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Quick Pulse

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FDA Advisory Committee Reaffirms LASIK Safety But Recommends Clearer Labeling

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An estimated 6 million Americans have had LASIK (laser-assisted *in situ* keratomileusis) eye surgery to reduce their dependency on eyeglasses or contact lenses. The FDA's Ophthalmic Devices Advisory Committee in the Center for Devices and Radiological Health (CDRH) met to discuss whether there is enough information about potential problems with LASIK and with phakic intraocular lenses (IOLs) in patient labeling and on the FDA's website and whether that information should be modified. The FDA does not regulate LASIK; it only regulates the equipment used in the procedure.

LASIK centers and surgeons got off relatively easy. It could have been a much more negative panel if victim after victim had gotten up and complained about aggressive marketing or greedy doctors who didn't read them the fine print or warn them about possible serious problems. Instead, dissatisfied patients mostly complained about blurred vision, dry eye, starbursts, and glare, and some linked poor outcomes with depression and thoughts of suicide, but they didn't rail against surgeons or laser centers for inappropriate LASIK promotion. In the end, it was the panel chair who mentioned aggressive LASIK marketing.

All in all, the panel was balanced, the speakers moved quickly, and the panel members were very patient during a very long list of speakers. The victims of flawed LASIK surgery appeared mollified by the panel's response and generally agreed that the blame for poor outcomes largely lies on the shoulders of their doctors, not the excimer lasers. After listening to the patients, surgeons, and FDA experts, the panel made numerous recommendations for label and website changes. They recommended labeling changes to more accurately and fully state what and how LASIK problems can occur, including ***extreme*** blurriness, haze, glare, halos, and starbursts. In addition, panel members wanted the FDA to include some language on the possibility of associated depression/psychological problems.

The panel also discussed new labeling addressing concerns about cataracts, endothelial cell loss (ECL), and induced astigmatism with phakic intraocular lenses (PIOLs) – Staar's Visian and Advanced Medical Optics' Verisyse. The panel also recommended adding specific concerns about ECL with Staar and AMO lenses. If the FDA takes the panel's advice, there will be substantially more information for patients about the potential hazards of both LASIK and PIOLs in FDA brochures and on the FDA website.

PUBLIC WITNESSES ON LASIK

The panel spent three and a half hours listening to patients – both satisfied and dissatisfied – as well as physicians and patient advocates. A few patients were agitated and angry, occasionally speaking in outbursts into the microphone. However, most, including the father of a LASIK patient who committed suicide after his surgery, were thoughtful and moderate. They described problems with dry eye, including incessant burning and pain, and with night vision, and they said that the FDA should consider such problems as complications, not symptoms.

Several patients had compelling stories about their problems after LASIK surgery, and the father of the LASIK patient who committed suicide read his son's last letter, in which the son described his severe depression after failed surgery. It is interesting to note that the LASIK patients who spoke did not attack the laser vision centers, which do most LASIK surgery in the U.S., which could have led to many pointed news articles and television pieces pointing to such centers as the villains.

- **Dr. Michael Patterson** told the panel that LASIK ruined his vision and his quality of life. He said that a failure rate of 5% is not safe and told the panel that doctors lied to him, accusing the FDA of being "intentionally negligent." He also asked the FDA to take action to regulate LASIK centers. In the middle of his canned presentation, Dr. Patterson charged that a panel member, Dr. Andrew Huang, a professor of ophthalmology and visual sciences at Washington University School of Medicine in St. Louis MO, had conflicts of interest and should not be on the panel.

- **Dean Kantis of Lifeafterlasik.com** told the panel that hundreds of victims have contacted him on his website to tell him about their suicidal thoughts. He said that his doctors all lied to him about his eye surgery, which resulted in damaged eyes, "I feel like I've been raped." He yelled into the microphone that he wants a class-action lawsuit and warned the panel, "You have desperate, suicidal patients."

- **Glenn Hagele, the founder of USAEyes.org,** which evaluates LASIK doctors, spoke **on behalf of the non-profit Vision Surgery Rehab Network,** describing what he called "Refractive Surgery Syndrome" and asked that the FDA recognize and accept that diagnosis, which includes psychological problems. Dry eye may have physiological attributes which may contribute to loss of vision.

  Hagele made presentations for two patients. He read Sandy Keller's story of her failed LASIK surgery: "During the surgery the blade jammed in my first eye, leaving a ridge" that still exists. She said the surgery by a "rookie surgeon" left her "more or less blind in my right eye." She was told that she'd need a corneal transplant. She also said that her optometrist had altered her pupil size on her pre-op chart. She said that she became suicidal. But Hagele also said another LASIK patient, a quadriplegic, was happy with the results.

  Hagele also made his own presentation and discussed his website, USAEyes.org. He said that quality of life has always been the selling point for LASIK, but his group's research found that if a patient is not fully informed or if the patient's expectations are unreasonable or unfulfilled, then LASIK is not successful. He described a survey of the patients of six surgeons that his group is doing. Out of 420 surveys completed so far:

  - 99% of respondents said that quality of life was as expected, better, or much better.
  - 90% would have the surgery now (again).
  - 98% would recommend the surgery.
  - 91% either didn't have complications or their complications were resolved.
  - 7.2% had complications, but they were seldom problematic.

  Hagele summarized that quality of life is higher than he expected. He told the panel that if the FDA is going to look at quality of life, it shouldn't look at that alone.

- **Gerard Dorrian** told the story of his son, Colin, who, before LASIK, was successful and outgoing, with no history of mental health issues. He said that Colin had LASIK surgery while a law student because he had dry eye as a result of contact lenses but was told pre-operatively that glare and halos would be no worse than with contacts. After the surgery, Colin experienced large starbursts and halos at night, triple overlapping images, and ghosting off-white objects in low light. He also complained about dry eye. Dorrian read Colin's suicide letter, which said that he fell into a suicidal depression because of his eye problems.

- **Don Morgan** said that he is legally blind and never a candidate for LASIK, but got the surgery anyway. He said that he believes his doctor knew that he was not a candidate but went ahead with the surgery. His doctor sued him when he put up a website telling his story.

- **A patient** called the day that he had LASIK surgery the "worst day in my life." He said that his eyes were problem-free for 50 years, but since LASIK he is "visually handicapped by double vision, halos, ghosts, impaired vision in dim light, starbursts…and that is with glasses." He showed large posters of what things look like through his eyes and asked the audience, "Does anybody want LASIK now?" He described his dry eyes as the feeling of shampoo in one's eyes and said that he can't sleep for the burning and stinging. He asked the FDA to reclassify such effects as complications, "I was never depressed in my life until I had LASIK eye surgery …LASIK surgery has inherent problems due to the nature of the procedure…Too many Americans have been harmed by this procedure."

