night vision impairment?

DR. DONNENFELD: I could not quote it. I'm sorry.

CHAIRPERSON WEISS: Thank you very much. Do any other members of the Panel have any questions for the public speakers? Is Dr. Schallhorn here, because I have a question? Has he left already? Ah, great.

What we have heard from many of the patients here who have had adverse effects after LASIK are, I think, very, very bad effects. What percentage of patients from the studies that you have reviewed or been participating in would have this severity of effects?

DR. SCHALLHORN: The studies that I have conducted -- the type of people that are very, very disabled. It is very, very rare. So, you know, to have the levels of disability that we have heard today is a very rare occurrence.

CHAIRPERSON WEISS: So when you say

very rare, would you say from the studies less than one percent?

DR. SCHALLHORN: Well, I would say much less than one percent.

CHAIRPERSON WEISS: And the reason I am asking that for the patients in the room is there are two aspects that the Panel needs and that everyone here needs to sort of understand the full complexion of this.

One is certainly what is happening in the real world, and what isn't good that the FDA and that perhaps organized medicine can do something about?

Then, two, individual stories are compelling, but we need to also as a Panel put it into perspective. If we could get all the patients in the United States here who have had LASIK, how many would fall on one side or another, to try to get some balanced viewpoint? Thank you.

Does anyone -- Yes, Mr. Bunner.

MR. BUNNER: Richard Bunner,

Consumer Representative. I just have a question perhaps for one of the physicians in the room.

When a patient is trying to attain informed consent, does the option of second opinion ever come into play? Are they encouraged to seek second opinions, and has anybody had any experienced in evaluating a patient to encourage him to receive a second opinion prior to making a decision on LASIK surgery?

CHAIRPERSON WEISS: Well, I think any -- This is a standard of practice, and every individual physician would answer themselves. But I think typically, patients are only offered a second opinion if there is an issue of a question or an issue of a problem.

If it is a standard case with no question that the doctor has or no question that the patient has, I think routinely they would not be suggested to have a second

opinion, although I will say personally in my practice, at the point that a patient ever says to me, should I get a second opinion, my answer is, yes, you should, because you have asked that question.

Does anyone else on the Panel have any other differing -- Yes?

DR. EDRINGTON: I would think that most informed consents, any informed consent form I've seen, has said you should get a second opinion if you feel you need one.

CHAIRPERSON WEISS: Any other questions from any member of the Panel to the public?

If not, we will conclude and break for lunch. It is now 11:45. We will come back at 12:45.

(Whereupon, the foregoing matter went off the record at 11:45 a.m.)

1

2

3

A F T E R N O O N S E S S I O N

Time: 12:47 p.m.

CHAIRPERSON WEISS: We are now going to begin the afternoon session of this Panel meeting. I would like to call the meeting to order. We will hear the FDA's presentation next. Would Dr. Donna Bea Tillman come to the podium, as she will be the first speaker?

DR. TILLMAN: Good afternoon, and thank you. I wanted to start off by thanking the members of the public who came this morning to tell us their experiences and their thoughts.

FDA very much believes in an open and transparent process, and we are very interested to hear of your experiences. The whole purpose of this meeting today is for us to attain some additional information from the public and to have a discussion among the Panel members about some important issues relating to LASIK and PIOLs.

So thank you very much for your participation, and you can be assured that you were heard and that we will certainly think long and hard about what you have told us.

Today I am going to give you a very, very brief overview of the medical device review program, particularly as it relates to the topics we are going to discuss today. This is short and sweet, and really attempts to kind of hit the highlights.

First of all, I think it is really important to understand that CDRH's mission is to benefit risks and balances to medical devices. We could ensure that all devices were 100 percent safe by never approving anything new, and then everything could be 100 percent safe. But that is, obviously, not the best way to address the public health needs of the American public.

So what we do is constantly balancing risks and benefits. We need to get safe and effective devices to market as

quickly as possible, but we also need to be ensuring that the devices that are on the market continue to be safe and effective.

Another important part of FDA's role which isn't, I think, as well understood is helping the public get science based, accurate information about medical devices: consumer outreach, helping people to understand the devices that are out there, and helping individual patients have the information they need in order to make appropriate risk/benefit decisions. That is very much an important part of what we do.

Now if you look at the regulatory framework that underlies the medical device review program, it is risk based. The reason for this simple. Unlike drugs, where a drug is a drug is a drug, I would hold -- although I am an engineer, and I get to say that -- medical devices span a broad spectrum of risk, all the way from sunglasses and toothbrushes to total artificial hearts and intraocular

lenses and LASIK.

So because we have such a wide spectrum of risks in devices, we also have a wide spectrum in regulatory approaches that we take to how we review medical devices.

Now this slide is rather ambitious. It attempts to put our entire pre-market review program on one slide, and as a necessity kind of gives short shrift to everything. But I did want to note that medical devices are classified into one of three classes, depending on level of risk.

That is Class I for the lowest risk devices. Most of those, FDA doesn't even see pre-market submissions for; Class II, which are the sort of moderate risk devices; and then Class III devices which require a pre-market approval. Those are Class III -- PMA products are the two products that we are talking about today. So I am going to spend a little time talking more briefly about that.

Additionally, we have several other

mechanisms that we use to classify novel devices that we haven't seen before. That's the de novo, and we also have a mechanism for ensuring that patients have access to devices where there is a relatively small patient population, and that is our humanitarian device exemption program.

Today, really, the products that we are here discussing were approved through our pre-market approval program, our PMA program. These are Class III products. They are generally high risk or first of a kind devices, and the regulatory bar that companies need to make, as those of you on the Panel who have been around a couple of times know, is a reasonable assurance of safety and effectiveness.

I think it is important to understand that there is that "reasonable assurance" in there, because, obviously, once again it would be very difficult to definitively prove absolutely safety and

effectiveness.

Now the other important thing to realize is that in determining reasonable assurance of safety and effectiveness, FDA considers valid scientific evidence.. Valid and scientific evidence can span the whole spectrum from randomized controlled trials through partially controlled trials to objective trials without matched controls -- for example, trials with OPCs -- case histories and even robust human experience.

So there is a wide spectrum of information that FDA can evaluate in determining valid scientific evidence.

Once again, those of you who have been on the Panel before have certainly seen this slide. This is the regulatory definition of safety, and I just want to highlight three pieces of that.

First of all, safety is determined based on valid scientific evidence, not based on hearsay and not based on just anecdotal

information, but it has to be valid scientific evidence.

Safety means that the probable benefits to health outweigh the probable risks. So that is another part, is understanding what we mean by safety.

Then finally, whenever we talk about safety, it is in the context of "accompanied by adequate directions and warning against unsafe use."

So this is the labeling part. This is the role that FDA plays in ensuring that both physicians and patients have access to the appropriate information about risks and benefits, and information about how to safely use devices.

You will notice a parallel, if you look at the definition of effectiveness. Effectiveness also has to be based on valid scientific evidence, and the definition of effectiveness is that in a significant portion of the targeted population, the use of the

device will provide clinically significant results.

You will notice that also in the definition of effectiveness, there is this same caveat talking about that it has to be accompanied by adequate directions for use and warnings against unsafe use. That's the labeling piece that we spend a fair amount of time talking about.

A couple of important points when thinking about some of the conversations that you are going to have today and some of the things we have heard this morning. That is that FDA doesn't just approve devices for any use that a physician wants to use them for. FDA approves devices for specific patient populations, and these are called Indications for Use.

The indications for use that FDA approves a device for generally reflect the patient population for which we have enough data to demonstrate a reasonable assurance of

safety and effectiveness.

So, for example, if you look at some of the devices we are talking about today, we've got data on specific myopic ranges for different devices, and those are the -- That's the basis for the indications for use for that device.

Now it is also very important to recognize that FDA does not regulate the practice of medicine. FDA regulates medical devices, medical device companies. We do have some regulatory authority over clinical investigators, but once a device is out there and it is approved, strictly speaking, a clinician is entitled to use that device however he or she thinks is appropriate in the context of a legitimate patient/health care provider relationship.

