

TRANSCRIPT OF PROCEEDINGS

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

OPHTHALMIC DEVICES PANEL

NINETY-EIGHTH MEETING

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Pages 1 thru 232

Rockville, Maryland
March 17, 2000

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

OPHTHALMIC DEVICES PANEL

NINETY-EIGHTH MEETING

Friday, March 17, 2000

8:42 a.m.

Main Conference Room
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, Maryland

MILLER REPORTING COMPANY, INC.

507 C Street, N.E.

Washington, D.C. 20002

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P A R T I C I P A N T SPanel Participants

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Sara M. Thornton, Executive Secretary

Alice Y. Matoba, M.D.
Joel Sugar, M.D.
Jose S. Pulido, M.D.
Janice M. Jurkus, O.D.

Michael R. Grimmett, M.D.
Arthur Bradley, Ph.D.
Marian S. Macsai, M.D.
Leo G. Maguire, M.D.

Diane K. Newman, M.S.N., Interim Consumer Representative
Marcia S. Yaross, Ph.D., Industry Representative

FDA Participants

Philip J. Phillips
A. Ralph Rosenthal, M.D.
James F. Saviola, O.D.
Donna R. Lochner
Morris Waxler, Ph.D.
Quynh T. Hoang
Malvina B. Eydelman, M.D.

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P R O C E E D I N G S

1
2 CHAIRMAN McCULLEY: I'd like to call the 98th
3 meeting of the Ophthalmic Device Panel to order and turn the
4 floor to Ms. Thornton for introductory remarks.

5 MS. THORNTON: Because it's March 17, I would like
6 to wish all of you the top of the morning and a hearty
7 welcome from the FDA.

8 [Laughter.]

9 MS. THORNTON: And, moving on, there are a few
10 announcements. I'd like to remind everyone to sign in on
11 the sign-in sheets out at the registration area just outside
12 the meeting room here. Please do that. It's important for
13 us to recognize those who are interested in our meetings and
14 to know that you've all been accounted for so we can judge
15 our space for next time.

16 All the handouts for today's meetings are
17 available at the registration table. Messages for the panel
18 members and FDA participants, information or special needs,
19 should be directed through Ms. Anne-Marie Williams, Ms.
20 Shirley Meeks, who are out at the registration area.

21 Phone calls--the phone number, sorry, for calls to
22 the meeting area is 301-433-8011. In consideration of the
23 panel, the sponsor, and the agency, we ask that those of you
24 will cell phones and pagers either turn them off or put them
25 on vibration mode while in this room.

1 Panel members who have not yet ordered lunch need
2 to do so now. I think I got all of you, but if not, you
3 will indicate to me, and I will have someone in the
4 registration area come to you to collect your form and
5 money.

6 Due to the limited seating, which we don't seem to
7 have--but we do have a section for FDA staff, and I'd like
8 them to stay in that area, if possible, so that the public
9 can have the access to these seats here.

10 I have been asked by the folks in the registration
11 area if you would please deposit your trash items in the
12 receptacles at the door and don't leave them under your
13 seats. Your mother didn't come to this meeting.

14 CHAIRMAN McCULLEY: My, aren't we clever today.

15 [Laughter.]

16 MS. THORNTON: That's what happens when I get up
17 early.

18 Lastly, will all meeting participants speak into
19 the microphone and give your name clearly? Only one time, I
20 am told. The transcriber does not need repetitive naming,
21 which I think will be a relief to most of the panel members.

22 CHAIRMAN McCULLEY: That means that as we are
23 going through the meeting, people don't have to identify
24 themselves as they start to speak each time?

25 MS. THORNTON: Each time, once they've done it.

1 He's made a diagram, and he knows where we all are, and he
2 feels comfortable that we don't have to keep repeating our
3 names each time.

4 CHAIRMAN McCULLEY: Great. Thank you.

5 [Laughter.]

6 MS. THORNTON: Now at this time, before I ask the
7 panel to introduce themselves, I'd like to extend a special
8 welcome and introduce to the public the panel and the FDA
9 staff our interim consumer representative who is with us for
10 the first time: Mrs. Diane Newman. Mrs. Newman is a
11 graduate of the University of Pennsylvania with a master's
12 in science in nursing, an American Academy of Nursing
13 Fellow, and a Rutgers University School of Nursing Visiting
14 Professor. She has served as a consumer representative to
15 the Gastroenterology and Urology Devices Panel since 1998.
16 Welcome, Diane.

17 I'd now like to ask the others on the panel to
18 introduce themselves, starting with Dr. Pulido.

19 DR. PULIDO: Jose Pulido, Professor and Chairman,
20 Department of Ophthalmology, University of Illinois-Chicago.

21 DR. MACSAI: Marian Macsai, Professor of
22 Ophthalmology, Northwestern University Medical School, Chief
23 of Ophthalmology, Evanston Northwestern Health Care.

24 DR. SUGAR: Joel Sugar, University of Illinois at
25 Chicago.

1 DR. GRIMMETT: Michael Grimmett, Assistant
2 Professor, Bascom Palmer Eye Institute, University of Miami.

3 CHAIRMAN McCULLEY: Jim McCulley, Professor and
4 Chairman, Department of Ophthalmology, University of Texas,
5 Southwestern Medical School, Dallas.

6 DR. MATOBA: Alice Matoba, Associate Professor,
7 Baylor College of Medicine.

8 DR. MAGUIRE: Leo Maguire, Associate Professor of
9 Ophthalmology, Mayo Clinic.

10 DR. BRADLEY: Arthur Bradley, Associate Professor
11 of Visual Science, Indiana University School of Optometry.

12 DR. JURKUS: Jan Jurkus, Professor, Illinois
13 College of Optometry in Chicago.

14 DR. YAROSS: Marcia Yaross, Director of Regulatory
15 Affairs at Allergan, Irvine, California, and industry
16 representative to the panel.

17 MS. THORNTON: Thank you. At this time I would
18 like to announce that Dr. Alice Matoba, formerly a
19 consultant to the panel, has been made a voting member
20 effective February 2000.

21 Now I would like to read for the record the
22 conflict of interest statement for this meeting. The
23 following announcement addresses conflict of interest issues
24 associated with this meeting and is made part of the record
25 to preclude even the appearance of an impropriety.

1 The conflict of interest statutes prohibit special
2 government employees from participating in matters that
3 could affect their or their employer's financial interests.
4 To determine if any conflict existed, the agency reviewed
5 the submitted agenda for this meeting and all financial
6 interests reported by the committee participants. The
7 agency has no conflicts to report.

8 In the event that the discussions involve any
9 other products or firms not already on the agenda for which
10 an FDA participant has a financial interest, the participant
11 should excuse him- or herself from such involvement, and the
12 exclusion will be noted for the record.

13 With respect to all other participants, we ask in
14 the interest of fairness that all persons making statements
15 or presentations disclose any current or previous financial
16 involvement with any firm whose products they may wish to
17 comment upon.

18 I'd like to read the appointment to temporary
19 voting status for the record.

20 Pursuant to the authority granted under the
21 Medical Devices Advisory Committee Charter, dated October
22 27, 1990, and as amended August 18, 1999, I appoint the
23 following individuals as voting members of the Ophthalmic
24 Devices Panel for this meeting on March 17, 2000: Dr.
25 Arthur Bradley, Dr. Michael Grimmett, Dr. Mary Macsai, and

1 Dr. Leo Maguire.

2 For the record, these individuals are special
3 government employees and consultants to this panel or other
4 panels under the Medical Devices Advisory Committee. They
5 have undergone the customary conflict of interest review and
6 have reviewed the materials to be considered at this
7 meeting. Signed, David W. Feigald, Jr., M.D., M.P.H.,
8 Director of the Center for Devices and Radiological Health,
9 March 3, 2000.

10 Thank you, Dr. McCulley.

11 CHAIRMAN McCULLEY: We have a special presentation
12 to be made by Philip J. Phillips. Mr. Phillips?

13 MR. PHILLIPS: Mr. Chairman and members of the
14 Ophthalmic Devices Panel, good morning. My name is Philip
15 Phillips, and that does seem to be a bit repetitive, but
16 there's little that I can do about that, so I hope that
17 you'll forgive me.

18 [Laughter.]

19 MR. PHILLIPS: You know, as I was just sitting
20 here and listening to the panel this morning, it sort of
21 occurred to me that, you know, the panel deliberations have
22 a tendency to be looked at as something that is so easy.
23 It's almost as if it's effortless as you go about reviewing
24 applications and making recommendations to the agency. And
25 I think that's sort of an illusion because of how smooth the

1 proceedings generally go, but there is a tremendous amount
2 of work and personal sacrifice that goes in to making these
3 ophthalmic panels run.

4 This morning I have the honor and privilege of
5 actually thanking one of the former members of the
6 Ophthalmic Devices Panel, and that's Dr. Marian Macsai, for
7 four years of services to this panel and to the Food and
8 Drug Administration. So I do have a certificate of
9 appreciation, which is signed by our Center Director, Dr.
10 David Feigald, and also our Commissioner, Dr. Jane Henney.
11 I would like to present this this morning, and it also comes
12 with a letter of personal thanks from our Commissioner. So
13 thank you very much.

14 [Applause.]

15 DR. MACSAI: Thank you.

16 CHAIRMAN McCULLEY: That does not mean you don't
17 still have to come periodically.

18 At this point I'd like to open the public hearing,
19 the open public hearing session. We've received no notices
20 prior to this meeting that anyone wishes to speak. However,
21 if there's anyone in the audience that would like to
22 approach the podium and make comment, please do so.

23 [No response.]

24 CHAIRMAN McCULLEY: Seeing none, the open public
25 hearing session is closed. We will now begin the Open

1 Committee Discussion, and we will begin with Division
2 Updates.

3 Dr. Rosenthal, would you like to introduce that?
4 No? I understand that Dr. Saviola has no comments. Is that
5 correct?

6 MS. THORNTON: That's correct.

7 CHAIRMAN McCULLEY: Donna Lochner, Chief,
8 Intraocular and Corneal Implants Branch, will now give us an
9 update.

10 MS. LOCHNER: Thank you.

11 First, I would like to announce that FDA approved
12 on February 3, 2000, PMA P980040 for Allergan's Sensar Soft
13 Acrylic UV-Absorbing Posterior Chamber IOL Lens Model AR40.
14 This lens was not reviewed at a panel meeting because the
15 clinical issues were substantially similar to issues
16 previously reviewed by the panel. However, during the
17 clinical study, epithelial cell ongrowth to the anterior
18 surface of the IOL was observed at a rate of 9.2 percent.
19 FDA required that the company continue to monitor this
20 phenomenon in their ongoing three-year study. We felt that
21 the company had shown that the lens was reasonably safe and
22 effective and, again, so we did approve it on February 3,
23 2000.

24 Next, we also approved a PMA on February 23, 2000,
25 for Allergan Laboratories P990023 Cellugel hydroxypropyl-

1 methylcellulose ophthalmic viscosurgical device. This
2 viscoelastic was also not reviewed at a panel meeting
3 because the clinical issues were substantially similar to
4 issues previously reviewed by the panel.

5 And, last, I'd like to announce that beginning on
6 March 27th, I will be going on a temporary reassignment as
7 the Deputy Director of the Division of General, Restorative,
8 and Neurological Devices, and this detail will last for a
9 period of six months. There will be an Acting ICIB Branch
10 Chief during that time period.