- **Diana Zuckerman, an expert on national health policy,** particularly women's health, criticized the FDA's LASIK booklets, saying that they "seem to be satisfying someone at the FDA who doesn't care if the patients actually read or understand these booklets." She also wondered aloud whether anyone looks at the FDA web pages on LASIK. She said that dry eye is the most common complication from LASIK, with half the patients developing dry eye – and 20% of these persisting after six months. Eye pain can be caused by dry eye or from other causes, she admitted, but added, "It is terribly debilitating, and these are serious complications that need to be included in the advice you're discussing today." She noted that 28% of eyes (35% of patients) needed additional correction after surgery, and she said that patients need that information. The possibility of higher suicide rates has been raised, and more research is needed on that. She said that Emory University is doing research on the subject, but she was unable to get any information from them about it.

- **Lauren Burch PhD, a molecular biologist and medical researcher,** described some complications resulting from LASIK and claimed there is no evidence that corneal nerves ever heal after LASIK.

- **A LASIK patient** said that he has suffered from debilitating and unremitting eye pain since his LASIK surgery two years ago. He called the marketing unethical and suggested that the complication rate is probably in the 20%-30% range. He also argued that dry eye and night driving syndrome are complications, not symptoms. He also said that although patients say that they are satisfied, they may still suffer from complications, including clinical depression. He called the panel meeting a "sham hearing, " adding, "Clearly the fix is in."

- His wife also spoke, saying "Despair, depression, disbelief, anger, suicidal ideation, and post traumatic stress disorder…almost destroyed our family. My children almost lost their father. I see that many of you are laser surgeons…I truly hope that today you can put your vested ties with LASIK aside and listen…LASIK is destroying thousands and thousands of patients and family lives…LASIK cannot continue in its current form." She asked the FDA to investigate post-surgery depression.

- **Dr. Richard Lindstrom,** the immediate past president of the American Society of Cataract and Refractive Surgeons (ASCRS), was ill and could not attend the panel meeting, but Dr. Kerry Solomon read his statement in which he said that nearly 30% of LASIK surgeons themselves have undergone LASIK. Dr. Lindstrom wrote that a review of 10 years of research found: "All the available clinical data reinforces the safety of LASIK. The overwhelming majority of patients are satisfied. Yet, a small percentage feels dissatisfied. To them we say: 'We hear your concerns, we care, and we will respond in a tangible and constructive manner.' The joint LASIK Study Task Force, to better understand the small percent of patients who do not get the result expected, is looking at the impact of LASIK on quality of life. Quality of life is the subject of experience…That is the level of understanding we are attempting with this study."

- **Dr. Eric Donnenfeld, clinical professor of ophthalmology at NYU Medical Center,** said that he has been performing laser-correcting surgery for 18 years, "The reality is that, following LASIK, the majority of patients see as well or better than they did with contact lenses or glasses…LASIK has always been very safe and has continued to improve. The majority of our patients have less glare and halo than before. However, we can't be satisfied until all complications have been eliminated." He talked about dry eye, which he said affects 55 million Americans, and gave preliminary results of 46 articles on dry eye (32,000 eyes), saying that 32% of these patients had dry eye before LASIK. The survey results showed, "The great majority had resolution of dry eye symptoms over a 2-4 week period following surgery…Severe dry eye following LASIK is extremely rare, and results are improving. Modern thin-flap LASIK has been associated with a reduced incidence of dry eye. Advances in artificial tears and immunomodulation with topical cyclosporine A …help improve outcomes." He concluded by emphasizing again that LASIK is safe.

- **Dr. Kerry Solomon, an ophthalmologist at the Medical University of South Carolina's Magill Vision Center and a LASIK patient himself,** presented an ASCRS-requested "*LASIK World Literature Review: Patient Satisfaction and Quality of Life*," an independent meta-analysis, which found that 95.4% of patients are satisfied with their LASIK procedure. The analysis reviewed 2,915 abstracts and incorporated 309 peer-reviewed studies from 1994-2008. Nineteen of the articles specifically addressed quality of life.

- **Todd Krouner, a malpractice lawyer from Chappaqua NY,** asked the FDA to do whatever it can to prevent the conversion of eyes to commodities by: encouraging the effective and safe training of surgeons, encouraging reporting of adverse outcomes, commissioning an independent study of LASIK patient satisfaction, and reporting those findings. He said that the LASIK industry does not police itself effectively and more should be done to screen out unsuitable candidates for surgery, "If the LASIK community really believes that patient satisfaction runs upwards of 95%, it should welcome with open arms an independent study. If just 1% of LASIK patients have a bad outcome, that may mean upwards of 10,000 patients per year will suffer potentially serious problems…Studies show that these cases are the result of doctor failure to screen properly, failure to diagnose (a possible problem), or the surgeon cutting the cornea too thin."

  Krouner also spoke on behalf of Amanda Campbell, whose police officer husband committed suicide in March

2008. He said that Dr. Richard Lindstrom was quoted as asserting that there is no correlation whatsoever between adverse LASIK outcomes and suicide, "Presumably, Dr. Lindstrom did not have the benefit of reading Mr. Campbell's suicide note…None of those comments are meant to cast aspersion on Dr. Lindstrom. However, I disagree with his assertion that there is no relationship between LASIK outcomes and suicide."

Krouner showed Mr. Campbell's suicide note, which said that LASIK surgery outcome was the cause of his suicide: "Eye surgery has taken my life out of me. The pain, distorted vision, chronic dry eye is not bearable." Krouner said that in this one case, "LASIK surgery constitutes a material contributing factor, if not the sole factor, to police officer Campbell's suicide." Amanda Campbell claimed that her husband suffered no mental illness before the surgery. Krouner told the panel, "For a small minority, their regret is profound…For a smaller minority still, depression associated with (surgery)…is real…cannot be dismissed, and warrants further investigation."

- **Dr. Peter McDonald, a corneal surgeon from Johns Hopkins School of Medicine, representing the International Society of Refractive Surgery of the American Academy of Ophthalmology** (ISRS/AAO) told the panel that about 700,000 Americans have LASIK surgery annually, "No elective ophthalmologic procedure has been as fully studied as has this procedure…Most complications can be treated without any loss of vision. Some patients experience temporary side effects that usually disappear after three to six months…It is important to recognize...techniques and technology have improved over time."

- **Dr. Jennifer Morse, a psychiatrist** and member of the joint LASIK Study Task Force who spent 20 years as a navy physician and is an expert in psychosomatic symptoms, said, "We know a great deal about the… benefits of LASIK. Clearly, however, based on what we've heard today, there are people who are raising concerns about quality of life issues. Psychological well-being is an equally important part of quality of life, and depression is a central and widespread cause of diminished quality of life. These events are not usually due to one factor. Rather, they are due to several factors… Depression and suicide are complex and have multiple causes. There is no scientific evidence to any link between LASIK and suicide or depression…I fully support increased research focused on psychological factors and their bearings on quality of life…in the case of LASIK. We need to take post-LASIK quality of life complaints seriously, but we also have to understand the real causes of these complaints and all their complexities."