In fact, this actually -- In the statute, it says that nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to

prescribe or administer any legally marketed device to a patient for any condition or disease.

So I think it is also important, given some of the discussions that we heard this morning, to understand where FDA has a role and where we don't. So we do regulate devices. We do regulate medical device companies, and we get involved in clinical trials.

We don't regulate practice of medicine and, frankly, we don't regulate how individual physicians or individual groups of physicians choose to interpret the approval of devices. That is a role that the academic clinical organizations play in writing practice guidelines and those sorts of things.

I already talked a little bit about the importance of labeling, and as I noted, our definitions for both safety and effectiveness acknowledge the need for appropriate labeling.

When we approve a PMA for a new product, we have physician labeling, and a lot of times when we bring a PMA to you all to discuss, we talk a lot about what are the appropriate indications for use, what do the data support.

We also include contraindications, and these are patients for whom we have data showing that the device should not be used. Then we have warnings and precautions, and this is information that is sort of a level down from a contraindication that talks about important considerations that patients and physicians should take into account when deciding whether to use a device.

The labeling includes a clinical study summary where we talk about the results of the clinical trials, so that clinicians know what the data from the clinical trials are, and then we have directions for use, sort of how to use the device.

Equally important in terms of our

role of educating and informing physicians is educating and informing patients. A critical part of our mission is ensuring that patients have appropriate information about devices.

I said at the beginning of my talk, when we approve devices and when we look at the whole device construct, it is a risk/benefit decision. I will stand here and tell you, there are no devices out there that are 100 percent safe. Everything comes with a tradeoff.

So a big part of our role is making sure that patients and physicians have appropriate information so that they can make appropriate risk/benefit decisions for each individual patient.

So one of the things that we do for many devices, we have patient labeling that provides patients with information about the procedure they are going to get, the risks and benefits, questions they should ask their doctor what to expect.

I heard some comments this morning about some concerns about the adequacy of our patient labeling for the LASIK devices, and that is certainly something that, if people have constructive comments about how we can make that better, we are certainly very interested to hear that.

FDA has got patient education websites. Nowadays we get a lot more of our information from the web. So we are trying to kind of fit into that niche, and we've got a very active LASIK website that is one that is one of the more frequently visited FDA websites.

We have consumer outreach programs. We outreach to students in school. We outreach to senior citizens with maturity health matters. We have a program where we develop videos that we send out to hospitals and physicians that they can play in their office. While patients are sitting waiting to see the doctor, they can watch these videos.

So we have a lot of different ways that we try to get information out to patients.

We also -- You know, where we have issues and problems with devices, we also outreach through public health notifications, letting people know about specific concerns with specific devices.

In terms of patient labeling, we review the labeling to ensure that it provides, as I already mentioned, a complete description of risks and benefits. We want patients to be able to make informed choices for themselves, and also information about what to expect.

Now once we have made a premarket decision and approved a device, our job is not over, and this is something, I think, that reflects a bit of a sea change, at least for my office, which does the premarket reviews over probably the past 10 years.

That is our recognition of the fact that our job is really never done on the

premarket review side. We have to continue to monitor device performance, and we do that by requiring post-approval studies for some devices that require companies to collect additional data.

There is a mandatory adverse event reporting system, the MDR program that you are going to hear a little bit more about this afternoon, that requires manufacturers and user facilities to provide information about adverse events; annual reports from manufacturers -- So if a company has an approved PMA, they are required to annually report, give us information about how that device is performing postmarket, and changes they have made to the device.

Our staff go to scientific and clinical meetings where they hear from the clinical community and the scientific community about what are the concerns out there. We monitor the scientific literature.

So my staff is constantly

monitoring device performance in the postmarket setting to ensure that devices continue to be safe and effective.

Basically, what we do with this information is -- you know, there are a number of different things. First of all, companies use the information they learn postmarket to make device modifications. Some of this is to make devices easier to use or meet physician preferences.

Some of this is to make new generations of devices. You know, in LASIK we had the original devices, and then we had a new generation of these wavefront technology devices. So we allow the technology to extend.

Information in the postmarket setting can be used to update labeling. Frequently, if a company goes off and does a post-approval study and collects additional data on their device, we ask them to present information in their labeling so that

physicians and patients have access to the most up-to-date information that is available.

We do directed physician and patient outreach, based on things that we learn in the postmarket setting, and we also use the information we learn to inform the next generation of premarket reviews. So we are constantly learning and evolving our premarket review program.

Some of you who have been coming to FDA meetings for a while have probably seen this. We call this concept the total product life cycle. This concept says, basically, that medical devices are constantly evolving.

You've got a prototype. It comes in. We do preclinical testing and clinical testing, and then eventually it will get approved. It goes out on the market. It is being used, and then that product becomes obsolete, and information that is learned about that product goes into the concept for the next generation, and we just cycle around

and around.

Really, that is the way that medical device technology evolves, and that is the way that FDA is approaching the medical device review paradigm.

So at today's meeting, we are seeking the committee's input on our efforts to protect public health throughout the total product life cycles. So we are in a stage where we've got some technologies that have been out there for a while, and we are trying to collect more information about what is going on in the postmarket setting.

The open public hearing is an opportunity for us to hear from the public, and we are also going to have the committee discussing some questions that we have about some things that we are considering doing, moving forward.

We will inform the committee and the public about our recent activities as well. So some of the presentations you are

going to hear this afternoon are going to tell you about areas that FDA has been involved with in LASIK and PIOLs.

I thank you for your attention.

MR. ULMER: Good afternoon. My name is Kwame Ulmer. I am the Chief of the Diagnostic and Surgical Devices Branch in the Division of Ophthalmic and ENT Devices in the Office of Device Evaluation, Center for Devices and Radiological Health.

This session, as Dr. Tillman has indicated, is devoted to discussing the postmarket experience with LASIK. At the end of this meeting, we would like your input on patient labeling, the LASIK website, ANSI laser standard, and the SightNet Program. These are some of the tools FDA uses to improve patient safety.

Specific topics to be presented include as regulatory background presented by myself. Dr. Hilmantel will discuss the ANSI standard for refractive lasers. Ms. Quynh

Hoang will discuss FDA 2006 assessment of LASIK postmarket experience. Dr. Eva Rorer will outline LASIK quality of life assessment, and finally Dr. Bernard Lepri will discuss the adverse event reporting program.

For the next few minutes, I will outline developments in LASIK, the types of data we typically ask for to support applications to market these systems, and labeling elements for physicians and patients, with an emphasis on patients. Finally, we will outline and seek your input on our LASIK website.

Conventional LASIK was first approved in 1998 by FDA, and it is a treatment based on the patient's vision where the treatment program is directly input by the surgeon. To improve patient outcomes, we have seen many technological advances over the past 10 years. You see here a list in approximate chronological order these advances.

They include innovations such as

eye tracker system to compensate for small eye movements, large optical zones to reduce halo and glare, and in 2002 we had a generational change where we approved the first wavefront-guided laser system that uses aberrometry data and a sophisticated software package to treat refractive errors.

As of today, we have approved the LASIK systems you see here and the refractive ranges, and for the indications shown on the screen.

All right. The next few slides present the depth and breadth of the pre-clinical testing we typically review.

The complete device description is key to understanding the functionality and mitigate any associated risks. FDA requests a robust device description of component property and principle of operation as part of the initial documentation.

We review many engineering tests. I will describe a few as we proceed. For

example, the beam output and stability would have direct impact on patient outcomes.

Ablation patterns and plastic are important for initial device characterization, including testing to understand beam path and the aiming system. Beam characteristics at treatment plane are also very important.

Software validation is key in evaluating the system. It begins a detailed narrative about the system functions. Patient alignment and centration are also evaluated on the bench.

Other data we request to include information is on maintenance procedures.

Labeling is one mechanism to ensure risks and benefits are communicated to the surgeon and, equally important, again as was previously mentioned, to the patient. The next few slides present the elements in physician and patient labeling with an emphasis on patient labeling.