11 Thank you.

12 CHAIRMAN McCULLEY: That's okay, as long as you
13 promise to come back.

14 MS. LOCHNER: I'm coming back.

15 CHAIRMAN McCULLEY: We wish you well.

16 MS. LOCHNER: Thank you.

17 CHAIRMAN McCULLEY: But not too well.

18 Any questions for Ms. Lochner?

19 [No response.]

20 CHAIRMAN McCULLEY: Thank you.

21 The next presentation will be by Morris Waxler,
22 Chief, Diagnostic and Surgical Devices Branch. I'm
23 refraining from saying anything about the flower today.

24 DR. WAXLER: Thanks for your restraint, Jim.

25 On February 23, 2000, FDA approved PMA P990027,

1 the Bausch & Lomb Technolas 217 scanning laser for the LASIK
2 treatment of myopia -1.00 to -7.00 diopter sphere and up to
3 less than -3.00 diopter cylinder.

4 Currently there are 29 PMA documents under review.
5 Manufacturers submitted 14 IDEs--25 documents--for clinical
6 studies, mostly, but not exclusively, for refractive lasers.
7 Sponsor-investigators submitted 11 IDEs--15 documents--for
8 clinical trials for refractive lasers. Eight premarket
9 notifications--510(k)s--were reviewed.

10 CHAIRMAN McCULLEY: Any questions, comments for
11 Dr. Waxler?

12 [No response.]

13 CHAIRMAN McCULLEY: Thank you. That is a nice
14 flower. You fooled me last time. I made a comment about
15 your blasted flower, and you had some kind of bush in there.

16 [Laughter.]

17 CHAIRMAN McCULLEY: Okay. Mr. Phillips? We won't
18 pick on your name, either. Philip Phillips will now return
19 for FDA presentation on least burdensome provisions of the
20 FDA Modernization Act of 1997.

21 MR. PHILLIPS: I'll see if I can keep you awake
22 during this presentation.

23 I think that most people realize that back in
24 November of 1997, President Clinton signed what is what at
25 least many people consider to be one of the most significant

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1 pieces of legislation in the history of FDA, certainly since
2 the passage of the Medical Device Amendments of 1976.
3 That's the FDA Modernization Act of 1997. We quite
4 frequently refer to that as FDAMA, so you've probably heard
5 it referred to as FDAMA whenever you interact with FDA.

6 That particular piece of legislation is very, very
7 complicated. There are a lot of different provisions, and
8 it is, like I said, one of the most significant changes that
9 we've seen in the history of the agency.

10 What I would encourage everyone to do is to go to
11 the FDA's website if you want to find more information about
12 this particular law. You'll find that FDA has done, I
13 think, a very good job of organizing all of the different
14 aspects of the guidance documents and regulations and
15 changes that affect this particular piece of legislation and
16 how we've attempted to implement it. And it's very, very
17 user friendly. You can go through it and find a lot of
18 different details.

19 This morning what I'm basically here to talk about
20 is just simply one of the provisions of FDAMA, and that
21 deals with the requirement for coming up with the least
22 burdensome way of allowing products to enter the
23 marketplace.

24 This morning I am going to be talking about the
25 actual references to the least burdensome provision that's

1 actually included in the law. I'm going to talk about some
2 of the things that we've done to implement this provision,
3 as well as some of the mechanisms that perhaps even the
4 panels will find useful in trying to lessen some of the
5 regulatory burden associated with what we do.

6 As far as the references to the terms "least
7 burdensome," you'll find that they actually appear in two
8 different sections under Section 513 of the Food, Drug and
9 Cosmetic Act. One of them is Section 513(a) that deals with
10 PMAs and 513(i), and we'll look at each of those in just a
11 little bit more detail.

12 Under Section 513(a)--and I think that this is
13 perhaps the one that will affect the advisory panels more
14 than perhaps the other provision that we'll get to in just
15 one moment. The reason that I say that is because this
16 applies to premarket approval applications, and, of course,
17 you know, panels quite frequently see premarket approval
18 applications. The other provision that I'm about ready to
19 discuss in just a second deals with 510(k) submissions. And
20 although it doesn't happen with very much frequency, it does
21 happen in some cases that 510(k)s are brought before
22 advisory panels, but typically it's probably premarket
23 approval applications that you deal with.

24 This particular section--and let me just read the
25 words that I think are the key part of this. It says, "The

1 Secretary shall consider, in conjunction with the applicant,
2 the least burdensome appropriate means of evaluating device
3 effectiveness that would have a reasonable likelihood of
4 resulting in approval." So I think that appears to be
5 rather straightforward, but then I think when you start
6 looking at the term "least burdensome," you'll find that
7 it's quite difficult for us to actually put that into words
8 to explain it so everyone has the same understanding.

9 If you look at Section 513(i)--and, again, this
10 primarily applies to, or strictly applies to premarket
11 notification or 510(k) submissions--the words are very, very
12 similar. Here it says that, "Making such requests"--and
13 this is requests for additional information related to
14 510(k) submissions. It says, "The Secretary shall consider
15 the least burdensome means of demonstrating substantial
16 equivalence and request information accordingly." So,
17 again, the words "least burdensome" actually appear in these
18 two provisions of the law.

19 I think it's something that's absolutely key for
20 everyone inside and outside the agency, but certainly
21 advisory committee members, to realize that even though
22 FDAMA made a lot of changes in the way that we regulate
23 medical devices, one thing that FDAMA did not do, and, that
24 is, it did not change the standard for approval of premarket
25 applications, either the clearance of 510(k)s or the

1 approval of PMAs.

2 For PMAs, it still remains reasonable assurance of
3 safety and effectiveness, and that threshold is the same
4 that you have been trained on in the past, and nothing
5 changes as a result of anything that I'm about to talk about
6 this morning. The same thing applies to 510(k)s. Even
7 though you don't see 510(k)s, the statutory criteria is
8 substantially equivalence. Basically, products that enter
9 the marketplace that are found equivalent to other products
10 or at least as safe and as effective as those other
11 products. So the criteria for clearance did not change.

12 We actually began implementation of this
13 particular provision a little over a year ago. We had an
14 open public meeting that was on January 4, 1999. It was
15 here in this very room. It was very well attended. There
16 were members from industry that attended the meeting. There
17 were a number of advisory committee meetings that found the
18 time out of their busy schedule to come and to listen to a
19 lot of the discussion that went on that day. There were
20 professional associations that were there, and there were
21 also consumer groups that were represented. So it was a
22 very well attended meeting.

23 Since that period of time, we have not issued any
24 final guidance, but we have had quite a bit of communication
25 inside through a review staff on what least burdensome is

1 and how we factor it into our thinking. There has been some
2 actual scientific reviewer training that we've put on.

3 There is also a draft guidance document that was
4 released. This was last fall. It's called the Evidence
5 Models for the Least Burdensome Means to Market. It's a
6 draft Federal Register notice. This particular slide, it
7 does show you the citation for that, including the website
8 where it appears. The comment period ended at the end of
9 November, so at this particular time, we're going back and
10 looking at the comments to figure out if we should revise
11 this guidance document or change it or completely go in a
12 different direction.

13 In addition to FDA's guidance document that we
14 issued, there was also an industry task force that was
15 convened. They provided a proposal, called the Least
16 Burdensome Industry Task Force Proposal. That was submitted
17 March 11th of last year. If you go to our website and if
18 you look up that FDA guidance document, what you will find
19 is that if you go to Appendix D of that guidance, you will
20 find this particular proposal that was submitted by the
21 industry.

22 That was also subject to the exact same comment
23 period. It's a 90-day comment period. We received comments
24 on our proposal as well as the industry proposal. We're
25 likewise looking at those comments to determine exactly how

1 we proceed from here on out.

2 We have come up with what we consider to be sort
3 of an interim FDA definition of least burdensome. What we
4 have said is that least burdensome really is a successful
5 means of addressing a premarket issue that involves the
6 smallest investment of time, effort, and money on the part
7 of the submitter and FDA.

8 Now, keep in mind successful means. I'm going to
9 go back and I'm going to harp on that statutory criteria
10 again. Successful means that the applicant has demonstrated
11 reasonable assurance of safety and effectiveness. That's
12 for a PMA; 510(k) it is substantial equivalence. That has
13 not changed.

14 But, nevertheless, this is something we're trying
15 to factor time, effort, and money into our decisionmaking to
16 see if we can come up with something that truly is the least
17 burdensome means of allowing products to go to market.

18 The least burdensome means requires what some
19 people have said, sort of a change in FDA culture. I don't
20 know that it's truly a change in culture, but clearly we
21 have to recognize there are multiple approaches to
22 satisfying any of our regulatory requirements. There's not
23 simply just one way of providing reasonable assurance of
24 safety and effectiveness or demonstrating substantial
25 equivalence. Likewise, I think it's important for everyone

1 to recognize that it's important for everyone to
2 communicate, collaborate, and compromise in the interest of
3 public health. And I realize that when I use that term
4 "compromise," sometimes it's viewed as a hot button, and you
5 say, well, we don't compromise for public health. Well, I
6 think sometimes there are good reasons for us to compromise,
7 but it's in a very positive way. Perhaps it's compromising
8 in the issue of premarket requirements versus postmarket
9 surveillance. Maybe there are things that we can lessen in
10 the premarket area that are more reasonable for us to get in
11 the post-approval area.

12 So, again, I think that there are certain times
13 that we will compromise, but, again, when we do so, it's
14 because there's a direct linkage to advancing the public
15 health of this nation.

16 Also, it's important that everyone recognize that
17 it's not just the letter of the law but the spirit of the
18 law. And I think when we talk about the FDA Modernization
19 Act, that was one of the most powerful messages that the
20 Congress gave us, that is, that we are to work closely with
21 all of the stakeholders that are interested in what we do to
22 see if we can smooth out the regulatory process and, of
23 course, one result of that would be lessening regulatory
24 burden.

25 We need to also factor time, effort, and money as

1 a consideration of our decisionmaking, and that is something
2 which is a little bit different than what we generally have
3 had in the past in the FDA culture.

4 If we talk about the concept--whoa, what happened
5 there? If we talk about the concept of least burdensome, I
6 think everyone needs to recognize what we're not talking
7 about is in any way compromising our scientific integrity.
8 We think that there's a way of actually reaching both goals,
9 of having good scientific integrity as well as also meeting
10 the statutory requirement for least burdensome.

11 I think we all recognize that all scientific
12 endeavors are affected by the availability of resources.
13 It's just a fact. Anyone who is involved in resources,
14 academia, certainly the rigor in which you do research is
15 directly affected by the resources that are available to
16 you.

17 Good science does include cost-effectiveness. I
18 mean, none of us, if, in fact, we're going to spend those
19 rare resource dollars, wants to waste those dollars. We
20 want to make sure that they're used for getting the biggest
21 bang for the buck.

22 Also, compromise is a necessity for successful
23 research. All of us have developed some--what we would
24 consider to be the perfect protocols, but you know it's
25 often difficult for us to implement the perfect protocol.

1 You'll find that there are always snags that you have along
2 the way, and compromise is something that is a very big part
3 of all research activities.

4 Also, it's important, I think, that we recognize
5 that lessening regulatory burden may serve to enhance the
6 scientific progress and advance medicine. If we can get the
7 appropriate amount of regulatory burden in our decision-
8 making, perhaps we'll be able to get safe and effective
9 devices to the marketplace and available for use by
10 practitioners and available to consumers in a much more
11 reasonable period of time.