- **Courtney Hendricks, a quadriplegic from Wisconsin,** said that LASIK improved her quality of life.

- **Dr. Steve Schallhorn, a San Diego ophthalmologist representing the American Academy of Ophthalmology,** said that he has performed thousands of procedures on members of the military, and that LASIK is safe. He said that while we can identify several reasons for dissatisfaction, "sometimes we can't." He said that the AAO plans a large study to look at quality of life in dissatisfied patients. "The academy agrees that LASIK is a safe and effective procedure…We will continue to refine and improve LASIK for our patients."

- **Dr. Terry Lynne Bankus, a volunteer physician counsel** for a group of patients in California, described some of her patients' problems after LASIK surgery. She said that some optometrists have told her that lens flap MRSA (*methicillin-resistant Staphylococcus aureus* infection) complications may be an epidemic.

- **Dr. Michael Mullery** discussed psychological problems related to failed refractive surgery, saying, "Patients are indeed killing themselves after unsuccessful LASIK…It is time to study the consequences of LASIK surgery on mental health." He questioned the proposed quality of life studies, charging that they would not be independent. He said that he has interviewed about 40 people who have had suicidal thoughts after failed LASIK surgery, adding, "Better screening for psychological problems is not the answer. Stopping vision loss is."

- **Roger Davis PhD, a clinical psychologist,** said that more than 100 of 300 LASIK patients with whom he has communicated have had suicidal thoughts. The single complication associated with suicidal ideation was dry eye syndrome. He talked about what he calls "Refractive Surgery Shock Syndrome," explaining, "Some patients feel that they paid to have their vision destroyed…In my experience no pre-existing pathology is necessary...or has to play a role…If the FDA wants to understand depression and suicide post-LASIK, forget about quality of life studies. If you want to study suicidal patients, find suicidal patients. There are plenty of them." He also argued that refractive surgery cannot be performed ethically, whatever its satisfaction rate.

- **Rebecca Petris, a LASIK patient and founder of Lasermyeye.com,** which helps patients with dry eye, said, "They told me I could get dry eye. It was on the form, but they said it will probably go away quickly, and they said, 'We'll give you the drops and the plugs.' My time is spent speaking with patients who are going through this for 3 months, 6 months, 12 months, 6 years…They have not found remedies, and I have no answers for them. There's been a lot of talk from the industry saying we care, but I'm not seeing the compassion. There are a lot of doctors here. I wish they could be flies on my office wall and hear the wreckage of these peoples' lives…Plugs and drugs are not doing it for us…I feel like a triage nurse for all these people coming and seeking help…I am appealing to you for help."

- **Jo Wills** talked about her husband, who has had the same problems as many of the other speakers addressing the panel and who blamed them on his surgeon. She pointed out that six out of the 13 panel members were wearing glasses.

- **Dr. Edward Boshnik, an optometrist from Miami FL,** said that he sees unhappy LASIK patients. Two of his patients have attempted suicide on multiple occasions, and several have told him of suicidal thoughts, "Most of my patients are depressed, and many are on antidepressants…LASIK presents a significant public health crisis."

- **Lt. Col. Scott Barnes, a Ft. Bragg cornea and refractive surgeon,** told the panel that the Special Operations Command asked him if LASIK is safe for special operations forces, "These guys are fairly unique…They complain a lot if something isn't perfect. They don't have any qualms in saying, 'You screwed up my life' if something goes wrong…We all know that problems can occur in any surgical procedure…The bottom line with these guys…is they said, 'Please don't take this away from us.' When they go off to battle, if they ever become a prisoner of war, the first thing that happens is that they break your glasses. If they're lost and behind enemy lines …they're not going to jump out of the bushes if they can't even see who it is."

  Dr. Barnes also read comments from **Dr. Doyle Stolting, professor of ophthalmology at Emory University** who helped write the first guidelines for excimer lasers, "Today most patients who undergo LASIK achieve 20/20 vision or even better. In addition, these patients reported less glare, less light sensitivity, and fewer night driving problems than before LASIK."

- **Dr. Joseph Schell, a LASIK patient** who had surgery last year, said that no other event in his life has affected him so negatively, "I'm amazed at how this procedure is pushed at the patient…I'm shocked at the many glowing testimonials from LASIK patients despite their vision being decreased from what it once was." He said that he has suffered from dry eye and poor eyesight and has had suicidal thoughts.

Panel Questions for LASIK Witnesses

The panel chair, Dr. Jayne Weiss, director of refractive surgery and ophthalmic pathology at the Kresge Eye Institute at Wayne State University in Detroit MI, asked for questions from the panel. The patient representative asked if surgeons who participate in peer-reviewed literature perform better than other doctors. Dr. Donnenfeld said that he couldn't comment on doctors who don't publish, but in the meta-analysis 35% of patients reported dry eye following surgery and 32% reported dry eye prior to the surgery, "Dry eye does occur after surgery. It's a very common problem that we see in about 1 in 4 adults in the U.S. At times, laser surgery can make dry eyes worse."

Dr. Weiss asked Dr. Schallhorn about the patients who had addressed the panel.

Dr. Weiss: "What percent, from the studies that you reviewed or participated in, would have this severity?"

Dr. Schallhorn: "The type of people who are very disabled is very, very rare. To have the levels of disability that we heard today is a very rare occurrence."

Dr. Weiss: "Less than1%?"

Dr. Schallhorn: "I would say much less than 1%."

Dr. Weiss: "There are two aspects that the panel and everyone needs to understand. One is certainly what is happening in the real world and what isn't good that the FDA and perhaps organized medicine can do something about. And second is individual stories are compelling, but we have to put them in perspective."

The health consultant on the panel, Richard Bunner, asked about informed consent and whether patients are encouraged to receive a second opinion. Dr. Weiss responded, "Every physician would answer themselves, but usually a second opinion would be suggested only if there was a question or there was a problem. If a patient ever asks me, my answer is always, 'Yes, you should (get a second opinion) because you've just asked me.'"

The FDA Perspective on LASIK

In the panel briefing documents, the FDA said that in 2005 it received complaints from patients "who were very dissatisfied with their quality of life after LASIK surgery." The agency created a Postmarket Issue (PMI) Action Team to look at the complaints and make recommendations to the FDA. The team said that the "vast majority of patients were satisfied with their outcomes; however, a small percentage of patients were dissatisfied" and recommended that the FDA consider a large, national, prospective study "to accurately quantify the small proportion of dissatisfied LASIK patients and evaluate the reasons for their dissatisfaction."