It is important to note that

contraindications, warnings, precautions in the patient labeling and physician labeling are identical. We are seeking your recommendations on ways to further improve patient labeling.

Physician labeling includes a detailed device description, along with special features of that particular system. There is a full list of indications, contraindications, warnings and precautions. Finally, the results from the clinical trial used to support the PMA are provided.

Patient labeling is written in plain language and includes basic concepts regarding vision and refraction, along with a glossary of terms. A listing of benefits, risks, complications such as dry eye or blurry vision, and what to expect after surgery are included. Examples of questions to ask your doctor are provided, and there is often a self-test to reinforce learning and a list of clinical results from the PMA.

One example of contraindications are patients with keratakonis.

Warnings are a second highest risk mitigating message. An important example of warnings to patients are for those who already have dry eye or severe allergies.

Precautions should be discussed with the doctor. Unstable vision is an important precaution for potential patients. Other precautions are a history of corneal injury or disease.

This is a long list. thin corneas are another area of concern. FDA encourages, via the labeling, that doctors check for undiagnosed dry eye.

We recommend your doctor measure pupil size in dim light, since pupil size may affect your vision. We also encourage patients to visit our website to learn more about the benefits and risks of LASIK.

We are interested in any input to improve our communication to patients via

labeling. We look forward to your thoughts.

A cornerstone of our public education effort is the LASIK website. This is a frequently visited website in a question based format intended to inform the consumer. The website launch was 2000. There has been an average of 650,000 visits per year. LASIK related inquiries was the number one search term on the FDA website for February 2008. The website is frequently updated.

One area of the website is a checklist consumers can use to identify what makes them a good candidate, outlines risks and expectations before, during and after surgery.

An entire section is devoted to determining when LASIK may not be right for the consumer. For instance, if your prescription has changed in the past year, this may mean that your eyes are not yet stable enough for this refractive procedure.

LASIK has not been studied in

children, because their eyes are still changing. You see a continued list of when LASIK is not for me.

Large pupils, thin corneas and again dry eyes are also in the risk section of the LASIK website.

The website also has a timeline of symptoms the average person might expect out to six months. These data are based on clinical studies used to support marketing applications we have seen.

A page that is among the top 15 CDRH pages visited is the "What are the Risks?" section of the website. Loss of vision and dry eye are highlighted here, along with complications you see. There is also a note that long term data are not available.

FDA does not recommend individual physicians or manufacturers of individual LASIK systems, as was already noted. However, we do provide items to consider when selecting a physician, and you see the list on the

screen.

Consumers are warned to be wary of too good to be true advertising. This is another reason -- This is another area where complications are discussed, and screening of patients is listed as an important consideration.

We are interested in your comments regarding the LASIK website to improve our education and consumer outreach.

Thank you. The next speaker is Dr. Gene Hilmantel.

DR. HILMANTEL: Hi. I am Gene Hilmantel. I am a clinical reviewer with the division of Ophthalmic Devices -- Ophthalmic and ENT Devices, excuse me.

FDA is currently evaluating the ANSI Z80.11 standard for recognition. This concerns laser systems for corneal reshaping. This is the first consensus standard concerning refractive lasers.

We will be asking the Panel members

to discuss whether you recommend that the FDA recognize this standard in its entirety, in part, or with specific additions.

CDRH and the Division of Ophthalmic Devices in particular are very active in the standards process. I am going to start out by giving you some general background about ophthalmic standards. Then I will be presenting some of the highlights of the specific standard, which are presented in more detail in your Panel pack.

There are two general categories of standards. A horizontal standard is one that addresses basic principles applicable to many devices across many product lines. An example is the ISO 10993, biological evaluations of medical devices.

A vertical standard is specific to one kind of device. An example is the ANSI Phakic IOL standard.

Standards generally include information concerning terminology, test

methods and acceptable levels of performance, and examples of clinical protocols.

For ophthalmic vertical standards, the standards organizations that are involved are ANSI, the American National Standards Institute, and ISO, the International Organization for Standardization.

ANSI is a private, nonprofit organization that administers and coordinates the U.S. voluntary standardization and conformity assessment system.

The hallmarks of the ANSI process include: Consensus on a proposed standard by a group of "consensus body" that includes representatives from materially affected and interested parties; broad-based public review and comment on draft standards; consideration of and response to comments submitted; incorporation of approved changes into a draft standard; and right to appeal by any participant that believes that due process principles were not sufficiently respected

during the standards development.

The International Organization for Standardization or ISO has participation by country. 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 use of standards helps assure consistency and predictability. It can reduce data reporting requirements in the FDA applications, and result in decreased review time for FDA.

The FDA Modernization Act, or FDAMA, was a 1997 law. It stated that FDA may recognize voluntary consensus standards, and FDA must publish a list of "Recognized Standards."

A recognized standard is a consensus standard that FDA has evaluated and recognized for use in satisfying a premarket submission requirement or other requirements under the Food, Drug & Cosmetic Act. FDA can

recognize a consensus standard fully, in part, or not at all.

The FDA currently recognizes 30 ophthalmic standards. The FDA recognized consensus standards database is available at the website shown here. A complete list is available in your Panel folder.

The ANSI standard for laser systems for corneal reshaping was approved by ANSI on July 31, 2007, and was published in 2007. It is currently in the FDA recognition process.

The pre-clinical section of the standard outlines laser safety requirements for protection against contaminants, protection against toxins and allergens, and protection against the other hazards as shown here.

The clinical section of the standard outlines the consensus for an adequate clinical study for new refractive lasers. It calls for patient enrollment to occur in stages for a new laser system for

which there are no prior clinical data, and it calls for a 300-eye study in order to be able to reliably detect adverse events that occur of a rate of one percent or greater.

The standard outlines a methodology to determine when refractive stability is attained. Analysis of refractive stability should consider whether: 95 percent of eyes are changing less than or equal to 1 diopter between visits at least three months apart ; whether the mean refraction is changing at a rate of less than or equal to half a diopter per year; whether the rate of refractive change is decreasing over time; and whether the rate of refractive change is statistically indistinguishable from zero.

Refractive change at a visit at least three months after the point of stability should be evaluated for confirmation.

The standard calls for effectiveness analyses that assess the

predictability of the refractive change and the uncorrected visual acuity.

Recommended predictability analyses include assessment of the percentage of eyes that achieve accuracy of the manifest refraction spherical equivalent within a half a diopter, one diopter and two diopters, that are overcorrected by greater than one or two diopters, and that are under-corrected by similar amounts, and that achieve accuracy of sphere and cylinder within a half-diopter and one diopter.

The recommended analyses of uncorrected visual acuity include assessment of the percentage of eyes that achieve uncorrected acuity of 20/40 or better and 20/20 or better, and that achieve an uncorrected acuity equal to or better than the pre-operative Best Spectacle Corrected Visual Acuity.

The recommended safety analyses include assessment of the percentage of eyes

that lose two lines or more of Best Spectacle Corrected Acuity, percentage of eyes with the Best Spectacle Corrected Visual Acuity worse than 20/40, percentage of eyes that have an increase of refractive astigmatism of greater than 2 diopters, and the rates of adverse events.

The clinical section of the standard recognizes that there are important subjective outcomes that cannot be assessed through only visual acuity and refractive measurements. The standard recommends that a subjective questionnaire should be administered to all subjects.

Validated questionnaires are recommended. Questionnaires should include questions regarding glare, halos, double vision, spectacle and contact lens use, and night driving. And the standard states that the scaling system for subjective ratings should be specified.

Subjective ratings should be

utilized to assess incidence of clinically significant symptoms and to assess postoperative change in symptoms from preoperative status. The postoperative subject's satisfaction with surgery and postoperative frequency of use of distance correction should be incorporated into the questionnaires.