12 What are some of the mechanisms that we would
13 suggest that you consider as panel members when you go about
14 evaluating applications and considering regulatory burden?
15 Well, I think that we need to ensure that all regulatory
16 decisions are made in accordance with relevant statutory
17 criteria. There is a tendency in some instances to ask
18 questions that are perhaps not related directly to the FDA
19 mission. You start getting into areas of cost-effectiveness
20 or other things that are not directly related to safety and
21 effectiveness. Sometimes we do get somewhat afar from what
22 are the responsibilities of the Food and Drug
23 Administration.

24 I think we also need to make sure that we use all
25 of the tools that are provided by the FDA Modernization Act

1 as well as some of the re-engineering activities that we've
2 undertaken inside the Center for Devices and Radiological
3 Health. And here I can point to just a couple of examples.

4 For example, the exemptions from 510(k)
5 submissions, if we can stop looking at some of the simpler
6 types of devices that consume quite a bit of time in
7 evaluating with little public health impact as a result of
8 those reviews, we could reprogram our resources so that we
9 can spend those into higher-priority activities such as the
10 review of premarket approval applications.

11 Likewise, there could be a lot of benefits from
12 using the tools of collaborative meetings with the industry.
13 If we can collaborate early on, we can certainly smooth out
14 a lot of the problems that--or avoid a lot of the problems
15 that we will later encounter when we start looking at some
16 of the study results.

17 Also, perhaps you're not aware of this, but in the
18 510(k) area there's also third-party review activities where
19 we have recognized third parties that are doing some of the
20 same types of evaluation that we're doing in-house. Again,
21 if we can use all of these tools that re-engineering and
22 FDAMA have provided, we'll be able to change and shift some
23 of our resources into doing higher-priority activities.

24 We also have to ensure that we factor all publicly
25 available information into the decisionmaking process, and

1 here I'm thinking perhaps about the public literature. I
2 think there's a tremendous amount of information that is
3 available, and if it is publicly available, we can use that
4 very freely in titrating the regulatory requirements that we
5 apply against new and developing technology.

6 We should rely on non-clinical testing for
7 decisionmaking whenever that is possible. I mean, let's
8 face it. If you want a tremendous amount of precision, the
9 way that you can get precision is by doing bench studies,
10 because here we can measure, you know, periods of time in
11 nanoseconds and we can measure things in kilograms and even
12 much smaller than that, get a tremendous amount of--
13 kilograms. I heard one of the biomedical engineers behind
14 me snicker with that. Micrograms and along that nature.

15 The fact is you can get a lot more precision if
16 you deal with the bench rather than actually doing clinical
17 studies, and a lot of times you'll find that bench studies
18 can answer a lot of the questions that we have perhaps even
19 better than clinicals.

20 We need to rely on conformance to recognized
21 standards more frequently in our decisionmaking process.
22 There's a tremendous amount of effort that's been put in by
23 the agency as well as parties all around the globe at trying
24 to develop better standards as part of the global
25 harmonization efforts that are ongoing. And I think we can

1 capitalize on the use of those standards and rely on
2 conformance with those standards so that we don't have to
3 ask a lot of the questions that we generally have asked
4 historically when we reviewed different types of marketing
5 submissions.

6 Whenever we review clinical data, I think it is
7 important for us to always consider the fact that there are
8 alternatives to randomized controlled trials. Yes, as I've
9 mentioned before, sometimes it is appropriate for us to rely
10 on the literature as a control, as well as there are times
11 when we should be using non-active controls. And I think
12 that what we should do is, whenever we talk about study
13 design, make sure that we choose the appropriate type of
14 study that's necessary in order to answer the questions that
15 are on the table.

16 There are other more specific examples when we
17 talk about issues of effectiveness. We all need to be
18 sensitive to the issue of time and how long it takes for us
19 to address different issues. And quite frequently we can
20 find that there are surrogate endpoints, particularly with
21 effectiveness, that we can focus on that can sometimes
22 shorten the duration of studies and get products to market a
23 little bit faster.

24 Lastly, if there's a bottom line to everything
25 that I'm saying this morning, I think that everyone needs to

1 factor the least burdensome concepts that we've talked about
2 this morning into all of our premarket activities. And here
3 I'm not talking about just simply premarket applications and
4 PMAs and 510(k)s. But we should factor these least
5 burdensome principles into everything, including guidance
6 documents. Quite frequently, we bring guidance documents to
7 advisory committees for reviews and recommendations, and,
8 again, whenever we do that, all of us, inside and outside
9 the agency, should also try to take the least burdensome
10 approach at trying to develop these different types of
11 guidance documents.

12 The same thing with regulations. When we put
13 regulations in effect, we should be sensitive to the issues
14 of regulatory burden, as well as any of the panel
15 recommendations that you may be making regarding any other
16 decisions, whether it's on marketing applications or
17 reclassification activities or classification actions. I
18 think it's something that all of us need to be thinking
19 about constantly.

20 All of us need to remain open-minded to
21 alternative proposals in satisfying all of our regulatory
22 requirements.

23 You know, I think that even though I said this is
24 the bottom line, maybe this is the real bottom line:
25 Congress did something, I think, that's somewhat unusual

1 with this particular provision in the law, and I think that
2 is by trying to build in a common-sense approach to
3 regulation. I think that that's what we're talking about
4 here is--our Commissioner has said that it shouldn't have
5 been least burdensome. She thinks that it should have been
6 most reasonable. Well, I think that if you talk about
7 whether it's least burdensome or most reasonable, they may,
8 in fact, be synonymous. I mean, if you really think about
9 it, what we should be doing as a regulatory agency is making
10 sure that we meet the statutory threshold by providing the
11 highest level of assurance of safety and effectiveness for
12 products, and do that in the most cost-effective and least
13 burdensome way. And I think that Congress was really just
14 trying to ensure that the agency does take a common-sense
15 approach to regulation.

16 Thank you very much, and unless there are any
17 questions, I'm finished.

18 CHAIRMAN McCULLEY: Can we have the lights back
19 on? Are there questions or comments?

20 [No response.]

21 CHAIRMAN McCULLEY: Seeing none, we thank you.

22 MR. PHILLIPS: All right. Thank you.

23 CHAIRMAN McCULLEY: We will now open deliberations
24 on PMA P970043/S7. We'll begin with the sponsor's
25 presentation and remind sponsor you have up to one hour for

1 your presentation. Following that, the panel will ask
2 questions until all of the questions have been asked that
3 the panel wishes to ask. Following that, we'll ask the
4 company if they have final closing comments.

5 So, with that, I would like to turn the floor to
6 sponsor and start the talk.

7 [Pause.]

8 MS. MCGARVEY: I'm glad I took my blood pressure
9 pills early this morning.

10 [Pause.]

11 MS. MCGARVEY: Sorry. Our computer decided to
12 open up in safe mode, and we're trying to figure out what
13 that means.

14 [Pause.]

15 CHAIRMAN McCULLEY: Should we take a break?

16 MS. MCGARVEY: Just give us one minute.

17 CHAIRMAN McCULLEY: Well, no, I wasn't being
18 facetious. If you think it's going to take you a little
19 while, then we could go ahead and take a break now rather
20 than sitting here and watching.

21 MS. MCGARVEY: Why don't we do that?

22 CHAIRMAN McCULLEY: We'll take a five-minute
23 break.

24 [Recess.]

25 CHAIRMAN McCULLEY: I call the meeting back to

1 order for sponsor presentation of PMA P970043/S7.

2 MS. MCGARVEY: I think we need to have a little
3 bit of dimming of the lights.

4 Good morning, Mr. Chairman, FDA panel members, FDA
5 staff, and ladies and gentlemen. My name is Shirley
6 McGarvey, and I'm the regulatory consultant to Autonomous
7 Technologies, and we appreciate your indulgence in our
8 getting set up this morning.

9 The reason we are here today is to seek the
10 approval for an expansion to the indication for use of the
11 LADARVision Excimer Laser System. The system was originally
12 approved for use in myopia with and without astigmatism up
13 to -10.000 diopters a sphere and -4.00 diopters a cylinder
14 using the PRK technique of refractive correction.

15 We will start with a chronology of events related
16 to the study and the analysis of the LASIK procedure and how
17 we evolved to the panel's review of the hyperopia range of
18 the study. This will be followed by a technology overview
19 from Dr. George Pettit, and then Dr. McDonald and Dr.
20 Christy Stevens and Dr. Salz will be dealing with both the
21 clinical results and the response to the medical and primary
22 reviewers.

23 The LASIK study was initiated in myopia and
24 hyperopia at different points in time under two separate
25 protocols, each of which reflected the patterns common to

1 both ranges and encompassed criteria and parameters of
2 interest unique to each range. After meeting with the FDA
3 early in 1999, we collectively agreed to file a PMA for the
4 LASIK procedure encompassing the entire refractive range
5 with both myopia and hyperopia, with and without
6 astigmatism.

7 As you can see from the balance of this slide,
8 there were several subsequent interactions with the FDA
9 where in it was decided that the hyperopic population of the
10 file represented a first-of-a-kind indication. In addition,
11 the FDA indicated that use of a single treatment instead of
12 a two-step approach of first treating the sphere and then
13 treating the cylinder may be in the public interest.
14 Therefore, the file was granted an expedited review for the
15 hyperopic range, leading to this meeting today. The myopic
16 LASIK population in that PMA continues under active review
17 internally by the agency.

18 After the agency had the opportunity to review the
19 hyperopia study report in depth, they raised the issue of
20 eyes that presented for treatment with more cylinder than
21 sphere, categorizing these eyes as a separate astigmatic
22 population. We provided information to the agency which
23 established that the algorithm for all refractive errors
24 treated is the same using the LADARVision system, and we
25 also provided a statistical analysis that supports the

1 poolability of the entire astigmatic population treated.

2 Nevertheless, the FDA requested a stratification
3 of the astigmatic clinical results as a function of mixed
4 astigmatism and hyperopic astigmatism. This has been done,
5 and you will see the data presented in this manner today.

6 So, to summarize, the topic of discussion today is
7 the expansion of the indication for use for the LADARVision
8 system to encompass the hyperopic range of refractive error
9 using the LASIK technique.

10 This PMA was filed in September 1999 based on data
11 that indicated stability was demonstrated at three months
12 postop and then confirmed at six months postop. In that
13 filing, more than 95 percent of the cohort was available for
14 analysis with one- to three-month data, and a significant
15 majority of eyes also had six-month data available to
16 confirm that stability was established at three months.

17 In November, an update was provided to the PMA.
18 The data provided further confirmation of stability of
19 refraction at three months while providing substantially
20 more six-month data and some further confirming nine-month
21 data. As you will see from the information presented by
22 Drs. McDonald and Salz, the mean change per each three-month
23 interval is well within the repeatability of refractive
24 measures.

25 George?

1 DR. PETTIT: Good morning. I'm George Pettit.
2 I'm the chief scientists for Autonomous Technologies, and
3 I'd like to give you a short technical overview of the
4 technology used in this clinical trial.

5 Briefly, I want to talk about the LADARVision
6 corneal shaping, the computer algorithm that lets us address
7 refractive errors, and the main thing I'd like to get across
8 to you is that we use a single algorithm to attack the
9 entire continuum of treatment prescriptions, and I'll show
10 you some examples of that.

11 Then I'd also like to talk just briefly about the
12 LADARVision eye tracking system, how we use an active eye
13 tracker to stabilize the LASIK eye for the excimer
14 treatment.

15 So, first the corneal shaping algorithm. Our
16 LADARVision system employs a relatively small-diameter, low-
17 energy excimer laser beam, and these beam characteristics
18 allow us to remove about 450 picoliters of tissue with each
19 shot of the laser. So each treatment typically requires
20 several hundred to a few thousand pulses to globally change
21 the corneal shape.