The FDA staff presented the regulatory background and history of refractive lasers and LASIK patient education materials. Kwame Ulmer, chief of the FDA's diagnostic and surgical devices branch in the Division of Ophthalmic and ENT devices in the Office of Device Evaluation (ODE), CDRH, described preclinical studies and labeling for excimer lasers.

Excimer Laser Approvals

Indication	Number of approvals	Highest refractive range approved
Conventional myopic astigmatism	10	Up to -14 D
Conventional hyperopic astigmatism	5	Up to +6 D
Wavefront-guided myopic astigmatism	4	Up to -11 D
Wavefront-guided hyperopic astigmatism	2	Up to +5 D

Labeling

The FDA asked the panel to make labeling recommendations. The warnings in the current labeling say that LASIK is not recommended in patients who have:

- Diabetes.
- A history of herpes simplex or herpes zoster keratitis.
- Significant dry eye that is unresponsive to treatment.
- Severe allergies.

Precautions on labeling **currently** include: *It is unknown whether LASIK is safe and effective for the following conditions. You should discuss these conditions with your doctor:*

- Unstable eyes that have changed in their visual acuity more than 0.5 diopters in nearsightedness or astigmatism in the last 12 months.
- Corneal disease or abnormality (e.g. scar, infection, etc.).
- History of injury or surgery to the center of the cornea.
- Corneas are too thin.
- History of glaucoma.
- Taking medicine that might make it harder for wounds to heal, such as sumatriptan succinate (Imitrex) used for migraine headaches.
- Younger than XX years of age or over 65 years of age.
- Nearsightedness is worse than XX diopters or astigmatism is worse than XX diopters.
- Over the long term.
- Treatment with this laser for LASIK.
- Undiagnosed dry eyes. Your doctor should also evaluate you for dry eyes before surgery.
- Large pupils. Before surgery, your doctor should measure your pupil size under dim lighting conditions. If your pupils in dim light are ≥XX mm, consult with your doctor about the risk that the surgery may cause negative effects on your vision, such as glare and halos and night driving difficulty.
- Dim lighting, rain, snow, fog, or bright flare. You might have difficulty seeing in dim lighting, rain, snow, fog, or bright glare.
- Any other medications you are taking.
- Additional information regarding LASIK may be found on the FDA website.

The FDA's patient information pamphlet and website list conditions which preclude a patient from the surgery and 16 conditions about which it is unknown whether LASIK is safe and effective.

Gene Hilmantel OD, the FDA's clinical reviewer, outlined the American National Standards Institute (ANSI) and International Organization for Standardization (ISO) refractive ophthalmology standards. ANSI is the sole U.S. representative to ISO, and only official U.S. delegates chosen by ANSI participate in the development of ISO standards.

The FDA currently recognizes 30 ophthalmic standards, and the American National Standard for Ophthalmics-Laser Systems for Corneal Reshaping (ANSI Z80.11-2007), published in 2007, is currently in the FDA recognition process. The clinical section of the standard:

- Outlines a consensus of an adequate clinical study for new refractive lasers.
- Patient enrollment to occur in stages for a new laser system for which there is no prior clinical data.
- 300 eyes study to detect adverse events with an expected rate of ≥1%.

Dr. Hilmantel summarized: The ANSI standard for Laser Systems for Corneal Reshaping has created a basic structure for preclinical and clinical studies to establish reasonable safety and effectiveness before marketing of the laser. It includes comprehensive evaluations of a number of important effectiveness and safety parameters, including ratings of subjective symptoms.

Quynh Hoang MS from the FDA's Office of Surveillance and Biometrics Issues management staff talked about the FDA 2006 LASIK post-market assessment. She said that the FDA decided to do the assessment because it had received complaints from patients and because ~700,000 LASIK procedures are done each year in the U.S., so it had a "potential significant impact on the public health."

An action team was created to compare post-market to pre-market LASIK data. Post-market data include peer review data, complaints to the FDA, reports by doctors to the FDA, and comments to FDA's web page. The team concluded that it was unable to compare post-market published studies to pre-market studies. Post-market and pre-market satisfaction surveys showed a high level of satisfaction, and post-market data in the literature failed to suggest widespread problems. The team decided that the surveys don't adequately evaluate the effects of rare serious events and recommended further evaluation of post-LASIK quality of life in a clinical setting.

Joint Collaborative Study on Health-Related Quality of Life (HR-QoL)

The FDA and the National Eye Institute (NEI) are conducting a joint study to compare all the different questionnaires used to assess quality of life in patients with ocular disease. The aim is to come up with a cost-effective way to gather clinical data on Patient Reported Outcomes (PROs) for future ophthalmic clinical trials.

Dr. Eva Rorer, chief ophthalmic medical officer in the FDA's Division of Ophthalmic and ENT devices, ODE, CDRH, reviewed the current use of PROs in device evaluation and

gave a quality of life assessment. She said that PROs "add an important dimension to the overall patient evaluation," but they must be standardized, with the ability to make meaningful evaluation of measures. Quality of life questionnaires usually focus on symptoms, functioning, and perceptions of health. The questionnaire must also be standardized and validated. She said that there are few validated ophthalmic HR-QoL questionnaires; the first validated refractive questionnaire was published in 2000, two years after LASIK was approved, "Only LASIK clinical studies initiated after 2000 would have had the opportunity to use a validated HR-QoL questionnaire."

Based on the recommendations of the FDA PMI action team, the FDA considered a large, national, prospective study to more fully evaluate LASIK outcomes. The FDA is asking for cooperation from NEI, ASCRS, and AAO in forming the joint LASIK Study Task Force. The protocol has not been finalized for what the FDA called a "prospective, multicenter, clinical trial." The HR-QoL assessment will determine:

- Level of satisfaction after LASIK.
- Changes in HR-QoL after LASIK.
- Factors associated with the level of satisfaction after LASIK.

Another joint FDA/NEI study will try to save money by comparing the computerized, web-based and paper-based versions of previously validated questionnaires used to assess ophthalmic HR-QoL in order to validate computer administration of ophthalmic HR-QoL instruments.

Monitoring LASIK device safety

The FDA panel discussed how to monitor LASIK device safety through the SightNet cooperative network of hospitals and outpatient centers.

Dr. Bernard Lepri, a Maryland optometrist and a clinical reviewer for the FDA, discussed adverse event reporting in CDRH. MedWatch is the FDA's safety information and adverse event reporting program. Types of medical device reporting include:

- Mandatory reporting to FDA
  - Medical device manufacturers: Adverse events such as deaths and serious injuries and some malfunctions
  - User facility (hospitals, surgical centers, etc.): Deaths to FDA and manufacturer and serious injuries to manufacturer
- Voluntary reporting to FDA
  - Reporting of any medical device adverse event by healthcare professionals and consumers

MedSun, which began in 2002, is a subset of the mandatory user facility reporting universe of MedWatch. It is made up of 350 healthcare facilities nationwide (mostly hospitals) which voluntarily agree to fulfill mandatory reporting requirements through the network.