The standard states that a contrast sensitivity sub-study should be performed by the manufacturer when features of the laser beam raise concerns that there may be visual performance losses not correctable by spectacles, or when the manufacturer wishes to reduce precautionary labeling statements concerning reductions in visual performance under poor lighting.

In recent years, virtually all submissions to FDA have, in fact, included contrast sensitivity studies.

The ANSI standard for laser systems for corneal reshaping has created a basic

structure for pre-clinical 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.

As I mentioned at the beginning, we will be asking the Panel to make recommendations concerning recognition of this standard. Thank you.

MS. HOANG: Hi. I am Quynh Hoang from the Office of Surveillance and Biometrics.

In 2006, the FDA conducted an assessment of postmarket LASIK data. In the following, I will present the reasons that led to the FDA's assessment, the steps taken, the conclusions, and the recommendation.

The FDA determined that an assessment of the postmarket experience with LASIK was warranted for the following reasons.

We received complaints from patients, and since there have been about 700,000 LASIK procedures performed annually in the United States, we believe there could be a potential significant public health impact.

It is the Center for Devices and Radiological Health, CDRH, usual practice to convene an action team when the Center believes that an issue requires the consideration of all its components. An action team was convened for LASIK.

The primary task for the team was to compare the data that has surfaced since FDA approvals, the post-market data, to the evidence upon which the FDA based its approval decisions, the pre-market data.

Post-market data consists of peer reviewed literature, adverse events reported to FDA, recall information, and comments to FDA's LASIK web page.

Pre-market data includes the protocols in FDA approved investigational

device exemption applications and clinical trial results submitted to the pre-market approval applications, the PMAs.

At the onset of the project, the team believed that post-market published studies could be used for a direct comparison against the pre-market data. To determine the parameters to be used to compare post-market and pre-market data, the team identified questionnaires in each approved PMA for LASIK device, compared the questionnaires, and identified the patient reported outcomes, the PROs, in most clinical studies.

The post-market data for the comparison were peer reviewed published articles. This slide shows the criteria by which we selected the published articles. We began with a search for articles with the terms "keratomileusis, Laser In Situ" or "Lasik". Then we looked for articles that were published discussing patient satisfaction and quality of life, terminologies related to

those two parameters, and the two criteria. We arrived at 130 articles, and from reading the abstracts, we limit to those studies that looked at patient satisfaction and quality of life.

So from these criteria, again, we identified 15 articles that we could potentially use for the comparison. These articles were in English and published from 1995 to 2006.

Having the post-market and pre-market data side by side for evaluation, the action team formed the following conclusions. There was not a valid basis for a statistical comparison, since most of the patient reported outcomes were covered by a very small number of articles, and the scoring methods in those articles were significantly different from those used in the PMAs.

Furthermore, the team concluded that 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. However, these surveys do not adequately evaluate the effects of rare, severe events.

Based on its evaluation, the action team that the FDA convened in 2006 to conduct an assessment of the post-market LASIK data recommended that the FDA consider further evaluation of post-LASIK quality of life in a clinical setting.

This recommendation was accepted by CDRH leadership and is currently being carried out. Thank you.

DR. RORER: Hello. I am Dr. Eva Rorer. I am Chief Ophthalmic Medical Officer in the Division of Ophthalmic and Ear, Nose and Throat Devices.

First, I will go over some definitions, including patient reported outcome measure or PRO and quality of life, or QOL. Then I will briefly review the current use of PROs in device evaluation, and finally

I will discuss FDA's recent efforts in the area of quality of life assessment.

A PRO is a measurement of any aspect of a patient's health status that comes directly from the patient without the interpretation of the patient's responses by a physician or anyone else.

PROs add an important dimension to the overall patient evaluation. For example, a procedure may be considered a clinical "success." Yet the patient may be unhappy. On the other hand, a procedure may not be a clinical "success." Yet the patient may be happy.

In clinical trials a PRO instrument can be used to measure the impact of an intervention on one or more aspects or concepts of patients' health status, ranging from the purely symptomatic, such as the response of a headache, to more complex concepts, for example, the ability to carry out activities of daily living, to extremely

complex concepts such as quality of life.

There are many definitions of quality of life. The World Health Organization defines quality of life as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment."

Health related quality of life refers to the patient's overall perception of the impact of a health condition and its treatment.

Patient reported outcomes can be categorized into several general broad areas. These three, symptoms, functioning, and perceptions, are the most relevant for

inclusion in a health related quality of life questionnaire.

The term instrument refers to the actual question or items contained in a questionnaire or interview schedule, along with all the additional information and documentation that supports the use of these items in producing a PRO measure, for example, interviewer training and instructions, and then scoring and interpretation manual.

Measurement of patient reported outcomes must be standardized, and the ability of questions to make meaningful measurements must be evaluated. The use of already existing instruments are desirable so that outcomes from different studies can be compared.

With any medical or research instrument, formal evaluation should be done to assess a questionnaires ability to measure what it is intended to measure.

So how do you know when a

questionnaire is reasonable to use? Ideally, a validated questionnaire should be used. A validated questionnaire is one that has had its performance formally evaluated. It should have a published description of how it was developed, and analyses and results pertaining to its reliability and validity.

There are several types of validity that are related to some extent. Content validity refers to whether you have measured all aspects of the thing you are trying to measure. For example, if you ask a patient about his or her vision, you would want to be sure to include both distance and near vision questions.

Criterion validity refers to how well your questionnaire measure agrees with some existing gold standard measurement. But in many cases, there really isn't an existing gold standard measurement.

Because of this, most evaluations focus on construct validity, which looks at

whether your measurements are behaving in logical ways. For example, someone with 20/200 best corrected vision should report more trouble reading street signs than would someone with 20/20 vision.

Just as there are different types of validity, there are different types of reliability, two of which are shown here.

Internal consistency reliability is when different questions asking about the same area, such as problems with glare, yield similar responses.

Test-retest reliability is when a person responds in a similar way each time that person is asked that same question within a short period of time.

The general approach to developing a quality of life instrument involves formulating a model for factors to be measured and how they may be related, developing questions using focus groups, expert opinion and existing questionnaires, pilot testing

early versions of the questionnaire and then analyzing the results and revising the questionnaire as needed.

Once you think you have a final questionnaire, its validity and reliability have to be assessed. Once a questionnaire's reliability and validity have been established, it is important to use it in additional studies of different populations to assess its utility, because the characteristics of the population under study may influence different aspects of validity.

So as you can see, questionnaire validation is a complex, lengthy and expensive process. Therefore, there are few validated ophthalmic health related quality of life questionnaires.

It is important to note that, although the first LASIK approval was in 1998, the first validated refractive questionnaire wasn't published until 2000. Therefore, only LASIK clinical studies initiated after 2000

would have had the opportunity to use a validated health related quality of life questionnaire.

How are patient reported outcomes used during device evaluation? Patient reported outcomes are assessed during device clinical trials. In general, PROs are not currently used as primary endpoints in clinical trials to support marketing of ophthalmic devices, although they may be used as primary endpoints for post-market studies.

They are considered during review of marketing applications and when making recommendations regarding approval or clearance. PRO data are incorporated into the labeling.

Based upon the recommendation of the PMI action team that was previously discussed, FDA considered a large, national, prospective study to more fully evaluate LASIK outcomes.

We solicited the cooperation of the

National Eye Institute, the American Society of Cataract and Refractive Surgeons, and the American Academy of Ophthalmology, forming the joint LASIK Study Task Force.

FDA, NEI, ASCRS and AAO have all committed resources toward a multi-center clinical trial to investigate quality of life after LASIK.

The objectives of the study are to determine the level of satisfaction after LASIK; changes in the health related quality of life after LASIK; and factors associated with the level of satisfaction after LASIK.

The protocol has not been finalized for the prospective, multi-center clinical trial, and the group is assessing the appropriate instrument for patients to report their quality of life after LASIK.

This will be a validated instrument which will be easy to use during pre-market and post-market trials and in clinical practice.

FDA has an integral role in the design and execution of this study. The study will be executed in accordance with the rules governing FDA and NEI clinical trials. Consumer representation will be included. The FDA will objectively evaluate the information collected.