22 Our shots are distributed in a precise pattern
23 that we calculate before the surgery starts. We use one
24 fundamental algorithm to calculate all shot patterns for all
25 types of refractive errors, and the calculated pattern

1 achieves the entire correction in a single treatment. We
2 don't do part of the treatment and then reconfigure either
3 the software or the hardware to finish. It's all done at
4 once.

5 The algorithm is designed so that no two laser
6 pulses are ever delivered to exactly the same corneal site.
7 The cumulative ablation is achieved by the partial overlap
8 of many of these one millimeter laser shots, and we get the
9 greatest tissue removal then in the regions where the laser
10 shot density is the highest.

11 We flatten or steepen the cornea appropriately
12 along each meridian so that we remove the minimum possible
13 tissue volume for every type of correction. And for
14 consistency, in all of our clinical trials we've used the
15 negative cylinder convention for all treatments.

16 So I'd like to show you some examples of how the
17 shot pattern algorithm works, and I'll start with the
18 simplest type of correction we could effect, which is a
19 simple myopic correction, and in all these examples, I'm
20 going to be talking about a six millimeter optical zone with
21 a 1.5 millimeter blend zone if required. So this is a 9
22 millimeter square region showing you the ablation shape that
23 we want to ablate on the corner, and over on this panel,
24 you'll see the actual laser shot pattern that we use to
25 achieve that. So this is a simple myopic correction. We're

1 trying to flatten the cornea along every meridian, and in
2 this 6 millimeter circle, you can see this is how we would
3 distribute the laser shots. These dots indicate the center
4 of each shot in the pattern. The shots actually extend out
5 a millimeter, so there's a significant overlap. But you can
6 see that the shot density is highest in the middle, and then
7 in every direction as you move radially outward, the shot
8 pattern falls off.

9 So now I want to gradually transition in equal
10 dioptric increments from a simple myopic correction to a
11 simple myopic astigmatic correction of the same magnitude.
12 So now we're talking about a 2 diopter astigmatic correction
13 over that same optical zone, and the main difference you see
14 between the previous and this is we've now had to add a
15 blend zone. We're trying to avoid a cylindrical profile
16 into the cornea, flattening it by 2 diopters in the vertical
17 meridian, not doing anything in the horizontal meridian. So
18 in order to have a uniform tapering of the ablation depth to
19 0 at the edge of the 9 millimeter circle, we've added a
20 blend zone.

21 Within the optical zone, the shot pattern as we
22 move up or down from the center line, the shot pattern
23 decreases steadily. As we go side to side along the
24 equator, if you will, the shot pattern is constant.

25 Now, if we gradually add 1 diopter of positive

1 sphere to this shot pattern, we're now talking about +1.00,
2 -2.00 correction. This is mixed astigmatism. So along the
3 vertical meridian, we're now still trying to flatten the
4 cornea by 1 diopter. However, along the horizontal
5 meridian, we're trying to steepen the cornea by 1 diopter.
6 Essentially, we're ablating a saddle-shaped profile onto the
7 surface of the eye.

8 So if we look at the shot pattern within the
9 optical zone, as we move from center up or down, the shot
10 pattern is generally gradually decreasing. As we move along
11 the equator off the center line, the shot pattern is
12 increasing out to the edge of the optical zone. The deepest
13 ablation occurs here, and this is where the shot density is
14 highest.

15 So now let's gradually in five steps add another
16 diopter of positive sphere to the treatment. So we move
17 from mixed astigmatism to simple hyperopic astigmatism, and
18 you can see now we're trying to ablate a positive cylinder
19 into the eye. The deepest ablations are going to be here
20 and here along the vertical meridian. We're not trying to
21 do anything to the corneal shape. So there's no shots right
22 along the vertical axis here, and the shot density increases
23 linearly as we move from side to side along the equator of
24 the shot pattern.

25 Now, if we take away 1 diopter--so this is simple

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1 hyperopic astigmatism. Let's take away 1 diopter of
2 negative cylinder gradually in five steps. We're not
3 talking about treating compound hyperopic astigmatism. So
4 along the vertical meridian, we want to steepen the corner
5 by 1 diopter. Along the horizontal diopter meridian, we
6 want to steepen it by 2 diopters. No shot is delivered to
7 the exact center of the corner within the optical zone. As
8 we move up or down, the shot density increases, and the same
9 thing happens but to a greater degree as we move side to
10 side. The deepest ablation, again, is right out here on
11 these wings.

12 Now, let's take away in five increments that last
13 diopter of negative cyl. Now we're talking about treating
14 simple hyperopia. There are no shots, again, in the center,
15 and as you move outward radially in any direction, the shot
16 density uniformly increases to the greatest depth all along
17 the rim of the optical zone to effect this global steepening
18 of the cornea. So that's how we attack every type of
19 refractive error with our 1 algorithm.

20 I'll talk briefly about our LASIK eye tracker.
21 Our tracker is designed such that it automatically acquires
22 the eye, and we track the pupil margin. So you'll see in a
23 short video segment in a minute that when the tracker is
24 engaged, it automatically makes a sweep across the eye,
25 locates that pupil margin, and locks on to it. It then

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1 optimizes several internal tracker performance parameters to
2 track that particular eye as best as possible. Given the
3 return signals we get for each eye, we optimize our tracking
4 internally.

5 We measure where the eye is 4,000 times every
6 second using an IR laser radar signal, and we have a closed-
7 loop tracking bandwidth of 100 hertz. We move internal
8 mirrors to compensate for the detected motion. Let me just
9 show you what that means with a graph.

10 This is a simple schematic showing time in the
11 horizontal axis and eye position of some reasonable
12 amplitude at the treatment plane. So the eye is shown
13 oscillating back and forth at 100 hertz with this yellow
14 curve here. And this is at 100 hertz, so it's very, very
15 rapid eye oscillation. So 40 times in each of those cycles,
16 those little blue dots indicate where we measured, where is
17 the eye, where is the eye, where is the eye. So we have 40
18 characterizations of this motion, and this green curve
19 indicates our actual closed-loop tracking. We follow it,
20 there's a slight lag here. For frequencies up to 100 hertz,
21 this lag is very, very negligible. So this is how the
22 tracker is rocking along following that eye motion, which is
23 very, very pronounced in this simplified example.

24 Those tracking characteristics allow us to do
25 very, very well during actual LASIK cases. This is actually

1 taken from one of Dr. McDonald's surgeries. This shows time
2 in the horizontal axis, and the vertical axis indicates eye
3 position. So these are 5-second steps going along here, and
4 these are 2 millimeter steps on the vertical axis here.

5 The red curve indicates lateral motion, side-to-
6 side motion of the eye. The yellow curve indicates up-down
7 motion of the eye. And you can see for this particular
8 surgery the eye took two pretty violent kicks off to the
9 left during the procedure, and the tracker followed it
10 without problem and the patient was well corrected.

11 This is a short video showing you how the tracker
12 actually works. This is our graphical user interface. This
13 screen shows the tracked image, and this shows the untracked
14 image. The tracker is not engaged yet, so you see eye
15 motion in both. The tracker's going to be engaged right
16 now. You can see it sweep across, locate the pupil margin,
17 and now this image will be stabilized. The eye will
18 continue to move, and so the lighting characteristics of the
19 eye will change. You'll see shadows. But here is what the
20 eye is really doing. This is the untracked image. This is
21 what the excimer laser actually sees. And so you can see
22 with fairly substantial eye movement, the eye is stabilized
23 for the treatment.

24 So the tracker performance in the current clinical
25 trials, we treated 360 eyes in the primary cohort, including

1 all types of hyperopic, mixed astigmatic, what have you,
2 corrections and we had no reported tracker problems during
3 any of these treatments.

4 That concludes my presentation.

5 CHAIRMAN McCULLEY: Is there an in-between on the
6 lights? Do we have to go all the way--no? Okay.

7 DR. McDONALD: Good morning. I'm Marguerite
8 McDonald. I'm the paid medical director of Autonomous
9 Technologies, and I'll be presenting the clinical results.

10 Our indications for use. LASIK treatment for the
11 reduction or elimination of hyperopia for up to +6.00
12 diopters a sphere, up to -6.00 diopters of cyl at the
13 spectacle plane, and subjects with documented stability of
14 refraction for the prior 12 months of less than or equal to
15 a half diopter for corrections up to +6.00 diopters in
16 subjects 21 years of age or older.

17 As far as our categorization of indication,
18 hyperopia with astigmatism defined as per our protocol as a
19 positive sphere in minus cylinder form. The data to be
20 presented includes all eyes in the primary cohort treated
21 for a spherical hyperopia and hyperopia with astigmatism.
22 The astigmats have been further stratified as requested by
23 the FDA into hyperopic astigmatic and mixed astigmatism.

24 Just to be very clear, we'll define our terms.
25 Mixed astigmatism is that in which the power in one meridian

1 is hyperopic and the opposite meridian is myopic. Here is
2 an example of mixed, +1.00, -3.00 at 180, and the optical
3 cross diagram here. Hyperopic astigmatism is that in which
4 the power in one or both meridians is hyperopic. Here is
5 simple hyperopic astigmatism, an example, +3.00, -3.00 at
6 180. Here is the optical cross for that example. And
7 compound hyperopic astigmatism, another example, +3.00, -
8 1.00 at 180, and the corresponding optical cross.

9 If we look at our accountability, here is the
10 percentage at 1, 3, and 6 months. We see for all eyes we
11 have 93 percent or greater accountability at each of these
12 three intervals.

13 Let me explain how our slides will be set up for
14 the rest of the presentation. Here we have all spheres and
15 all astigmats. Then FDA requested that we break this group
16 into hyperopic astigmats and mixed astigmats. You will
17 often see all eyes totaled on the far right.

18 Here you see that we had 360 eyes, 152 of which
19 were spheres, 208 of which were astigmats. Please note that
20 a 3 months we had 344 eyes, which was 96 percent of the
21 cohort, and at 6 months, we had 271 eyes, which represented
22 75 percent of the cohort.

23 We did attempt a monovision target in 12.5
24 percent, which was 45 eyes, but we did not include the mono
25 eyes and the UCVA analysis.

1 Here's enrollment by site. We had 14
2 investigators at six clinical sites in the continental U.S.,
3 and, really, the patients were well distributed with no
4 preponderance of patients from one particular site.

5 Let's look at the preop refractive parameters.
6 Since MRSE doesn't really reflect accurately the amount of
7 sphere and cyl that we treated in either cylinder group or
8 the spheres, either--in other words, with mixed astigmatism,
9 we had patients that were, say, +3.00, -6.00 at 180, which
10 is a preop MRSE of plano(?), and you would wonder why
11 someone would have refractive surgery in that case. So it
12 doesn't really reflect the refractive state. Therefore,
13 we're going to look at the sphere alone first; then we'll
14 look at cylinder alone for these patients. And here you see
15 the bins from 0 to 1, 1 to 2, all the way up to the 5 to 6
16 diopter preop sphere bin. And let me point out that we had
17 153 eyes that had between 3 and 6 diopters of preexisting
18 sphere and 88 eyes that had between 4 and 6.

19 Now we're going to look at cyl alone, the same
20 bins on the left, and see on the far right that between 3
21 and 6D, we had 53 eyes, and between 4 and 6D we had 33 eyes.