SightNet is MedSun's newest subnetwork as of 2007. It is designed to provide a "real-world view" of ophthalmic medical device use in a variety of clinical settings, including hospitals, the VA, NEI, ambulatory surgical centers, and private practices. Reports can be submitted online, by phone, fax, and regular mail. Problems to report include instructions, packaging, manufacturing defects, software problems, interactions with other devices, problems encountered with off-label use, and human factor issues. LASIK-related problems that can be reported are:

- infectious keratitis.
- endemic cases of DLK.
- abnormal trends in post-operative topography.
- significant losses of BCVA.
- glare, halos, starbursts, and distortions.

The panel was asked for recommendations regarding the list.

Panel Questions To FDA Speakers

Panel member Dr. Dale Heuer, a Wisconsin ophthalmologist and a professor with expertise in clinical trials, commented that the panel heard quite a bit about dry eye from doctors and patients and asked the FDA to include dry eye questions in the questionnaires and in the NEI/FDA pilot study. Dr. Malvina Eydelman, a senior medical adviser in the FDA's Division of Ophthalmology and ENT Devices, was somewhat defensive; she said that the protocol for the planned study has not yet been finalized. The questionnaire will be given pre- and post-surgery, so each patient will be his/her own control, she explained.

The panel's patient representative, Paula Cofer of Brandon FL, asked what the enforcement is for labeling, commenting, "It's my experience as a patient that they were never given the labeling." The FDA's Dr. Eydelman answered, "We regulate device manufacturers. We don't regulate individual physicians. Every LASIK device does have patient labeling, and it can be downloaded from the website. It is part of the approval package. We hope that today's meeting will give publicity that this labeling exists, and it is easily downloadable from the web."

Panel member David Musch PhD, MPH, a professor of ophthalmology at the University of Michigan, asked about the ANSI standard, and Dr. Eydelman said that the excerpts presented from the ANSI standard were just snippets, and the FDA just provided a synopsis. Dr. Musch also asked about the contrast sensitivity testing, and an FDA official said there is a substandard that explains in great detail how to do the contrast sensitivity training.

Dr. Musch also asked about quality of life and the planned trial, "Trials are comparative in nature, and I didn't understand what you are comparing." The FDA's Dr. Rorer said, "The protocol hasn't been completed, and there are still discussions about the design, so we can't say what comparisons can be made." Dr. Musch added, "Health-related quality of life has a number of domains, and we heard concern from patients… regarding an outcome of LASIK that you might want to consider assessing in some way – maybe not a thorough assessment of psychological impact but certainly you should consider using a validated instrument for measuring emotional impact, depression, and I know that's probably on the table."

Dr. Heuer asked about the adverse event reporting, suggesting that more than one operation should be included in adverse events. The private public health consultant asked about how the FDA recommends choosing a doctor. The FDA's Dr. Eydelman reiterated, "We do not regulate the practice of medicine." Richard Bunner, the Ohio private public health consultant with expertise in special education for the visually impaired, asked, "Should I be prepared to present to my physician my refractive history?"

Panel member Dr. Huang, the Missouri ophthalmologist, asked if the FDA has another layer of screening or validation beyond the public screening system (SightNet), so that there is no risk of "mass hysteria." Dr. Eydelman responded, "The data don't get dumped back. The FDA analyzes the data, and a summary of the outcomes is presented to the public."

The panel chair wanted to know if there's a double check to see if the data are being reported, and an FDA official said, "It is voluntary, and many of these hospitals have patient safety staffs which address the issues, so we have a significant amount of confidence that they are reporting everything that does happen. After the initial report is filed, this is followed up with phone calls and interviews." Dr. Eydelman added, "There is mandatory reporting of adverse events…so there is a cross check anyway."

The patient advocate, herself a LASIK patient, asked about the ANSI standards. She said the guidance document for refractory surgery lasers is dated 2006. Will the ANSI standard replace that? Dr. Eydelman said that the FDA has not accepted the ANSI standard yet, "After the process we'll go back and see what we want to do (about what's on the website)."

Cofer called some of the terms being used confusing, "The patients and I think something needs to be done about some of this terminology. If glare is a starburst, then I don't know why it's called a starburst." Dr. Eydelman said, "In all our patient labeling we have an index of terminology where we try to explain the technical terms used by physicians. And one of our questions today is for suggestions about improving them."

The industry representative asked if there is a plan to include industry in the new quality of life study. Dr. Eydelman said, "At this point there was no intent to involve industry. The efforts are between the NEI, the FDA, and the two professional organizations."

Dr. Heuer mentioned that some of the facilities where LASIK is performed aren't subject to FDA reporting requirements, but Dr. Eydelman said, "Most of the surgeries are in ambulatory surgical centers, and problems there are a mandatory (reporting) requirement."

Dr. Musch asked, "We heard some concern from doctors about the quality of life studies. Can you answer how that concern will be addressed and how the FDA will stand above the money being provided?" Dr. Eydelman responded, "The protocol is not finalized, but every precaution is being taken that there will be no potential conflicts of interest and that it will be done consistent with FDA and NEI regulations."

LASIK AND THE MILITARY

Commander David Tanzer MD, U.S. Medical Corps, director of the U.S. Navy Refractive Surgery Program, gave a compelling argument in favor of LASIK, saying that it is especially useful in aviation and in special operations. He also said that contact lenses are prohibited for personnel deployed in Iraq, Afghanistan, and Korea.

Dr. Tanzer described some of the 45 clinical trials conducted in the military. In PRK in 785 navy aviators, all 100% treated to date have successfully returned to full flight status. A laser comparative study showed the majority of 960 eyes showed no change or increases in visual acuity at six months. Overall, 224,000 laser procedures have been performed in the military to date, and there has been only one military disability retirement related to laser vision correction (LVC).

Dr. Tanzer summarized: "LVC has been overwhelmingly successful in the military, in all job types…It has shown tremendous operational benefits and is approved for military aviators, divers, special operations personnel, and NASA astronauts. LVC has been proven to have extremely low risk, with the likelihood of disability 0.009%, and satisfaction is 'incredibly high' in service members receiving LVC, with 95% of naval aviators showing improvement in effectiveness …Since the inaugural case, we have treated more than 1,000 aviators, several with whom I have flown. If I did not personally believe that LVC was in their best interest, I would not be treating anyone on active duty with LVC or advocating that it be done in the civilian community."

