it would be available in.

The ISO PIOL standard contains the suggested design of a clinical investigation that will collect the data needed to determine the safety and performance of the PIOL. It is a non-controlled study with a minimum duration of three years to evaluate both the maintenance of ECD, and the rate of cataract development. The primary endpoint is ECD. Changes in ECD in the subjects are compared to the normal rate of loss. Patients with less than the minimum ECD by age are excluded from the study. The recommended sample is 300 patients. Enrollment will be in phases: first 10 patients, then 100, then all remaining patients. Subjects will be followed for 6 months.

For the pre- and post-op exams, both ISO and ANSI recommend distance UCVA, BSCVA, near VA with distance spectacle correction, manifest refraction, cycloplegic refraction, axial length, anterior chamber depth, intraocular pressure, slit lamp exam, status of crystalline lens, gonioscopic exam, fungus exam, mesopic pupil size, pachymetry, keratometry, subject questionnaire, and spectral microscopy.

The standard requires two sub-studies: a study to assess potential PIOL-related contrast sensitivity losses and an analysis to determine the clearances between the PIOL and the ocular tissue. Recommended safety analyses include the rate of ECD change, the rate of cataract development, and the percentage of subjects that lose two or more lines of BSCVA. The clinical labeling requirements specify a summary of the clinical results of the investigation, any recommendations for periodic evaluations after implantation, and any restrictions in the indications for use.

FDA QUESTIONS AND PANEL DISCUSSION

1) **Please discuss any recommendations you may have for modifications to patient labeling of phakic intraocular lenses (PIOLs).**

Because many Panel members had not yet seen the labeling, the Panel returned to this question after they had skimmed the labeling and addressed the other questions. FDA said it would apply the recommendations for

modifications to the website to the labeling. The Panel said cataracts are a concern, as well as the possible inducement of astigmatism from the corneal wound, so there should be more information on astigmatism. The labeling should use strong wording on endothelial cell loss. Information on pupil size should be included. Dr. Heuer found editorial and typographical errors that he passed on after the meeting.

2) **Please discuss any recommendations you may have for modifications to FDA's PIOL website.**

The Panel recommended including a diagram of the two different types of IOLs, indicating there has been documented endothelial cell loss, indicating that patients should not only be out of contact lenses a certain period of time but also should have contact lens stability, and indicating the specifics of the retinal and rear eye problems. FDA should document the issues with cataract removal in patients with PIOL. There was discussion of keratoconus and complications in future procedures. The website does not specifically state that PIOL does not treat astigmatism, though the labeling does and states that the procedure will not make the patients free of glasses. If the data shows that the visually significant astigmatism is a result of the procedure in some patients, the website and labeling should include the information.

3) **Please discuss any recommendations you may have for future revisions of ANSI and ISO phakic intraocular lens standards.**

After discussions and questions for the FDA, the Panel recommended no additions to the standards. Dr. Heuer asked that the standards be made available in future meetings in which a Panel is addressing the standards.

4) **The training manual for SightNet participants currently emphasizes evaluation for and reporting of the following PIOL-related adverse events and complications: toxic anterior segment syndrome (TASS); endophtalmitis; explants; significant endothelial cell density (ECD) losses; corneal decompensation; significant losses of best corrected visual acuity (BCVA); retinal detachments; intraocular pressure (IOP) spikes/elevations; cataractogenesis; device extrusions; device failures/damage. Please discuss any recommendations you may have for revisions of this list of adverse events and complications for which reporting is emphasized.**

The Panel recommended adding uveitis and giving more specific information on what is meant by “significant endothelial cell loss.”

ADJOURNMENT

The day’s agenda completed, Chairperson Weiss thanked the participants and adjourned the meeting at 4:48 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel on April 25, 2008, and that these minutes accurately reflect what transpired.

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Karen F. Warburton, M.H.S.
Executive Secretary

I approve the minutes of the April 25, 2008 meeting as recorded in this summary.

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Jayne S. Weiss, M.D.
Chairperson (Acting)

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