22 If we look at treatment parameters, for the
23 spherical hyperope, hyperopic astigmats, and the mixed
24 astigmats, by preop sphere, cyl, and spherical equivalent,
25 let's start over here first. Here you see that the mixed

1 astigmats had the lowest amount of preop sphere by a lot.
2 On the other hand, we did treat all the way up to +5.00 in
3 this group. The hyperopic astigmats had by far the most
4 sphere compared to the other two, and we treated up to +6.00
5 in this group and in the spherical hyperope. When we drop
6 down to the cyl line, we see the mixed astigmats had by far
7 the most cylinder to be treated. The next was hyperopic
8 astigmats, and, of course, the spherical hyperope had the
9 least. But we did treat up to 6D of cyl in this group and
10 this group.

11 When we come down to spherical equivalent, these
12 are very similar between the spherical hyperope and
13 hyperopic astigmats, and, of course, the mixed astigmats had
14 a spherical equivalent that averaged almost plano, with a
15 very different range. The treatments were based on
16 cycloplegic refractions for all patients.

17 Our surgical parameters. We had a 6 millimeter OZ
18 with a 1.5 millimeter blend zone, for a total ablation zone
19 of 9. The 3 to 9 o'clock positions were marked for
20 astigmatic treatments to compensate for cyclotorsion, and
21 the preop cylinder axis was scrutinized very carefully for
22 consistency. Our microkeratome specs included a flap
23 thickness of 160 microns and a minimum diameter of 8.5 for
24 the flap.

25 The protocol allowed us to go between 5 and 6

1 millimeters for the OZ, but everybody had a 6 millimeter OZ,
2 with the exception of two eyes. One had a 5.7 and the other
3 had a 5.9, and that was done to respect the rule regarding a
4 250-micron residual stroma.

5 As far as tracking under the flap, the eye
6 tracking system was used for all eyes in the LASIK study.
7 This was not an optional feature. All the eyes enrolled in
8 the study were able to be tracked. There was no loss of
9 track, not even for a moment, and no tracker-related
10 problems reported in the study.

11 Our postop regimen included a broad spectrum
12 antibiotic and, if the surgeon desired, steroid and NSAID
13 immediately postop. Steroid/antibiotic was given QID for 3
14 to 7 days, and no other medications were routinely
15 prescribed.

16 If we look at the demographics, for sphere
17 hyperopic astigmats, mixed, and all eyes, by gender, race,
18 age, and contact lens-wearing history, we see a few
19 interesting things. For all eyes, there was almost a 50/50
20 split for sex. It was predominantly a Caucasian population.
21 The mean age was 53, which is 10 to 15 years older than the
22 myopes that have been presented before the panel. And the
23 contact lens-wearing history is very different than myopic
24 patients as well, with more than half never having ever worn
25 a contact lens.

1 There are two other things of interest on this
2 slide. The mixed astigmats are very different
3 demographically in two respects: 75 percent of them were
4 male, and they were on average six years younger than the
5 whole cohort or the other two groups. So they were younger
6 and predominantly male.

7 If we look at our demographics according to age,
8 stratified by decade, we see that we had a remarkable number
9 of mature patients. We had 69 percent greater than or equal
10 to 50 years in age and 28 percent 60 or greater.

11 In regard to our presentation of our results, we
12 compared our results to the criteria stated in the guidance
13 document dated October 10, '96, for a range of myopia from 1
14 to 7D. The proposed guidance that was generated on
15 September 5, '97, involved recommendations for hyperopia
16 that were basically the same as for myopia. We'd like to
17 point out that our current study ranges up to 6D of
18 hyperopia and astigmatism, which is a very wide range, and
19 also that the draft guidance of '97 defined performance
20 criteria that were intended to describe an entire
21 population, not dioptric subsets of the population.

22 So let's talk about effectiveness first, starting
23 with uncorrected acuity. Here you see spheres and astigmats
24 at 3 and 6 months and the FDA guidance on the far right. If
25 we start here with the blue line, which represents UCVA of

1 20/20 or better uncorrected postop in eyes that had a preop
2 BSCVA of at least 20/20, we see that the results are stable
3 and there's very little difference between 3 and 6 months.
4 If we look at the 20/40 or better uncorrected gate, we see
5 that once again the results are stable between 3 and 6, and
6 we meet the guidance criteria.

7 This for the first time is where you will
8 encounter the bar graphs by indications. Spherical hyperope
9 are always blue, hyperopic astigmatism always yellow, and
10 mixed astigmats always red. You can see the results at 3
11 and 6 months are basically the same for each indication with
12 a tendency to improve in the mixed group in red.

13 If we look at UCVA 20/40 or better at 3 and 6
14 months, we meet or approximate the guidance for all
15 indications and at both intervals. We wanted to see what
16 percentage of our cases had a postop UCVA equal to or better
17 than the preop BSCVA, and we were pleased to see that this
18 ranged between 30 and 46 percent of our cases.

19 We also looked at near acuity. J3 is about the
20 size of the stock quotes in the back of the newspaper. It's
21 half the size of normal newspaper print, and you see preop
22 in green, 3 months in purple, and 6 months in white. For
23 our monovision target patients, we were very largely
24 successful and about half of our emmetropia target patients
25 saw this well at near also.

1 If you look at the accuracy of the MRSE, at 3
2 months and 6 months for spheres and all astigmats and the
3 guidance criteria on the far right, you see there is really
4 plus/minus half, plus/minus 1, plus/minus 2, very little
5 change between the 3-month data and the 6-month data, and we
6 meet the guidance criteria at both intervals.

7 If we look at the accuracy of MRSE by plus/minus a
8 half, according to indication, we see once again at 3 and 6
9 months we meet the guidance criteria for all indications and
10 both intervals.

11 And if we look at accuracy of MRSE plus/minus 1,
12 there is once again little change between 3 and 6 months,
13 and we meet the guidance for all indications and at both
14 time intervals.

15 Now let's look at the accuracy of the sphere
16 alone, for reasons we've just described, and here we see the
17 3- and 6-month data for all eyes, hyperopic, astigmatism,
18 and mixed astigmatism. We meet the guidance for all groups
19 at both intervals, even for the hyperopic astigmats, where
20 we had a very large amount of sphere to be corrected. We
21 meet the plus/minus half and plus/minus 1 guidance criteria.

22 If we look at the accuracy of cylinder, now mixed
23 astigmatism is the worst-case scenario because of the huge
24 amount of cyl that we were attempting to correct. We see
25 once again we meet the guidance for all groups and at both

1 intervals, even for this group with very high cyl,
2 plus/minus half, plus/minus 1. We successfully met those
3 criteria.

4 Let's look at mean MRSE over time. Here you see
5 for all eyes the 3-month cohort in red, 6 months in yellow,
6 9 months in blue, and you'll see that we are close to plano
7 and quite stable with time.

8 Now let's look at spherical hyperope alone. All
9 the lines are now superimposed. We're close to plano and
10 quite stable.

11 Here are the hyperopic astigmats: slight under-
12 correction, little residual hyperopia, but stable with time
13 also. And our mixed astigmats, this time a slight over-
14 correction into the myopic range, but also quite stable with
15 time.

16 Now let's look at stability of MRSE at the 6-month
17 cohort as defined by the agency as less than or equal to a 1
18 diopter change in MRSE between 1 to 3 months and 3 to 6
19 months. Here you see the spheres, all astigmats, hyperopic
20 astigmats, and mixed for those two time intervals. We meet
21 or approximate the 95 percent guidance criteria for all
22 indications and at both intervals.

23 Now let's look at the same thing but by mean
24 difference, as defined in diopters. So here, same four
25 categories, 1 to 3 months and 3 to 6 months. We have very

1 small changes per month in the MRSE. As a matter of fact,
2 the mean change per month is less than or equal to 0.07D
3 from 1 to 3, and less than 0.04D from 3 to 6 for all
4 indications.

5 If we look at stability of cylinder again and we
6 look at the change as defined by less than or equal to a
7 diopter for 1 to 3 or 3 to 6, we see once again we meet the
8 95 percent guidance criteria for all groups and at both time
9 intervals with a mean change per month less than 0.04D from
10 1 to 3 and less than 0.02D from 3 to 6 months.

11 Now we move on to vector analysis stratified in 1
12 diopter bins all the way up to the 5 to 6 diopter bin, the
13 number of patients, percent achieved, angle of error, and
14 index of success where 1.0 is no change and 0 is perfect
15 success, complete success. As you can see, with the higher
16 preop cyls we're getting better and better, because it's
17 much easier to identify the high cyl axis and magnitude. As
18 we all know, when the cyl is very small it's hard to find.

19 So, in summary for effectiveness, looking at UCVA,
20 MRSE, and stability from 1 to 3 and 3 to 6, we meet the
21 guidance criteria for all our spheres and astigmats. We
22 establish stability at 3 months and confirm it at 6 months
23 and show no real change at all from 3 to 6 months.

24 So let's move on to safety data for all eyes.
25 Here's the 3-month data, 6 months, and the guidance criteria

1 in those areas where guidance has addressed them.

2 Here you see loss of more than two lines of BSCVA,
3 0 and 0; loss of two lines, 5.1 to 4.1; basically 5 percent
4 or less at both intervals with a trend going down. BSCVA
5 worse than 20/40, 0 and 0; greater than 2D of induced cyl, 0
6 and 0; and BSCVA less than 20/25 for eyes that were 20/20 or
7 better preop, 2.8, similar but going down to 2.1 at 6
8 months.

9 If we look at the change in BSCVA for all eyes,
10 here you see at 3 and 6 months, purple and white, basically
11 there's no real change, with most people remaining the same,
12 once again no one with greater than two lines of loss.

13 If we look at loss of two lines of BSCVA by
14 indication--though, the performance criteria in the guidance
15 are not defined for this level of loss; it only addresses
16 greater than two lines--we can see that there's no
17 statistically significant difference between indications for
18 the loss of two lines of BSCVA at either 3 or 6 months.

19 Now, for eyes with the preop BSCVA of greater than
20 or equal to 20/20 who now have a postop BSCVA worse than
21 20/25, first let me point out that no eyes had BSCVA worse
22 than 20/32, and you can see that it's very similar between
23 the indications and at very low levels of occurrence at both
24 time intervals.

25 Let's move on to IOP. We looked at increase in

1 IOP for more than 5 millimeters of mercury above baseline,
2 greater than 10 millimeters of mercury above baseline, and
3 IOP at any time of greater than 20 or greater than or equal
4 to 20/25.

5 First, only the second and fourth item are
6 considered adverse reactions, and they occur within an
7 incidence of 0. And here, though at 1 month we had no one,
8 there was one eye at 1 week that had an IOP increase of
9 greater than 10 millimeters. This was reported as an AR,
10 but it had resolved by 1 months.

11 Endothelial cell density was studied in a subgroup
12 study of 144 eyes at 3 months and 132 eyes at 6 months, with
13 no clinically significant difference in the endothelial cell
14 density from preop.

15 Now let's go on to complications occurring at any
16 time in the primary cohort, and these are listed by the five
17 most common. You can see that they occurred at an incidence
18 of 3 percent or less for all of them, and there are no
19 performance limits in the guidance document for
20 complications, but these numbers are quite low. Other
21 complications occurred at a rate of 0.03 percent, which is
22 basically one eye, and they include the following things
23 that you see at the bottom of this slide.

24 If we look at complications by indication once
25 again, epithelium at the interface, sterile interface

1 inflammation, double or ghost images, and corneal edema at
2 present, either at 1 week or 1 month, these are the four
3 comps that occurred at greater than or equal to a 1 percent
4 incidence. There's no clinically significant difference
5 between indications in the complications from the primary
6 cohort.