Panel questions on military LASIK

Dr. Stephen McLeod, chair of the department of ophthalmology at the University of California, San Francisco, observed that patient selection is critical and asked how it works in the military. Dr. Tanzer explained, "They've already been screened and deemed to be a good candidate before they go to a laser vision center in DOD (Department of Defense). They then take the standard tests, and it's a very extensive and

informed consent process. We tell our divers, aviators, that if they lose function, they could lose that job."

Dr. McLeod also asked whether the military has a position on pupil size, for example. Dr. Tanzer said, "We published on that and said that pupil size can't be used as a predictive factor. We do measure pupil size, but we don't base treatment criteria on pupil size."

Dr. Weiss asked what percent of patients are screened out at the local level (optometrists). Dr. Tanzer said there is about a 10% rate of patients who are not deemed a good LASIK candidate.

FDA Questions for the Panel about LASIK

Question #1. Discuss recommendations for modifications to patient labeling of excimer lasers for LASIK.

The panel agreed to the following recommendations regarding patient labeling:

- Indicate that there are some issues with intraocular pressure post-operatively. Panel chair Dr. Jayne Weiss said, "We should include something like that."
- Indicate problems related to figuring out the implant measurement for cataract surgery after LASIK. The panel chair said, "Everyone is in agreement on this."
- Include a couple of pictures of what glare, halos, and starbursts might be like.
- Indicate that there may be other problems for people with keratoconus and mention them by name.
- Advise persons with a strong history of keratoconus that they should consider surgery more carefully.
- Indicate that hormonal replacement therapy (HRT) may affect some patients.
- Something should be included about psychological issues – either before surgery or when dealing with a bad outcome.

Dr. Huang wanted to include an indication for women taking hormone replacement therapy. He also said that most of the patient labeling is not specifically indicated, so "I think it doesn't clarify to the patient what rate of correction can be used."

The patient advocate had a long list of ideas. She suggested:

- Something in the labeling warning patients that they may have problems with future corneal surgery because they have already had LASIK. She also said that the change in the cornea after refractive surgery causes problems with intraocular pressure, "That is something that could become a problem for patients, especially someone developing ocular hypertension and glaucoma, so that should be in the labeling."
- She mentioned some Mayo Clinic studies on increases in cortical keratocytes, saying, "We don't know what that might do to the cornea long term."
- "Patients don't know that the flap heals only 2% of the original tensile strength; there is a scar at the margin that heals stronger, but if that scar is broken the LASIK flap easily lifts many years – or forever. Patients are told that the LASIK flap heals, and they go on, and they're not told to wear protective eyewear. I think patients should know that the flap heals minimally after LASIK."
- "We know that creation of a corneal flap leaves the cornea much, much weaker after LASIK than prior to LASIK. The cornea has to withstand the intraocular pressure of the eye, and the permanently weakened state of the cornea could cause problems for patients. I see reports of late-onset ectasia many months and many years after seemingly successful LASIK, and I think patients should be warned of that. I think that it's clear that myopia patients should be told they need reading glasses after the age of 40, and it's misleading to tell patients that they'll need glasses whether they have LASIK or not. That should be included in the labeling."
- "Loss of visual quality is not a rare event; it is a common event. And I don't think patients expect that they will lose visual quality after LASIK. There is a loss of visual quality." Dr. Weiss (the panel chair) said that she might have a problem with that, "Do we then want to list every single aspect? Dr. Tanzer showed that, overwhelmingly, patients were happy with the visual quality. We can open up to the panel how detailed the labeling becomes. We heard that already it's too difficult for the average patient. We do want something that people will read and see the data." Dr. Huang agreed with Dr. Weiss.
- "Symptoms such as dry eyes and night vision impairment should be moved from the Symptoms table to Adverse Events and Complications. We heard a lot of testimony today about dry eye – these are clearly complications and it's deceptive to put them in a separate category and call them symptoms and downplay them. They are very serious life-changing issues." The FDA's Dr. Eydelman said, "All those are usually reported under Adverse Events and Complications. The dry eyes would be in that section already." The patient advocate added, "I think night vision impairment has always been under symptoms." Dr. Eydelman responded, "We'll take that under consideration."
- "Pupil size outside the optical zone of the LASIK – I'd like to see that on all lasers because anyone who has LASIK with an optical zone smaller than pupil size is going to see these night vision disturbances." Dr. Weiss said that Dr. Schallhorn and Dr. Tanzer had already said that there was no evidence for that, and then she asked, "Should you warn the patients that if the ablation zone is less than the pupil, they should not have the surgery performed?" Dr. McLeod said, "Publishing the study

doesn't correlate with actual practice…It's a difficult area, and I don't think patients' interests would be well served by an inaccurate description of the situation."

The patient advocate suggested perhaps recalling lasers for eye surgery. The industry representative, Barbara Niksch, a Visiogen vice president, answered, saying that drastic changes based on anecdotal information would not be a good idea.

Dr. McLeod said that it is important to point out that there is a variability in the healing of the flap but that a categorical statement on such are not good ideas, "In practice, it's widely recognized that there is tremendous variability in flap healing after surgery. A statement that there is variability, but there is not a categorical problem, would be all right." He said the vast majority of corneas suggest stability over time." Dr. Musch said that he had some problems with the patient advocate's suggestions.

QUESTION #2. Discuss recommendations for modifications to FDA's LASIK website.

The panel made the following recommendations for the FDA website:

- Give more information to the patient on what is meant by being a "risk taker."
- Add photos of what visual disabilities mean.
- Have statistics for some of the side effects/complications.
- Link to patient labeling for each particular laser for more detail.
- Underscore the fact that if patients have LASIK and get excellent distance vision, they may still need reading glasses when they get to middle age. Or if they are middle aged, with excellent reading vision, they still lose their near vision.
- Have a separate area concerning re-treatment.
- Stability indication for contact lens removal is not just the duration, but refractive stability needs to be reached.
- Possibly link to a dry eye website – if there is a valid instrument that can be linked.
- The "When is LASIK Not for Me" portion of website should be rewritten for clarity.
- The mention of steroid use and pupil size should be revised to what is now known.
- Describe autoimmune disease vs. autoimmune disease with dry eyes.
- Describe microkeratome problems.
- Update improvements in manufacturer specs.
- Improve download speed.

The private public health consultant, Richard Bunner from Ohio, said that he thought the phrase on the website: "Are you a risk taker?" might be considered more of a challenge than a warning. He also said that the website's bandwidth is so huge that he couldn't download the pages on his rural, dial-up connection. Bunner suggested putting possible problems related to LASIK surgery closer to the top of the pages; he couldn't find them in the short time he was able to view the site. He also suggested that the "Questions for your Doctor" section in the booklet should be on the website.