Now I will discuss another study related to quality of life.

FDA initiated a collaborative study with NEI to decrease the resources associated with administration of quality of life instruments in order to facilitate their use in device trials. The objective of the study is to validate computer administration of ophthalmic health related quality of life instruments.

This study will add to the body of knowledge in the field of PROs, and will be the first to compare the computerized, web based and paper based versions of the previously validated questionnaires used to

assess ophthalmic health related quality of life.

Outcomes of all studies will be made public, and could lead to modification of FDA's LASIK website, revision of patient and physician labeling, and educational outreach.

Thank you for your attention. The next speaker will be Dr. Bernard Lepri.

DR. LEPRI: Good afternoon, Panel members, guests and FDA colleagues. I am going to speak to you this afternoon about the major ways that FDA obtains information on the occurrence of adverse events.

One of the most well known avenues of adverse event reporting is MedWatch, FDA's safety information and adverse event reporting program. MedWatch monitors medical product experience after FDA approval or clearance of medical device products.

These medical products include drugs, biologics and medical devices. MedWatch also receives adverse event reports

from manufacturers, user facilities, health professionals, patients and consumers.

There are two categories of medical device reporting, mandatory and voluntary. Mandatory reporting is required of medical device manufacturers and user facilities. User facilities include hospitals, ambulatory surgical centers, nursing homes, outpatient treatment centers and diagnostic centers, emergency services, and home health care services.

Serious injuries and device malfunctions are -- Excuse me. Mandatory reporting requires manufacturers to report adverse events such as deaths, serious injuries and device malfunctions, and user facilities report deaths to both FDA and the manufacturer.

Serious injuries are reported to the manufacturer. Health care professionals and consumers, however, fall into the category of voluntary reporting of any medical device

adverse event.

MedSun is a subset of the mandatory user facility reporting universe of MedWatch and has been in existence since 2002. It is comprised of 350 health care facilities nationwide, mostly hospitals, who voluntarily agree to fulfill their mandatory reporting requirements through this network. It provides an interactive two-way collaboration between FDA and the MedSun participants.

MedSun is a network of highly trained reporters who recognize and report medical device problems, and these reporters are comprised of individuals from risk management, patient safety, quality improvement, biomedical or clinical engineers, physicians and nurses, individuals from materials management, and surgical services. MedSun also has several sub-networks.

Medsun is designed to identify, understand, and solve problems via an Internet based reporting system. It collects both

voluntary and mandatory reports to FDA, such as close calls, potential for harm, poor device interface design, as well as what is required by user facilities under mandatory reporting.

MedSun provides regular feedback via newsletters, conferences and Webcasts, as well as alerts on major actions regarding recalls and changes to instructions for use. MedSun also disseminates safety tips and educational programs.

SightNet is Medsun's newest sub-network as of 2007, and is designed to provide a real world view of ophthalmic medical device use in a variety of clinical settings, such as hospitals, ambulatory surgical centers, the Veterans Administration, the national Eye Institute, and private practices.

SightNet's goal is to improve the recognition, reporting, and understanding of ophthalmic device related adverse events. The goal among the network members is to

expeditiously amplify signals of actual or potential medical device problems, so that timely interventions may be implemented with the aim of mitigating risk.

In addition to bringing FDA's attention to potential problems before serious injuries occur, SightNet members collaborate with FDA and other facilities to disseminate, clarify and understand potential safety issues as they become known.

SightNet participants receive reports from FDA on adverse event occurrences via newsletters, conferences and Webcasts. They also receive safety tips and alerts as well as educational programs.

What is expected of a SightNet participant? Each site must designate at least one reporter. A reporter can be a technician, nurse, ophthalmologist, optometrist, risk manager, patient safety director, quality assurance staff member, and biomedical or clinical engineers. They must

also agree to actively participate for at least 12 months.

Reports are confidential. The location of the adverse event and the names of individuals and staff involved remain anonymous to all other participants. Reports are typically submitted online, but can also be done by phone, FAX or mail.

Problems with the medical devices per se include problems with: Instructions and labeling; packaging; manufacturing defects; software problems; failure to work as intended; interactions with other devices; problems encountered with off-label use; and human factors issues.

Additional, FDA aims to collect reports on all ophthalmic medical devices in use, and of a wide variety of adverse events.

Besides providing a description of the adverse event, there are specific pieces of information that should always be included in ophthalmic device reports.

These include: The time elapsed since implantation or use of the device; was the event in the right eye, the left eye, or both eyes; are there any pre-existing ocular conditions; what were the baseline, post-treatment and post-adverse event best corrected visual acuities; and what was the intraocular pressure at baseline, post-treatment, and post-adverse event.

With regard to LASIK, FDA is aiming toward collecting data on adverse events such as infectious Keratitis; endemic cases of DLK; abnormal trends in post-operative topography; significant losses of best corrected visual acuity; and complaints of glare, halos, starbursts and distortions, along with device failures.

Today the Panel will be asked to discuss this list of events and make recommendations for additions to this list.

MedSun reports are encrypted and stored securely behind FDA's firewall, and

these reports are only accessible to staff with government security clearances.

The initial review process uses paper printed versions of the reports, but these are only kept for a limited time and then destroyed.

FDA has several websites emphasizing safety issues wherein one can obtain patient safety news, MedSun information, public health notifications, one page descriptions of new device approvals, and information on contact lenses, LASIK, and Phakik IOLs.

Individuals or institutions interested in more information can contact any of the three individuals identified on this slide.

Today the Panel will be asked to address this question: The training packet for SightNet participants currently emphasizes evaluation for and reporting of the following LASIK-related adverse events and

complications.

Please discuss any recommendations you may have for revision of this list of adverse events and complications for which reporting is emphasized.

Thank you for your attention.

CHAIRPERSON WEISS: Thank you very much. I would like to thank the FDA speakers for their presentations.

At this point, we will open up the questions from the Panel to the FDA speakers, but the Panel members can also speak to the questions a little bit later today for the FDA speakers.

Does anyone from the Panel have any questions for any of the speakers? Dr. Heuer?

DR. HEUER: Way outside my realm of expertise, but in terms of the quality of life issues, one of the things we heard repeatedly this morning is one of the driving problems is dry eye.

My understanding is that there are

validated dry eye instruments, and I would urge the FDA and, in terms of the ANSI folks, to consider.

CHAIRPERSON WEISS: Dr. Eydelman.

DR. EYDELMAN: We are aware of the validated dry eye questionnaires, and we have -- we are actually utilizing it as part of our NEI-FDA pilot.

CHAIRPERSON WEISS: Ms. Niksch.

MS. NIKSCH: Barbara Niksch. I have a question on the quality of life proposed study, a couple of questions, actually.

When the protocol was being created, can you give an indication if the questionnaire will be administered pre-operatively as well as at different times, post-operatively?

Also, in that questionnaire will there be psychodynamic type of profiling questions to monitor the patient's status pre-operative as also post-operatively? Again,

that directly relates to the testimonies we heard earlier.

CHAIRPERSON WEISS: Dr. Eydelman.

DR. EYDELMAN: Again, as mentioned previously, the study has not been finalized. The protocol has not been finalized.

There is a lot of discussion for incorporating several different domains of previously validated questionnaires in order to create the best possible quality of life survey that will address as many issues as possible, while still remaining short enough that it is doable in a real time frame.

One thing that I can probably say for sure is that the questionnaire will be administered prior and post-surgery, so that each patient will be their own control.

CHAIRPERSON WEISS: Ms. Cofer.

MS. COFER: Yes. I actually have a list of things. I don't know if it's for the FDA or just Panel discussion, but if I have some recommendations for labeling changes, is

that for the FDA or is that a separate Panel discussion?

CHAIRPERSON WEISS: Right now we are just directing questions toward the FDA speakers. So if you have any questions for these individual speakers, this would be the time to ask them. If they are recommendations, this will meet more toward the question period of discussion for the Panel. Do you have any questions for the FDA speakers?