7 If we go on to adverse reactions occurring at any
8 time, we broke them into two categories related to LASIK or
9 not related to the LASIK procedure. We had a 0.8 percent
10 incident of miscreated flaps, 0.8 percent of corneal
11 peripheral infiltrates, 0.3 percent of IOP increase greater
12 than 10 millimeters of mercury, and there was one
13 complication not related to LASIK. It was a myocardial
14 infarction occurring 1 month after the treatment in a man
15 who had a previous history of angioplasty. So we meet the
16 guidance criteria for less than 1 percent for each type and
17 less than 5 percent total.

18 If we look at the adverse reactions by indication
19 that we thought were related to LASIK--miscreated flaps,
20 sterile peripheral infiltrates, and IOP increases--we see
21 that the incidences of are very low and there's no
22 clinically relevant association between the indications and
23 the adverse reactions related to the LASIK procedure.

24 Now we'll talk about patient satisfaction. The
25 patient satisfaction data was analyzed at greater than or

1 equal to 3 months in an effort to include the data on all
2 the eyes in the cohort: 76 percent at 3 months, 25 percent
3 were tested at 3 months--76 percent at 6, 25 at 3, with no
4 6-month evaluation available for these people; 1.4 percent
5 had an unscheduled testing. That means they had no 3- or 6-
6 month evaluation that was available. And 3.6 percent were
7 not reported largely because they were retreated prior to
8 another self-eval; 1.4 percent of the total population had
9 no report at all.

10 The satisfaction data was resubmitted in response
11 to the medical reviewer's request in February and stratified
12 by visit, and it shows just marginal differences between the
13 3- and 6-month reports, with symptoms slowly abating over
14 time. We can make that available to the panel if they would
15 like to see it.

16 Now let's look at patient satisfaction, spheres,
17 all astigmats, hyperopic astigmats, and mixed, for 3 months
18 or later. We would like our patients to be extremely
19 satisfied or satisfied, and you see we have a fairly high
20 percentage, and it is pretty much the same in all four
21 categories.

22 As far as extremely unsatisfied, we have a 4.8
23 percent incidence in the mixed astigmatic group, but I'd
24 like to point out that the n is smallest in that group, and
25 these are generally younger patients who are overcorrected

1 who are now slightly myopic and are awaiting retreatment.

2 Now let's look at quality of vision. We would
3 like our patients to fall into one of the top three
4 categories: no change, better, or significantly better.

5 You can see that we have a very high percentage that fall
6 into that category with significantly worse, there was only
7 one eye, and it fell into the spherical group.

8 As far as the need for distance correction, we had
9 a very high percentage of patients in all four categories
10 who never wear a distance correction.

11 If we look at the symptoms that are significantly
12 worse, these symptoms are organized by the most common in
13 the whole cohort and in descending frequency. They occurred
14 in less than or equal to 5 percent of the population, the
15 most common, of course, being dryness, which is a recently
16 recognized problem occurring in all LASIK patients, lasting
17 for a few weeks or months, probably at least partially
18 neurotrophic in cause because of cutting all the corneal
19 nerves in the center of the cap when we generate the flap.

20 If we look at the next batch of symptoms in
21 descending order--so this is number 8 going down to number
22 14--in this second group all occurred at a very low
23 incidence, less than or equal to 2 percent in the whole
24 cohort.

25 Now let's move on to retreatments. The

1 retreatment rate was 11.4 percent, mostly for
2 undercorrection; 1.1 percent for induced cyl; and only 0.3
3 percent for overcorrection. At 3 months or later post-
4 treatment in these 14 eyes, we saw that 40 percent had a
5 UCVA of 20/20 or better if their preop BSCVA was 20/20 or
6 better; 75 percent had a UCVA of 20/25; 91.7 percent 20/40
7 or better. Here you see the percentages plus or minus a
8 half, plus or minus 1, and there was no loss of BSCVA of
9 greater than two lines or BSCVA worse than 20/40. So this
10 looks very much like primary data. The data was included in
11 the primary cohort until it was exited for retreatment.

12 So, in summary of effectiveness, our effectiveness
13 data for the LADARVision system meets all criteria for UCVA
14 and manifest refraction accuracy in the draft FDA guidance
15 document for hyperopia, including for all eyes and for each
16 indication, spherical hyperopia, hyperopia with astigmatism,
17 and mixed astigmatism.

18 It demonstrates refractive stability as defined in
19 the FDA guidance between 1 to 3 and confirmed between 3 and
20 6 months.

21 As far as safety, our safety data for the
22 LADARVision system meets all criteria in the draft FDA
23 guidance document for hyperopia, for loss of BSCVA, BSCVA
24 worse than 20/40, and induced cyl. It meets the criteria in
25 the FDA guidance for the incidence of adverse reactions by

1 type and overall, and demonstrates no other significant
2 safety issues regarding IOP and endothelial cell density.

3 Now, in the next few moments that I have left in
4 my time, I'd like to start to address some of the reviewers'
5 issues, and the rest will be addressed after Dr. Eydelman
6 speaks.

7 The refractive stability issue, is 3- to 6-month
8 data enough, or do we need 9-month data?

9 The file was submitted to the FDA based on
10 demonstration of refractive stability from 1 to 3 months as
11 per the guidance document. We had greater than or equal to
12 95 percent of the eyes with a change in MRSE of less than or
13 equal to a diopter between 1 and 3 and 3 to 6 months.
14 Additional updated data has been subsequently provided at 6
15 and 9 months in response to the reviewers' comments.

16 Let's look at the stability of the MRSE for the 9-
17 month consistent cohort which was provided February 21st.
18 We have more eyes now. We used to have 46. Now we have
19 131. You can see from 1 to 3, 3 to 6, and now 6 to 9 we
20 still meet the guidance criteria. The mean change in MRSE
21 is less than 0.03D per month for all eyes in the 9-month
22 cohort at each interval and less than or equal to a 0.4D per
23 month for each indication in the 9-month cohort. So we're
24 still meeting guidance.

25 Let's look at stability of cylinder. Now, it's

1 been suggested before many times that stability of cylinder
2 is the best way to look at the mixed astigmatic groups. Now
3 we're looking at 9-month consistent cohort mixed astigmats.
4 We had 20 at 9 months. We see that we are stable at these
5 three time intervals and we meet the guidance. The mean
6 change in cyl is less than 0.04D per month for mixed
7 astigmatism eyes in the 9-month cohort at each interval.

8 Now let's look at long-term stability, 1 to 9
9 months for this group, that's an 8-month interval, much
10 longer. We'll see that for all eyes and mixed astigmatism,
11 we meet guidance. The change of less than 0.02 diopters per
12 month for MRSE and cylinder is very small and shows no drift
13 to hyperopia.

14 Now, that consistent cohort is a subset of the
15 total 144-eye 9-month cohort, so we've shown stability of
16 MRSE over time, and now we'd like to demonstrate safety and
17 effectiveness are also stable right out to 9 months. In our
18 summary of effectiveness, here are all eyes that were
19 submitted in the PMA at 6 months. Here's our updated group;
20 the n goes up at our 6-month and our 9-month cohort. And
21 you can see now we have 40 percent of the group reporting
22 in, and we meet guidance. There is very little change
23 between the 6 and 6-month group, the expanded group, and the
24 6 and 9. So, if anything, there is great stability, perhaps
25 a tiny bit of improvement in some categories such as UCVA,

1 and we meet guidance.

2 In summary of safety, provided March 1st, you see
3 once again the 6-month cohort submitted in December, the
4 expanded 6-month cohort, and the 9-month cohort, and the
5 results are virtually identical in all the categories and
6 meet guidance.

7 Thank you.

8 DR. SALZ: Good morning. My name is Jim Salz, and
9 I'm from Los Angeles, and I'm glad I didn't see the Laker
10 game out here yesterday.

11 I'm to address one of the questions raised by the
12 reviewers, and that is: How high should we be allowed to go
13 in the treatment of hyperopia?

14 The FDA guidance document performance criteria for
15 myopia were defined for the range of correction of 0 to 7,
16 and there was really no specification for hyperopia. In the
17 past, guidance performance criteria have not been defined
18 and adopted by diopter basis. I've been involved in several
19 FDA excimer studies, and I was in the PRK(?) study for
20 myopia, even though it wasn't an FDA study, obviously. And
21 when you look at these reports and reports that are
22 published in the literature, as you go up in the higher
23 ranges, the efficacy definitely falls off. You're not going
24 to correct, you know, 90 percent of the -9.00 to -10.00
25 myopes or the patients that have 5 diopters of astigmatism

1 to the same efficacy that you do in the lower groups. And I
2 think this is particularly true in hyperopia. I think it's
3 just harder to steepen a cornea than it is to flatten a
4 cornea.

5 And I remember the discussions we had when we
6 talked about hyperopic PRK, and there was some concern about
7 allowing approval above +4.00, for example, because it
8 wasn't quite as effective. And after a lot of discussion,
9 it was decided that even though these patients may not get
10 an emmetropic result, they were in general quite happy with
11 their result because their hyperopia was dramatically
12 reduced. And that's certainly been my clinical experience
13 with these patients.

14 I personally love working on the hyperopic
15 patients because they don't bug you about being a minus half
16 like the myopic patients.

17 Next slide?

18 The data in the PMA are stratified by spherical
19 equivalent, and because we're using this minus cylinder
20 format, it includes a wide range of sphere and cylinder
21 combinations. For example, if you look at spherical
22 equivalent between 3 and about 4, this would include a +3, a
23 +3.5, +4, but it would also include a patient, for example,
24 that was a +6, -6, so obviously a much harder eye to work on
25 even though the spherical equivalent is +3. And when we

1 stratify it into these subgroups, the sample size in each
2 little cell can be a little bit smaller.

3 So the data has been stratified by sphere and
4 cylinder to better assess the effectiveness of treating the
5 full amount of hyperopic sphere and astigmatism.

6 Now, this slide shows you the influence of this
7 combination of sphere and cylinder. If we just looked at
8 preoperative sphere alone, regardless of cylinder, we had 54
9 eyes that were in this group that we're concerned about, the
10 +5 to +6, and another 34 eyes that were 4 to 5. That would
11 be combined. This could be a +3, -5, for example.

12 If you take the spherical equivalent, then this
13 number dramatically drops down, the +5 to 6 group is now 21
14 eyes because of the influence of the cylinder in these
15 patients.

16 Next slide?

17 Now, if we look at the uncorrected visual acuity
18 stratified by the sphere, you can see that the results are
19 obviously better in the lower corrections where they all
20 meet the guidance document of 85 percent, and in this
21 subgroup of patients, it's only 74 percent. But by 6 months
22 it rises almost to guidance levels of 81 percent. So this
23 group is obviously a harder group to work on.

24 Next slide?

25 If we take the accuracy to within a half a diopter

1 of the intended correction and you look at the
2 stratification, again, the guidance document calls for 50
3 percent, and at 3 months we certainly met that, even in
4 these higher ranges. And then there was some drop-off in
5 the patients that were above +4, and to me that's sort of to
6 be expected. Your reoperation rate in these cases, because
7 it's harder to steepen these corneas, is probably going to
8 be a little bit higher. But I think it's still a
9 respectable number.

10 Next slide?

11 If we then look at it by plus or minus a diopter
12 of accuracy, and the guidance document calls for 75 percent,
13 we pretty much reach that both at 3 and 6 months with the
14 exception of a couple of percentage points low in this high
15 group, the 5 to 6 range, but we still achieved 72 percent or
16 almost 73 percent of the eyes to within 1.