The panel chair suggested that photos be placed on the website similar to those described by patients who testified before the panel regarding what they can and cannot see, "What's been underscored here is that even if the risk is 0.5% or 0.05%, if it happens to you, it's 100%, and some times some of my patients don't want to think about 'What happens if the risk happens to me.' Certainly, in many laser practices it is not underscored and not emphasized. But there should be a section in which to emphasize it slightly stronger. 'If you could not tolerate an adverse event, you should not have LASIK.'"

Dr. Weiss continued, "One of the last public speakers commented that there are a lot of people on this panel who wear glasses. The reason for me is twofold. One is that I like my up-close vision…I emphasize that, as an eye surgeon, I can read without my glasses, and I love that. I can operate without my glasses, and I love that. If you tell me that, as a myope, you sit in front of your desk all the time, and you need it for golfing, you don't need LASIK. And I can't tolerate any risk."

Dr. Weiss concluded, "It is important to learn all you can about the procedure and not put a moratorium on it, but I think we need better screening, better information, in some cases better doctors, but not to throw out the baby with the bathwater. It's not that the device is bad. If you weren't told that if you took off your glasses before surgery, you wouldn't be able to read after surgery, that's lack of information."

Dr. Timothy Edrington, a California optometrist on the panel, said that the guidelines about how long to take contact lenses out before surgery are misleading. He said he agreed with the patient advocate that patients don't understand that they won't be able to see up close after the procedure, "They won't (see up close) after the procedure, and that needs to be clarified strongly to the patient. As to maybe needing glasses, I think that should be clarified. It could mean right after surgery, a year after surgery, or 10 years after surgery. Also, some patients may go to the website seeking help, so it might be good to describe some of the things that could go wrong, for example, a picture of red eye."

Dr. Heuer, an ophthalmologist, said that a lot of patients don't know that they have dry eye, and he suggested a link to a self-test for dry eye test patients. He also suggested modifying the dry eye box to include what to expect after surgery. He added that the box should say that dry eye might not end after six weeks.

Answering the question about why some panel members were wearing glasses, Dr. Musch, an ophthalmologist, said that he's worn glasses since first grade, and his degree of myopia exceeds what most LASIK can correct. He said that some of the website language was too complicated for average Americans and suggested lowering some of the language so that high school-level readers could understand it.

Dr. McLeod seconded Dr. Heuer's idea about a self-test for dry eye. He criticized the organization and writing of the "Why LASIK is NOT for Me" webpage, saying that it doesn't help patients understand what are true contraindications and what is less significant. He also urged the FDA to look again at the question of pupil size and decide what to say about it.

QUESTION #3. Discuss recommendations to the ANSI standard.

No significant changes were recommended to the ANSI standard.

One panel member complained that the panel was not able to look at the complete ANSI standard and was told that the panel was given snippets of the standard due to copyright reasons. He said that was ridiculous and hoped that the same thing wouldn't happen to future panels.

QUESTION #4. The training manual for SightNet participants currently emphasizes evaluation for and reporting of the following LASIK-related adverse events and complications. Discuss any recommendations for revision of the list.

a. Infectious keratitis
b. Endemic cases of diffuse lamellar keratitis (DLK)
c. Abnormal trends in post-operative topography
d. Significant losses of best corrected visual acuity (BCVA)
e. Glare, halos, starbursts, distortions
f. Device failures

The panel recommended:

"Interoperative complications such as flap complications should be differentiated from post-operative complications. For this question, (the SightNet training manual) should not only include significant losses of visual acuity but also visual abnormalities such as halos and glares, which would impact on patient life."

Dr. Heuer said that re-operations ought to be included. Dr. Huang suggested that re-operations be categorized to make reporting easier. The panel chair questioned whether BCVA specifies what "significant" is, "We heard from patients who might have been told they had 20/25, but they still couldn't see anything. It would be good to capture patients with good visual acuity who still had problems…The presence of glare, halos, starbursts, distortions – those are two different animals. We have patients who come in the next day, and they're thrilled and have a halo for a day or week. But then there are patients who have visually-disabling halos and starbursts. We should make a difference between the effect that disappears and the one that is a serious problem." Dr. Janine Smith of the National Eye Institute suggested adding "and any other unexpected abnormalities." Dr. Huang said, "Making the car superfast doesn't make the car industry guilty of killing people. The procedure itself is causing the problem, not the machine. We should be reporting it accordingly."

In her closing statement, the panel chair addressed the dissatisfied patients who had testified during the morning session, "Although we don't have all the statistics we need, we are working to get better statistics, and we have information that the vast majority of patients with LASIK do very well and are very happy and see very well. However, we have heard from the FDA that the LASIK post-market assessment surveys don't adequately address the severity of adverse effects. That does not negate the importance of when that rare side effect happens to you because you have to deal with it…Listening to the many people who were testifying, there were certain commonality of things that came up. One was aggressive marketing. The other was LASIK as a commodity. It is a surgical procedure, but it is being sold as a commodity. The FDA does not regulate marketing, but I agree that it is a problem. Another (theme) that comes up is inadequate informed consent and the fact that some patients were poor candidates. That comes under malpractice, and that's something the field should monitor and your local malpractice lawyer should be helping…This is really a referendum on the performance of LASIK (surgery) by some surgeons who should be doing a better job…The FDA will help to get better information to make it better for future patients."

PHAKIC IOLS

The PIOL discussion went quickly. There were three major concerns – the possibility of cataracts, endothelial cell loss, and induced astigmatism – and the panel recommended adding concerns about those issues to the labeling. The panel wanted the labeling changed to indicate that ***both*** U.S.-approved PIOLs (Advanced Medical Optics' Verisyse and Staar's Visian) can result in significant endothelial cell loss.

The panel agreed to recommend additional language in patient labeling and on the FDA website stating concerns about cataracts, induced astigmatism, and endothelial cell loss regarding PIOLs.

PUBLIC WITNESS ON PIOLS

There was one public witness, Dr. Stolting, who said that 99% of patients in clinical trials reported that they were satisfied with the results of PIOL implantation.

THE FDA PERSPECTIVE ON PIOLS

Kesia Alexander, chief of the FDA's Intraocular and Corneal Implant Branch, gave an overview of PIOLs. There are two approved PIOLs: Ophtec's Artisan (sold in the U.S. and Japan by Advanced Medical Optics as Verisyse), which was approved in 2004, and Staar's Visian Implantable Collamer Lens, approved in 2005. Both have ongoing post-approval studies.

Patient Labeling

Patient labeling currently includes the following ***precautions*:**

- Abnormality of the iris
- Recurrent ocular inflammation
- History of ocular diseases
- Congenital bilateral
- Glaucoma
- Diabetic retinopathy

Patient Labeling – ***warnings*:**

- Long-term rate of cataract formation secondary to implantation, removal/replacement is unknown.
- The occurrence of lens opacities in the future is unknown.
- Long-term effects on the corneal endothelium have not been established. Patients should be advised about potential risk of corneal edema, possibly requiring corneal transplantation.
- The potential of the lens to alter intraocular pressure and long-term risk of glaucoma, peripheral anterior synechiae, and pigment dispersion are unknown.