MS. COFER: Yes.

CHAIRPERSON WEISS: You do?

MS. COFER: My question is regarding the labeling and any changes that are made to the labeling, and even the current labeling. What is the enforcement that the patients are actually given the labeling, because it is my experience and that of most LASIK patients that I know that they were never given the labeling that doesn't contain -- that has these important warnings in it,

but they were never given the labeling. So what is FDA's enforcement of that?

CHAIRPERSON WEISS: Dr. Eydelman?

DR. EYDELMAN: Again as Dr. Tillman addressed in her presentation, we regulate device manufacturers. We do not regulate individual physicians. However, all of the patient labeling -- I want to emphasize that every LASIK device legally on the market in the U.S. does have a patient labeling. This patient labeling can be downloaded from the website. It is part of the approval package.

So we hope that today's meeting will give publicity and will give a better acknowledgment to the U.S. patients that this labeling exists, and they should seek -- and it is actually very easily obtainable, even if their physician doesn't provide it. It is very easily downloaded from the web.

CHAIRPERSON WEISS: David?

DR. MUSCH: I had one question

about the ANSI standard and one question about quality of life, or several probably.

Regarding the ANSI standard -- well, I had a number of questions. At times, the time point post-operative is mentioned. At times, it is not. I just think that, if it is going to be a standard, you should specify at what times things are going to be measured.

CHAIRPERSON WEISS: Dr. Eydelman? And perhaps for the transcriptionist, it might facilitate things if each of us identified ourselves before we start to speak. So I will do that as well.

DR. EYDELMAN: Duly noted. Dr. Eydelman. I just want to bring to attention that the excerpts you received from the ANSI standards are just short excerpts. There are times specified in the actual standard. Due to the -- We cannot duplicate the actual standard, because it is ANSI's property. So all we provided is a synopsis of the information in it, but I can assure you that

the data and the time frames are indeed in the standard.

DR. MUSCH: Also regarding the ANSI standard, you might check with your biostatisticians about the statement that the refractive change is not statistically different from zero, and in particular, the parenthetical comment that the 95 percent confidence interval does not include zero.

If a 95 percent confidence interval does not include zero, it then means that that change is significant. So check on that.

I wondered if your Pelly-Robson -- if your contrast sensitivity testing is Pelly-Robson --

CHAIRPERSON WEISS: Perhaps, David, we could have Dr. Hilmantel just answer the -- respond to the question on the ANSI standard.

DR. HILMANTEL: You are right on the confidence interval. That was just a mistake in the slide. So the standard calls for looking at whether the confidence interval

includes zero and, if it doesn't include zero, then it is not stable.

CHAIRPERSON WEISS: Thank you.

DR. MUSCH: Thank you. Then I have a question about contrast sensitivity testing. That tends to be a very complex thing to do, and controlling ambient lighting is very essential for it.

I wondered if you -- You probably have a more extensive description of how that is carried out.

DR. HILMANTEL: Yes. There is actually a whole subsection within the standard that puts in quite a lot of detail how that testing is done. So you are correct, but that is well controlled in the standard.

DR. MUSCH: Then regarding Dr. Rorer's presentation on quality of life and your planned prospective, multi-center clinical trial, trials are comparative in nature, and I didn't get a sense for what exactly you are going to be comparing.

CHAIRPERSON WEISS: Yes, please?

DR. RORER: As Dr. Eydelman already said, the protocol hasn't been finalized yet, and there is still discussion on the very basic elements of the study design. So at this time we can't say definitively what comparisons will be made.

DR. MUSCH: I think my final question then, at least for now, regarding the quality of life measurement, health related quality of life: As you comment, it has a number of domains.

We heard this morning concerns from patients and from a variety of the public regarding an outcome of LASIK that you might want to consider at least assessing in some way.

I am not sure that you want to get into a thorough assessment of psychological impact, but certainly consider using a validated instrument for measuring the emotional impact, depression.

There are really patient friendly instruments that are validated like the Centers for Epidemiologic Studies of Depression instrument that you should consider, and I think that is probably on the table.

DR. EYDELMAN: You are correct.

CHAIRPERSON WEISS: Dr. Eydelman. Dr. Heuer.

DR. HEUER: I had one question about the adverse event reporting, and I would have to defer to my cornea colleagues. But it seems to me that an epithelial ingrowth, at least those that require re-operation, should be included among the adverse events for which reporting would be important.

CHAIRPERSON WEISS: Noted. Mr. Bunner.

MR. BUNNER: Richard Bunner. I guess, not being the technical expert here, a clarification: One of the contraindications is changes in refractive state. So when a

patient goes in for consideration of refractive surgery, how is that baseline history on their refractive changes over time evaluated by the provider?

CHAIRPERSON WEISS: Dr. Eydelman.

DR. EYDELMAN: Well, again we don't regulate the physicians. We can only make recommendations in our labeling and our website about how we recommend that it is done, and that was spelled out on the slide. But as pointed out several times during this meeting, we cannot regulate the practice of medicine.

MR. BUNNER: Just to clarify then, I understand that part. So being a consumer, if I go in for consideration of refractive surgery, am I expected to come in with documentation?

Since you are recommending -- you are making recommendations to consumers, should I be prepared to present to this physician my refractive history or would that

physician be getting some baseline history of my refractive state before recommending surgery?

I just wonder what those recommendations are to consumers related to what you tell the physicians?

CHAIRPERSON WEISS: Dr. Eydelman.

DR. EYDELMAN: Well, it is usually -- Again, what the recommendations are is that you somehow establish the refraction. It can be done in several different ways.

One would be by having clinical history documentation of actual refractive error at the previously measured exams by either ophthalmologist or optometrist or anywhere else where you were examined, and that being somehow conveyed to your current physician.

Alternatively, if it somebody who has not seen an eye care provider for several years, usually we ask -- we recommend that the current refractive correction be brought in,

so your current specs or your current contact lenses, so that the physician whose care you are currently seeking can see if there is any difference from what you are wearing to what you are currently.

Did I answer your question?

MR. BUNNER: Yes. It just seems like that sounds like -- Apparently, that is an important issue when you are making a decision about refractive surgery, and yet just thinking of it from a patient's standpoint and the way that you might seek different eye care providers over time or the lack of care over time, that that might be a point that is not really addressed at the time making this decision on the surgery.

I am just hoping that physicians direct those patients on that issue.

CHAIRPERSON WEISS: I would just say as a refractive surgeon, usually it does not end up being too much of an issue. If someone comes in there with glasses and you

see your refraction is significantly different than the glasses, then you will cease and desist in terms of pursuing any surgery, and you may ask for old medical records or tell the patient there is a possibility they are not stable and they need to come back.

Most times, for good LASIK candidates you will find that their eyeglass prescription is fairly similar to what the refraction is in the office.

Any other comments from any other Panel members on that issue? Dr. Huang.

DR. HUANG: I think the creation of SightNet is a good idea. However, I wasn't clear if the public will have access to the information gathered from the SightNet. If so, the problem is, since this is a voluntary reporting system, and I'm wondering if the FDA has another layer of screening or validation of the self-reporting system before the public discourage us. So, therefore, we will not create a mass hysteria.

CHAIRPERSON WEISS: Dr. Lepri.

DR. LEPRI: Yes. The MedSun website, which includes the sub-networks, and this would include SightNet, is available to the public on the website, and they can review reports and recommendations that come through.

They would not get information about practitioners or institutions where events have occurred, but all that information is available on the MedSun website.

DR. EYDELMAN: I think, just to add to, hopefully, something that will help clarify what you are saying, the data does not just get dumped back. The data gets collected and analyzed by FDA personnel who are trained to analyze the data, and then a summary of those outcomes are presented back to the public.

CHAIRPERSON WEISS: I have a follow-up question on that. Is there any double-check loop to see in a particular institution how compulsive individuals would

be in terms of reporting these events? Is there any double-check to see if, actually, what is happening is getting entered?