17 Next slide?

18 If we look at patient satisfaction in this group,
19 which I think is the bottom line here--are these people
20 pretty well satisfied, even if they may not have reached
21 emmetropia? So we're looking at all the eyes now between 5
22 and 6 diopter sphere, and 72 percent were either extremely
23 satisfied or satisfied with their outcome. And that
24 compares favorably to the group as a whole. If you take the
25 whole group of 307 eyes, that number is pretty much the

1 same, and those numbers pretty much are the same at 6
2 months.

3 Next slide?

4 The quality of vision is another way to assess
5 that, and I think this is particularly impressive in this
6 group of patients where we have some patients that had up to
7 4 or 5 diopters of astigmatism. Ninety-five percent of them
8 felt that their vision--the quality of their vision was
9 either significantly better, better, or at least no worse,
10 and those numbers held out and compared very favorably in
11 this high group that had spheres between +5 and 6 with the
12 group as a whole, 95 percent versus 90. And, again, high
13 numbers also at the 6-month gate.

14 Next slide?

15 The need for distance correction in these patients
16 that had the high spheres, still 90 percent of them
17 basically said that they were pretty much independent of
18 their glasses, again, comparing favorably to the group as a
19 whole, and the same thing held out at 6 months. So there's
20 very high incidence of patient satisfaction both in terms of
21 the quality of vision and their need for wearing corrective
22 lenses.

23 Next slide?

24 In terms of symptoms that are worse, if we look at
25 the data at 3 months and at 6 months and compare this high

1 group to the low group, you can see there's still a small
2 number of cases that have what we call side effects or
3 symptoms of their surgery. The one difference here in this
4 high group, 5 percent, only 2 patients, had more complaints
5 of halos that compared to only 2.5 percent basically, if you
6 group all the eyes together, and this pretty much held out
7 to 6 months. So I think that there's not much difference
8 subset--this subset of 5 to 6 from the group as whole.

9 Next?

10 Significantly worse symptoms in all the eyes, this
11 is a continuation of the side effects with decreasing
12 frequency as we go down, and, again, not too much difference
13 between the group that complained of double vision, for
14 example, in the 5 to 6, one eye compared to all the eyes.
15 There was a slight increase in this at 5 to 6 months, but
16 still only two eyes of about 40. But I think on the whole
17 these side effects are still low, and from my remembering
18 the data that's been presented in the past on particularly
19 myopic astigmatism, most of these numbers were much higher
20 in that subgroup of patients.

21 Next slide?

22 Loss of two lines of BSCVA for the entire cohort
23 at 3 and 6 months, there was no case of greater than a two-
24 line loss, and no eye ended up with the best corrected
25 visual acuity of less than 20/40.

1 Next slide?

2 If we stratify this, then, there was some concern
3 about safety in these higher corrections, and you can draw
4 your attention to these two groups of patients, the ones 1
5 to 2, the yellow bar, both at 3 and 6 months, where the
6 incidence of two-line losses--not greater than two lines,
7 but two-line losses was about 7 percent, and then, again,
8 the high group, 5 to 6, where it was also about 7 percent
9 here at 3 months, going up to 12 percent at 6 months.

10 If we then look at these seven eyes that were in
11 this 5 to 6 group on the next slide, we'll take a look at
12 all seven of these eyes. None of these eyes had a BSCVA
13 that was worse than 20/32 at 3 or 6 months, and that's
14 because some of these eyes started at, say, 20/15 or 20/20.
15 Two of these seven eyes have now been seen at 9 months, and
16 they're now back to within one line of their preop BSCVA.
17 Four of these eyes have been retreated for an under-
18 correction between 6 and 9 months, and now three of these
19 are within one line of their preop, both at 3 and 6 post-
20 treatment gate, and one was within two lines and ended up
21 with a BSCVA of 20/25, meaning that he probably started at
22 20/16, and one eye of these seven has not yet been seen and
23 is scheduled for retreatment.

24 Next?

25 When we look at the other group that I mentioned,

1 the 1 to 2 diopter range, there were six eyes in that group
2 that lost two lines. None were worse than 20/32. Three
3 were within one line by the time they reached the 9- or 12-
4 month gate. Three that were within two lines, two of these
5 were from 20/12 preop and 20/20 preop. And one was at 20/16
6 preop and now 20/25 at 3, 6, and 9 months. So I don't think
7 that even though these do have two-line losses that these
8 are really clinically significant losses. And,
9 interestingly, three of the eyes that were treated for
10 monovision fell into this group, and, again, when you're
11 doing monovision, you're trying to steepen their cornea a
12 little bit more, so it's more likely to have a side effect
13 like this.

14 Next slide?

15 If we then look at the range of correction of all
16 the eyes stratified by the amount of cylindrical correction,
17 this is the preop refractive parameters, and one of the
18 problems, of course, is there aren't a lot of people out
19 there that have 5 to 6 diopters of hyperopic astigmatism or,
20 for that matter, 4 to 5. So we do have a small group.
21 We're going to look at these results now stratified by the
22 cylinder correction.

23 If we look at this bar graph again that shows the
24 guidance document of 85 percent, even in these high
25 cylinders, for example, this group of 4 to 5, we have 92

1 percent and 100 percent by 6 months, or within what would
2 meet these criteria. And it does fall off a little bit in
3 this high cylinder correction. When you're trying to
4 correct 5 to 6 diopters of cylinder, it's not surprising to
5 me that the results in terms of 20/40 vision or better are
6 going to be a little bit less.

7 Next slide?

8 If we look at this, again, in terms of accuracy
9 within a half a diopter, most of the group falls into the 50
10 percent guideline. Even this high group out here, almost 50
11 percent, rising to 60 percent. This group in here from 3 to
12 4 for some reason is a little lower, but the cells on either
13 side of that look respectable, so we're not too concerned
14 about that group.

15 Next slide?

16 And the accuracy to within 1, again, except for
17 that one subgroup of patients that were between 3 and 4, we
18 can see that actually the 4 to 6 range did almost as well as
19 the low corrections in terms of accuracy to within a
20 diopter.

21 Next slide?

22 If we then look at the loss of two lines acuity
23 stratified by cylindrical correction, we can see again that
24 there is this slight peak in two-line loss at this 1 to 2
25 group at 3 months, also at 6 months, but a fairly low number

1 in this high group, only about 5 percent, with a greater
2 than two-line loss.

3 Next slide?

4 So in the full range of correction, there was very
5 high patient satisfaction across the board, even in the
6 higher corrections, the higher sphere and the higher
7 cylinder. There appeared to be no loss of the quality of
8 vision. There was no greater than two-line loss in any eye,
9 and no eye was worse than 20/40. So there don't appear to
10 be long-term safety concerns, and there were significant
11 improvements in both UCVA and manifest refractive spherical
12 equivalent.

13 Next slide?

14 The mixed astigmatism group is a particularly
15 interesting group, I think, because we really haven't had
16 much to offer these patients in the past.

17 Next slide?

18 The current surgical options for mixed astigmatism
19 are using double treatments with existing lasers, astigmatic
20 keratotomy alone, astigmatic keratotomy followed by LASIK.
21 For example, a patient with a +1, -2 could have an AK alone,
22 and I've done quite a few AKs for patients like this. It
23 would be my preference to use a laser because I think it's a
24 little bit more accurate.

25 Interestingly, lasers are being used to correct

1 these patients. The first time I heard of this, one of the
2 guys called me and said, "I just corrected a +4, -2
3 patient." And I said, "How'd you do that?" And he said,
4 "Well, I just used two cards." Well, that isn't even
5 approved yet. But it's being widely done out there, and I
6 don't think it's the optimal way to do it. It results in
7 more tissue removal, and it's not the proper algorithm for
8 correcting these cases.

9 Next slide?

10 Another example for pure hyperopic cylinder, for
11 example, of what's being done in the community, +6, -4, some
12 surgeons are doing an astigmatic keratotomy first, just to
13 bring this down into a range where they think they can
14 correct it. Then they'll do LASIK, correct the cylinder
15 first, and then correct the sphere. Once again, I don't
16 think it's an ideal way to do it.

17 Next slide?

18 Now, this mixed astigmatism group I think are some
19 of our best results. When you really look at these
20 patients, at 6 months 53 percent of them are 20/20, 75
21 percent are 20/25, and 93 percent are 20/40, well within the
22 guidance guideline of 85 percent. Similarly, the accuracy,
23 75 percent are within a half and 90 percent are within plus
24 or minus 1.

25 Next slide?

1 In terms of safety in this mixed astigmatism
2 group, again, I think it's quite respectable. Only 3.6
3 percent had a two-line loss, none greater than that. No
4 induced cylinder of greater than 2, and only, I think, one
5 eye, basically, or two eyes that ended up with less than
6 20/25.

7 Next slide?

8 We then looked at the vector analysis to see if
9 we--in this mixed astigmatism group, did we do as well, for
10 example, in the 5 to 6 group as we did in the 2 to 3 group.
11 And remember, the ideal number here, the lower the number,
12 the better the result. And I think we did very well in this
13 high range of patients, the ones with the high cylinder, up
14 to 4 to 6. And I'm hoping that that range will be included
15 because that's really some of our happiest patients.

16 Next slide?

17 The agency asked us to stratify the mixed
18 astigmatism group by the absolute difference between the
19 meridians. For example, a +350, -6 at 180, the spherical
20 meridian would be +350 and the opposite grid would be -250;
21 therefore, the difference would be 1 between these two
22 meridians. So we looked at that stratification, and I don't
23 think it really changes the outcomes much across the board.
24 It's still--all groups would still meet the guidance
25 guideline of 85 percent or greater, 20/40 or better.

1 Next slide?

2 And most of them would still be within the
3 guidance document of over 50 percent within plus or minus a
4 half in this mixed group, and, similarly, in the plus or
5 minus 1 group on the next slide, they would still meet the
6 guidance criteria.

7 Next slide?

8 So in this mixed astigmatism group, there was a
9 high level of effectiveness. There were no safety concerns,
10 no losses of greater than two lines, and I think a very high
11 accuracy of the cylinder corrections, maybe even exceeding
12 the normal hyperopic astigmats.

13 Patient satisfaction by visit. We were asked
14 about this. Marguerite has talked a little bit about this,
15 and we've provided additional data to stratify these results
16 by subsequent visits.

17 The 3- and 6-month cohort is similar to the
18 greater than three presented on all the eyes. These
19 symptoms do tend to abate over time, and we will follow,
20 obviously, the recommendations of the panel on how to handle
21 this in terms of the labeling. But this data has been
22 updated.

23 Thank you very much.

24 CHAIRMAN McCULLEY: Does that conclude sponsor's
25 presentation?

1 DR. McDONALD: Yes.

2 CHAIRMAN McCULLEY: Can we have the lights back
3 on?

4 Okay. This point, just so we keep protocol clear
5 on what we're doing, is the opportunity with sponsor
6 remaining at their table for panel members to ask questions
7 of the sponsor. At the conclusion of the question period,
8 which does not have a clock running on it, and hopefully
9 Parkinson isn't around--if you get the point--we will ask
10 questions until all of our questions have been answered that
11 we wish to pose.

12 The sponsor will then have an open forum for a
13 moment to make comments at the conclusion of our question
14 period before you're excused from the table.

15 At this point I'll open the floor for questions
16 from the panel. Marian?

17 DR. MACSAI: In your presentation, you talked
18 about making a 8.5 millimeter flap diameter, and your
19 treatment parameters are to a 9.0 millimeter optical zone.
20 Could you explain that?

21 DR. McDONALD: That was minimum required. In the
22 vast majority of cases, all but 1.9 percent, the
23 Hansitome(?) was used and a much bigger flap was generated.