Patient Labeling – ***contraindications*:**

- Younger than 21 years old.
- Has an anterior chamber depth outside of the approved range.
- Abnormal iris (e.g., peaked pupil or elevated iris margin).
- Pregnant/nursing.
- Does not meet the minimum endothelial cell density (ECD).

FDA Website

The FDA website asks: "Are Phakic Lenses Right for You? You are probably not a good candidate if:

- You have large pupils, a shallow anterior chamber, an abnormal iris, had uveitis, had problems with the posterior part of your eye.
- You are not an adult (no PIOLs approved for under 21).
- You have a disease or are on medications that may affect wound healing.
- You have a low endothelial cell count or abnormal endothelial cells.
- You actively participate in sports with a high risk of eye trauma.
- You only have one eye with potentially good vision."

Alexander discussed the ***risks*** delineated on the website:

- You may lose vision.
- You may develop debilitating visual symptoms.
- You may need additional eye surgery to reposition, replace, or remove the PIOL.
- You may be under treated or over treated.
- You may develop increased intraocular pressure.
- Your cornea may become cloudy.
- You may develop a cataract.
- You may develop a retinal detachment.
- You may experience infection, bleeding, or severe inflammation (pain, redness, and decreased vision).
- Long-term data are not available.

Questions for your Doctor before undergoing Phakic Lens Implantation:

- Do I have any conditions that would increase my risks?
- Are the size of my pupils under low lighting conditions bigger than the size of the lens?
- Is my anterior chamber shallow? If so, what are my additional risks?
- What are the risks of having the phakic lens implanted?
- What is my risk of needing a corneal transplant in the future, if I have the phakic lens implanted, based on my age and my endothelial cell count?
- What quality of vision can I expect in the first week, first few months, and a year after surgery?

PIOL standards – American National Standards Institute (ANSI) and International Standards Organization (ISO)

FDA senior biomedical engineer Don Calogero discussed the ophthalmic standards for PIOLs. ISO 11979-10 (Phakic IOLs) is recognized by the FDA in its entirety. ANSI Z80.13 (Phakic IOLs) is being reviewed for recognition.

Adverse event reporting

Current avenues for device adverse event reporting include Medical Device reporting (MDR) and MedWatch. The FDA staff explained how PIOL safety will be monitored through SightNet, a network of hospitals and outpatient centers. SightNet is part of the MedSun product safety network. Panel members will be asked for recommendations on specific PIOL information to be collected by SightNet.

FDA Questions and Panel Discussion on PIOLs

Question #1. Discuss recommendations for modifications to patient labeling of phakic intraocular lenses (PIOLs).

Panel members had not read the patient labeling. At the end of the meeting, the panel agreed to make the recommendations made to Question #2 below.

The panel chair said that cataracts and endothelial cell loss are a major concern and need to be addressed in the labeling. She also mentioned concerns about induced astigmatism and suggested mentioning both in the labeling.

Question #2. Discuss recommendations for modifications to the FDA's PIOL website.

The panel made a number of recommendations.

Dr. Weiss, the panel chair, said, "Basically, for the patient labeling, depending on what the original study showed, we will have comments on the astigmatism, comments on endothelial cell loss, or underscoring it, and pupil – if there was an issue with pupil – will be included, as well as including those recommendations the panel made for the FDA website:

- Have a diagram of the two different types of IOLs approved in the U.S.
- For the two types approved in the U.S., say that there has been documented endothelial cell loss.
- Indicate that not only do patients want to be out of contact lenses for a period of time, but they want contact lens stability (before surgery).
- Indicate specifics about possible retinal problems. There may be some problems if a patient needs a cataract removed, but that's something the FDA would want to document.

Dr. Weiss wondered if, because one of the lenses has a larger wound, it should be stated that certain types of PIOLs, because of the wound size made, can induce astigmatism, "If the data show from the studies that astigmatism did result in some patients, the website and patient labeling would benefit from having this added information."

During the discussion, the patient advocate said the website was misleading and contended that the website should include in its labeling that both devices show an increased rate of endothelial cell loss. The panel chair agreed, and it was included in the recommendations. Dr. Weiss said that she basically wanted to distill/underscore the two major risks with PIOLs: endothelial cell loss and cataracts.

Question #3. Discuss recommendations for future revisions of the ANSI and ISO PIOL standards.

The panel suggested no additions.

Dr. Weiss, the panel chair, asked about the six month follow-up. An FDA official said that that was for the initial phase, for the first 10 subjects and that the second and third phases are consistent with what the FDA does. He said that the second phase is 100 additional subjects followed for six months.

Dr. Heuer asked about phasing in ANSI and ISO standards, "What information do you expect to attain by following 10 subjects for six months? I think you would probably rule out any really bad implant. Then, you'd go on to 100. I know the number varies across devices. Can you only recruit 10 patients, follow them for six months and not have any recruitment until after six months?"

The FDA's Dr. Eydelman answered, "In any device trial, Phase I usually means 'Make sure it's not a disaster.' So for that, the kind of patient that's enrolled in Phase I will typically have a very different profile than a patient involved in Phase III…There are more Phase I trials that do not go on to Phase II trials than you can imagine."

Question #4. The training manual for SightNet participants currently emphasizes evaluation for and reporting of the following PIOL-related adverse events and complications. Discuss recommendations for revision of the list.

a. Toxic anterior segment syndrome (TASS)
b. Endophthalmitis
c. Explants
d. Significant endothelial cell density (ECD) losses
e. Corneal decompensation
f. Significant losses of best corrected visual acuity (BCVA)
g. Retinal detachments
h. Intraocular pressure (IOP) spikes/elevations
i. Cataractogenesis
j. Device extrusions
k. Device failures/damage

The panel recommended adding uveitis and some specifics about what is meant by significant ECD loss.

Panel members concluded that the list is sufficient as it stands. Dr. Huang asked if iris atrophy should be included in post-operative complications, and Dr. Heuer said that would be a long-term complication.

Dr. Weiss asked how to quantify endothelial cell density losses. An FDA official said that for an individual patient, you have to take into account the variation, repeatability of a measurement, and the instrument, "It's certainly something that hopefully we could clarify." Dr. Weiss then said, "Yes, for something that important, you want people triggered to report this sooner than later."

The FDA's Dr. Eydelman said, "We do have criteria for ECD losses…You have to make sure that the same instrument was used pre-op and post-op, the same technicians, a lot of things in pre-market studies that do not necessarily parallel in the real world…We will utilize what we know to come up with a better definition." ♦