DR. LEPRI: To the best of my knowledge, there is no way for us to go back and find out if everything that goes on there is being reported. However, since it is a voluntary system through MedSun, they voluntarily join, and they have a strong willingness to improve patient safety.

In fact, many of these hospitals have patient safety staffs which particularly address these issues throughout the hospital or throughout the clinic. So we have a significant amount of confidence that they are reporting everything that does happen.

Additionally, after an initial report is filed, these are followed up with phone calls and additional interview to find out more in depth information on the occurrence of the event, devices involved, individuals, and then we also track, you know,

do these things happen repeatedly at one site or do they just happen randomly.

CHAIRPERSON WEISS: Dr. Eydelman.

DR. EYDELMAN: Just to add one more. As was evidenced in Dr. Lepri's slides, there is mandatory reporting of adverse events by both the manufacturers and user facilities. So there is a cross-check anyway.

CHAIRPERSON WEISS: Ms. Cofer.

MS. COFER: Yes. On the ANSI standards, I just want to be sure I am clear. The guidance document for refractive surgery lasers is dated in October 1996. Will the ANSI standards replace that?

CHAIRPERSON WEISS: Dr. Eydelman.

DR. EYDELMAN: First of all, we have not recognized the ANSI standard as of yet. We are in the process, and that is why the Panel is being broached that question.

As of now, the '96 guidance still exists and is still up on our web. After the recognition of the standard process, we will

have to go back and see what we want to do with that.

MS. COFER: And just a follow-up question. Is that okay?

I'm looking at the ANSI standards, and it mentions symptoms, and one of the symptoms in the ANSI standards talks about glare, and we've heard a lot about glare today.

As a patient that lives with this every day, I'd just like to say that some of the terms that are being used by LASIK surgeons and the LASIK device manufacturers are very confusing to patients.

I think that something needs to be done about some of this terminology. If glare is a starburst, then I'm not sure why it is not called a starburst, because I --

DR. EYDELMAN: Again, you have a heard a lot of reference to our patient labeling, and in all our patient labeling we have an index of terminology where we try to

explain the clinical terms used by the physician in a language that will be clearly understood.

One of the questions the Panel is being asked today is for any possible modifications or improvement we can do to that. So if you don't find that acceptable, we would love to hear from you.

CHAIRPERSON WEISS: Ms. Niksch.

MS. NIKSCH: Just one more question on the future quality of life assessment. It was pointed out that consumer representation will be included. But I have to ask this, being industry rep. Is there a plan to also include industry in this process?

Again, industry has many experts. We conduct clinical trials. We analyze the information, and ultimately conclusions from the study may go back to industry for us to change labeling, etcetera.

So at some point, I just have to ask. Would there be a consideration to have

industry involved in the design of this instrument at all?

CHAIRPERSON WEISS: Dr. Eydelman.

DR. EYDELMAN: At this point, there was no intent to involve the industry. As we pointed out, the collaborative efforts are between the two professional organizations, the National Eye Institute and the FDA.

CHAIRPERSON WEISS: Dr. Heuer.

DR. HEUER: For Dr. Lepri or Dr. Eydelman: This morning, there were several references to the fact that some of the facilities in which LASIK is being performed apparently aren't subject to the reporting requirements. Could you clarify that?

CHAIRPERSON WEISS: Dr. Eydelman.

DR. EYDELMAN: Most of the LASIK surgeries are done in ambulatory surgical centers, and we tried to address that in one of Dr. Lepri's slides.

The serious adverse events occurring at the ambulatory surgical centers

are a mandatory requirement.

CHAIRPERSON WEISS: Dr. Musch.

DR. MUSCH: We heard this morning some concern regarding the support from the cataract and refractive surgery group about -- for the proposed study's quality of life studies.

Could you talk to us about how that will be -- how that concern will be addressed, and how the FDA will stand above the money being provided?

CHAIRPERSON WEISS: Dr. Eydelman.

DR. EYDELMAN: Again, as we pointed out several times, we are not in a position where everything is figured out. The protocol is not finalized, but I can assure you that every precaution is being taken that there are no potential conflicts of interest, and that everything will be done in consistence with FDA and NEI regulations.

CHAIRPERSON WEISS: Ms. Cofer.

MS. COFER: Since we are going to

be -- Since you started the discussion about the quality of life study, I do have some comments about that. Is it appropriate to go into those now?

CHAIRPERSON WEISS: It is only appropriate to ask questions now. Again, comments will stay for the discussion.

So if you have any specific questions for FDA, a good time to ask it. Otherwise, I think, if there are no other questions, then we may just proceed on to the next speaker.

Are there any other questions? If not, we will proceed on to the next guest speaker for the FDA, and that is Dr. David Tanzer.

DR. TANZER: Good afternoon. I'd like to thank Dr. Eydelman and Dr. Weiss, and the members of the panel for allowing me to present this afternoon. I'm Commander David Tanzer. I'm a cornea transplant cataract and refractive surgeon currently stationed at the

Naval Medical Center in San Diego, and I'm also the Director of the United States Navy Refractive Surgeon program. It's my pleasure to provide for you an overview of what laser vision correct means to the military.

My standard DOD disclaimer is I have no financial or proprietary interest in any material or methods discussed here, and my views are my own. They don't necessarily reflect the position of the Department of the Navy, Department of Defense, or the United States Government.

Just for your perspective, the military has a demanding set of visual requirements, one might call them unique in terms of aviation, whether it's taking a pilot flying a high-performance aircraft to the pitching deck of an aircraft carrier with or without wearing the unique set of optical devices, whether that's a special operations personnel diving or jumping out of airplanes, whether that's an infantryman or infantry

woman wearing night vision goggles, night vision devices for the safe conduct of their operations.

Many of the weapon systems that are used today use very sophisticated optical devices for their scopes. And we're all trained in the use of chemical and biological personal protective gear in the safe conduct of our operations.

In terms of the impact of laser vision correction in the military, we're constantly looking for improved functional vision with anything that we provide for our fighting force. And in point of fact, the wearing of contact lenses is actually prohibited when our servicemen and women are deployed to Iraq, Afghanistan, and Korea, so anything we could do to lower the risk for casualties in our fighting force, we're all about it.

In terms of lowering the risk of casualties with Lasik versus contact lenses, I

want to drive this point home by quoting a study published last year in the *Archives of Ophthalmology* from Oliver Schein, Johns Hopkins University, who databased a cumulative annual risk of infection with contact lens wear of 0.18 percent.

Likewise, a cumulative annual risk for infection following Lasik is 0.05 percent. Therefore, over the lifetime of a patient, that equates to an increased risk of 180 times greater having an infection following the wearing of contact lenses, versus Lasik procedure.

And from the ASCRS Corneal Clinic Committee in 2007, there were two cornea transplants for infections following Lasik done last year, versus 55 transplants for infections related to contact lens wear.

In terms of our patient population in the military, we have approximately 30 percent of our patients needing to wear spectacles or contact lenses, or potentially

who could benefit from laser vision correction.

In terms of laser vision correction research, in clinical trials that are performed in the Department of Defense, we have over 45 studies performed to-date, including 15 under investigational device exemption. Our goal is constantly an independent evaluation of the safety and efficacy of laser vision correction as it specifically applies to our fighting force.

We always look at quality of vision, visual recovery, environmental issues that I've mentioned to you in terms of aviation, diving, special operations. Whenever industry expands the parameters for laser vision correction, we want to safely and effectively evaluate that in an independent fashion. And, also, when they bring to us the latest technology that potentially improves the quality of vision of our fighting force, we want to, again, evaluate that

independently.

I'd like to briefly take you through the series of studies that I'm showing you here, looking at first the results of PRK in Naval Aviation. This is a landmark study that actually resulted in the approval of laser vision correction in Naval aviators. The Laser Comparative Study, which prospectively randomized 480 patients over four different excimer lasers.

We did our own satisfaction analysis via our own meta analysis, and I'll show you that. I'd like to have you take a look at a night driving study that we performed. Also, a LASIK Flap Stability Study, and I'll summarize with the LASIK and Naval Aviation Study that we just recently completed.

First, looking at PRK Naval Aviation in terms of efficacy, looking at uncorrected visual acuity at six months, you can see that 94 percent of the eyes treated

were 20/20 or better uncorrected.

As a measure of safety, looking at change of best corrective visual acuity, you could see that the majority of eyes treated had either no change, or a gain in lines of best corrected visual acuity.

There were complications that we saw in this patient population, including one corneal erosion for an incidence of 0.1 percent. There was late haze that we saw in seven eyes of four aviators that temporarily decreased their best corrected vision worse than 20/20, temporarily removing them from flight status. However, they were all safely and effectively treated with topical steroids, and they all did resume flight status. The incidence of this complication is 0.5 percent.

Finally, we saw one infection in one eye of one patient that resulted in a scar, and a decreased best corrected visual acuity of 20/32, two lines worse than 20/20. Fortunately, his fellow eye was better -- was

uncorrected 20/16, and he safely returned to flight status. And that incidence was 0.1 percent.

The aviators that we've treated to-date have accumulated a significant amount of flight experience, including over 48,000 flight hours accumulated within the six months following PRK. That includes over 19,500 landings, and over 2,600 carrier arrested landings to-date. As I've mentioned, 100 percent of our aviators treated to-date have successfully returned to flight status.

Looking next at the Laser Comparative Trial, which, again, prospectively randomized 480 patients over four excimer lasers. You can see in terms of an efficacy measure, approximately 90 percent of all eyes treated were 20/20 or better uncorrected, and approximately two-thirds of eyes treated were 20/16 or better uncorrected at one month.

Changes in best corrected visual acuity again show the majority having no

change, or actually a gain in lines of best corrected visual acuity at six months.

Moving next to a Comparative Trial where we randomized patients over three different keratomes to create the LASIK flap, this enrolled 300 patients or 600 eyes. Two surgeons performed the procedures. They used one excimer laser which is the wavefront-guided or custom laser, and we randomized the patients over three different flap creation devices, two mechanical keratomes, and one laser keratome.

Looking at the efficacy, uncorrected visual acuity at one month, you can see that the majority of patients have excellent uncorrected visual acuity, three-quarters or greater have 20/16 or better uncorrected visual acuity at one month.

Looking at the change of best corrected visual acuity at three months, as you can see, the vast majority of patients have either no change or a gain in lines of

best corrected visual acuity at three months following surgery.

Our meta analysis, looking at the overall satisfaction following LASIK, we looked at 1,200 patients, and we databased an overall satisfaction rate of 98.1 percent in our patients, and dissatisfaction rate of 1.9 percent.

We've also carried out a night driving simulator study, specifically looking at night driving performance with glare following LASIK. You can see that in terms of the ability to detect a target in the night driving simulator, approximately 15 percent of patients are improved following surgery over the pre-operative evaluation. And approximately 25 percent have an improvement in their identification of that target compared to pre-operative measurements.

In terms of the significant change in night driving performance in terms of detection first on the left, you can see that

28 percent have a significant improvement in their ability to detect a target, versus only 3 percent having a significant decrease in their ability.

In terms of the accurate identification of a target, 46 percent of patients are improving in that metric, versus 3 percent of patients decreasing in a significant fashion.

In terms of adding a glare source to that metric, 18 percent have an improvement, a significant improvement in their ability to detect a target at night, and nobody had a significant decrease in that metric.

Finally, in terms of the ability to properly identify a target with glare source at night, 41 percent of patients that we saw had a significant improvement in that metric, versus only 3 percent that had a decrease.

We always want to know if the flap is stable in our fighting force when we bring

LASIK to the issue. We completed a Flap Stability Study, which is a study done in an animal model. It was done with the approval of our local IRB, and we subjected these flaps to a force that we could equate to a service member jumping out of an airplane. We call that HALO, or high altitude low opening jumps, or the ability of a flap to sustain a 400 knot ejection, and you can see that on the left no flaps were displaced with a force equivalent to a HALO jump, or a 400 knot ejection. In fact, all the way to the right you can see that it required the force of approximately a 700 knot ejection, which isn't compatible with life, before the flap was removed.

Finally, looking at our most recent study that we've completed to-date, which is the LASIK and Naval Aviator Study. I'd like to show you the uncorrected visual acuity, or the efficacy of this procedure two weeks following surgery.

You can see that 100 percent of

eyes treated for 20/20 or better uncorrected, 94 percent were 20/16 or better, and 57 percent were 20/12 or better uncorrected two weeks following LASIK. Change of best corrected visual acuity, the vast majority of patients actually are gaining lines of best corrected visual acuity following this procedure at one month.

We asked these aviators how they felt they did following the surgery. First question, "Do you feel that LASIK has helped or hindered your effectiveness as a Naval aviator"? Ninety-five percent felt it helped their effectiveness as a Naval aviator, nobody thought it hindered their functionality. Finally, "Would you recommend LASIK treatment to a fellow Naval aviator"? One hundred percent of the enrollees said they definitely would.

So with that as a backdrop, in the year 2000, the Department of Defense, all three services, stood up their War Fighter

Refractive Surgery program, and to-date, the Army has eight centers, the Navy has seven centers, and the Air Force has five centers, for a total of 20 centers amongst the Department of Defense. And to-date, since the year 2000, we've treated over 224,000 eyes.

In terms of the average age of a military member receiving Laser Vision Correction, the average age of our patients is 34, and that compares quite comparably to the average age of a civilian receiving Laser Vision Correction, which is 37. The age range that we treat, between 18 and 60. There's a slight gender predilection toward males, 82 percent of our patients are male, 18 percent are female. And that obviously reflects a greater number of males serving on active duty.

The refractive errors that we treat range from plus 6 diopters of farsightedness or hyperopia, to minus 13 diopters of nearsightedness or myopia.

Again, the number of treatments to-date, over 224,000 procedures performed in the military, the Air Force is responsible for over 51,000 procedures, the Army over 100,000 procedures, and the Navy over 73,000 procedures to-date.

The impact of all this is if Laser Vision Correction is approved for all aspects of military service, including aviation, special operations, and support personnel, and you may know that Laser Vision Correction is also approved for NASA astronauts. However, we fully acknowledge that surgery is not without risk, and we always inform our patients to do an extensive informed consent process about those risks, benefits, and alternatives to Laser Vision Correction. And, in point of fact, nobody in the military is required to have refractive surgery. Anybody that gets refractive surgery in the military does so voluntarily.

Having said that, there's been only

one Department of Defense medical disability retirement related to Laser Vision Correction to-date. This medical board was due to quality of vision complaints in this individual, despite him having 20/20 uncorrected vision, so the rate of this, one out of 112,500 patients treated to-date, yields an incidence of 0.009 percent. I'll emphasize that point. 0.009 percent incidence of somebody not being able to return to duty status following Laser Vision Correction in the military.

So the summary of Laser Vision Correction in our fighting force is that it has been overwhelmingly successful in the military in all types of jobs. It's shown tremendous operational benefits, approved now for military aviators, divers, special operations personnel, and NASA astronauts. It's been proven to have an extremely low risk in our patient population, with a likelihood of disability of 0.009 percent.

The satisfaction, as I've shown, is incredibly high, with 95 percent of aviators feeling that it's improved their effectiveness as a Naval aviator, and 100 percent of treated aviators recommending it to a fellow Naval aviator.

And, in closing, I'd like to provide a personal summary here, personal perspective. I've actually had the privilege of treating and flying with the first F-18 Hornet pilot to have refractive surgery, and we then landed on board an aircraft carrier. As we flew toward the ship that night, he relayed to me that he had never seen the carrier and landing lights better. I took great pride and comfort in that fact, not only because I was in his jet at the time, but because I had permanently provided this individual, this aviator with an improvement in his ability to perform this critically visually demanding task, arguably, the most visually demanding task that exists anywhere