24 DR. MACSAI: I don't understand how you can do a 9
25 millimeter treatment in an 8.5 millimeter flap, is the

1 question.

2 DR. McDONALD: That was generated as a criteria
3 for aborting, and we never had small enough flaps. Yes, if
4 you did have an exactly 8.5, you would lose a few shots in
5 the blend zone, only not the power cut. But as a matter of
6 fact, we had to measure all the flap diameters and they were
7 excellent.

8 DR. SALZ: Just a comment. There's an interesting
9 little software adaptation that they have. When you cut the
10 flap, there's an overlay that fits in the bed that shows you
11 what's going to be ablated, and you can tell whether it's
12 going to hit the hinge or not, for example, whether to
13 protect it and whether there's going to be a little overlap
14 on the epithelium.

15 In the cases we did, we used the Hansitome in all
16 of them, and we never really had a problem with flap
17 diameter, and we never had to cut back on the ablation. But
18 I guess there were two cases that they made it slightly
19 smaller.

20 CHAIRMAN McCULLEY: But as I understood it, those
21 were because of ablation depth concerns. And, Marian, as I
22 understand it, when you get out in that blend zone, there
23 are just a few hits, so they're hitting epithelium, so it's
24 no big deal. But the issue would be--the question would e
25 relative to your hinge, did you place--did you try

1 differentially to place the hinge? Of course, if you're
2 using the Hansitome, you can't do that. But relative to
3 your planned treatment?

4 DR. SALZ: Personally, we try to de-center the
5 hinge, you know, like we do in most hyperope, superiorally
6 to allow enough room. And in the rare case where we thought
7 the hinge was going to be hit by the laser, we took a little
8 strip of contact lens material which didn't interfere with
9 the tracking, and we'd just lay it on top of the hinge. But
10 it was usually minimal. I frankly don't think it would have
11 mattered if it hit the hinge, but we did do that in a couple
12 of cases. But the majority of cases at least that we did,
13 we didn't have to worry about it.

14 CHAIRMAN McCULLEY: So your tracker would not
15 allow the use of the standard hinge protectors that have a
16 handle?

17 DR. SALZ: I think it might interfere with the
18 tracker if you used a metal object. The contact lens system
19 worked pretty well. Actually, they're going to have a
20 software upgrade where it will block the pulses over the
21 hinge if you wanted it to, but that's not in the study.

22 CHAIRMAN McCULLEY: So there were no problems with
23 the tracker with the hinge? That had previously been an
24 issue, I think.

25 DR. SALZ: Right. There were no problems tracking

1 under a LASIK flap, correct.

2 CHAIRMAN McCULLEY: Arthur?

3 DR. BRADLEY: Arthur Bradley. The first question
4 for Jim Salz. Just a puzzle for me, when you look at the
5 satisfaction data, they're hovering just over 70 percent.
6 But then when we look at the percentage of patients who are
7 no longer having to wear a corrective lens, they're
8 considerable over 90 percent. And I'm just curious. I
9 presume the major reason patients are having this procedure
10 done is they don't want to wear their corrective lens.
11 Well, over 90 percent are achieving that goal, and I'm just
12 wondering why the satisfaction rates are so low. Is there
13 an explanation for that?

14 DR. SALZ: I mean, all I can say is that on the
15 whole the hyperopic patients to me are more satisfied than
16 myopic patients, even when they don't achieve 20/40 vision.

17 CHAIRMAN McCULLEY: But you had a 10 percent,
18 roughly, unsatisfied, which was a shocker to me. That's a
19 pretty high unsatisfaction rate. It was 9-point something.

20 DR. SALZ: Yes, 9.9. The ones that were extremely
21 unsatisfied were 1.2.

22 CHAIRMAN McCULLEY: Right, but the unsatisfied--
23 and, again, you know, the reality in practice, approaching a
24 10 percent unsatisfied or extremely unsatisfied really
25 surprised me. That to me is a very high level of

1 dissatisfaction.

2 DR. SALZ: Some of these eyes are undercorrected
3 and are going to be retreated or have been retreated and
4 aren't included.

5 CHAIRMAN McCULLEY: Well, as we get to it, I think
6 that's something that's going to need to be--

7 DR. SALZ: I mean, there was a 10 percent
8 incidence of reoperation in this which is--

9 CHAIRMAN McCULLEY: Which is acceptable.

10 DR. SALZ: --kind of normal.

11 CHAIRMAN McCULLEY: Yes.

12 DR. SALZ: So those people are obviously
13 unsatisfied.

14 CHAIRMAN McCULLEY: Well, you'd need to then break
15 out the reasons for unsatisfaction. What you're implying
16 we'd need to see that that indeed is reality. And 10
17 percent's respectable for the beginnings of a procedure--
18 retreatment rate.

19 Jan?

20 DR. JURKUS: I had a two-part question. Could you
21 please tell me how the eye that was corrected for monovision
22 was determined? And, also, if you have the information
23 about the average amount of dioptric difference between the
24 two eyes in monovision? And I guess the third part of that
25 question is: With contact lenses, we know that night

1 driving for patients with monovision can sometimes be
2 problematic. Have you been able to pick out if the
3 monovision patients were more dissatisfied with their night
4 vision than people that had both eyes corrected for
5 infinity?

6 DR. SALZ: I can just tell you about the ones we
7 do. First of all, we always demonstrate it to them with
8 contact lenses to make sure they're going to be happy with
9 it. And I would say at least half of them will wear a
10 distance correction for driving, but they're not completely
11 satisfied with their monovision if they don't have a
12 corrective lens for driving at night, and sometimes for
13 sports. But on the whole, I think those are among the
14 happiest patients we have.

15 If you take a hyperopic woman and allow her to put
16 her makeup on without glasses, then you have a happy camper.
17 And the difference is usually between 1 and 2 diopters,
18 would be my answer. I don't know if we have the number in
19 the whole study. But most of you, you know, if they're 60
20 or 65, will aim for maybe up to 2 if they tolerate that with
21 the contact lens. And if they're in their 40s or early 50s,
22 we'll usually do about 1. But we usually demonstrate it to
23 them and see what they like. If they don't like it all, we
24 just don't do it.

25 CHAIRMAN McCULLEY: Alice?

1 DR. MATOBA: This is a question regarding loss of
2 two lines of best corrected visual acuity, which I realize
3 was not in the FDA guidance document. But when you
4 subcategorize, the hyperopic astigmatic group had a loss of
5 two lines of best corrected visual acuity of 5.5 percent at
6 3 months and it went up to 6.9 percent at 6 months; whereas,
7 in the other categories, it was going down. And I wondered
8 if you have 9-month data on that sub--in that category.

9 CHAIRMAN McCULLEY: And I would say, having been
10 around when we did that guidance document, our intention was
11 two or more lines. It may have gotten written two, but it
12 was--I think the two-line or more was how we were thinking.

13 DR. MATOBA: Okay.

14 CHAIRMAN McCULLEY: Janice, you had another
15 question while they're looking.

16 DR. JURKUS: I guess it was part of a follow-up to
17 your answer. You had said that was your information. Did
18 most of the other investigators also prescribe over-glasses
19 to be worn when driving? And is there any information about
20 how often patients actually used those over-glasses? Since,
21 again, looking back at the contact lens world, there is
22 information that people will maybe use over-glasses for a
23 month or so and then tend to discard them.

24 DR. SALZ: I don't think we have any firm numbers
25 about that, because that wasn't part of our questionnaire.

1 The only study I've ever seen on monovision was Ken Wright
2 did one when he was at the Cleveland Clinic on myopic
3 patients. As far as I know, there's nothing in the
4 literature on hyperopic patients achieving monovision. But
5 I can't really answer that. My personal experience is about
6 half of them will wear glasses at night for driving.

7 CHAIRMAN McCULLEY: Dr. Sugar?

8 DR. SUGAR: Questions about tracking. Tracking,
9 my understanding, is dependent on the pupil, uses the pupil
10 at the guide for tracking. Is that correct, the pupil
11 margin?

12 DR. SALZ: Correct.

13 DR. SUGAR: There is a population, not in this
14 study, that has high cylinder, that is, people who are
15 albinotic tend to have high cylinders and would be
16 presumably candidates for this procedure. They're also
17 myopic, though.

18 Can you track a low-contrast iris?

19 DR. PETTIT: The trackers actually -- [microphone
20 off] -- so the visible appearance of the pupil is not really
21 a factor, and the infrared, the contrast from that pupil
22 margin is very, very high for all eyes. Does that answer
23 your question?

24 DR. SUGAR: I think so.

25 DR. SALZ: As an aside, those patients often have

1 a little nystagmus, too, and I've seen it track eyes with
2 nystagmus beautifully. We didn't do any in the study, but
3 it does track an eye like that.

4 DR. SUGAR: The other issue is dilating a pupil to
5 7 millimeters in someone who is a +6 diopter hyperope. You
6 only had one patient have a pressure elevation that was
7 significant, but they weren't measured at the time of the
8 procedure, presumably. They were measured at the first
9 postop visit. And I'm concerned about the risk of inducing
10 angle closure glaucoma in some of these patients, any
11 warning for that.

12 DR. McDONALD: We did preop gonioscopy in advance
13 of this.

14 DR. SALZ: And, of course, preop dilation is part
15 of their workup, so they had all been dilated before.

16 CHAIRMAN McCULLEY: You had a specific exclusion
17 criteria of occludable angles.

18 DR. SALZ: Correct.

19 CHAIRMAN McCULLEY: Do you have answer yet for Dr.
20 Matoba?

21 DR. SALZ: They don't have it right here. We can
22 look. Do you have it here somewhere?

23 They might be able to find it.

24 CHAIRMAN McCULLEY: Okay. Arthur?

25 DR. BRADLEY: This is a question for Dr. Pettit.

1 In your slide show, you gave us sort of the data on how you
2 arrange your ablation sites, the dot pattern, effectively,
3 and on the left side of each slide, you had a smooth version
4 of that indicating this is the overall sort of smooth change
5 that's occurring.

6 I just was curious about at what density you fail-
7 -at what low density you fail to get that smoothing effect.
8 I'm particularly concerned about the low hyperope and the
9 center of their optical zone where you have widely spaced
10 ablation points. Is there some concern there?

11 DR. PETTIT: Yes, I understand what you're saying,
12 and we don't have specific data on that.

13 If you look at the ablation profile caused by each
14 shot, each laser pulse, we talk about it as being less than
15 1 millimeter in diameter. But it's not a little top hat.
16 It's a little gaussian. So you have sort of a little very,
17 very shallow gaussian divot, if you will, taken out of the
18 eye, and overlapping a tiny fraction of shots, if they're
19 uniformly distributed, you get a general smoothing. I don't
20 have specific numbers on how smooth is it right in the
21 middle versus at the edge. Certainly its smoothness is
22 going to be the greatest where you have the highest shot
23 density. But even a relatively modest shot density--and I
24 don't know the number specifically, but for 1 diopter
25 treatment, certainly that smoothness would extend very well

1 into the middle.

2 DR. BRADLEY: I'd just be concerned that the most
3 important part of the optics, arguably--

4 DR. PETTIT: Sure.

5 DR. BRADLEY: --is the very center in these
6 hyperope--

7 DR. PETTIT: And the thing that helps us the most
8 there is the gaussian profile of the beam because that sort
9 of gets imprinted, and when you overlap the next one over,
10 very quickly, it gets pretty smooth.

11 DR. BRADLEY: I guess I'm a bit concerned that you
12 have not formally resolved that in the sense that--we're
13 mostly concerned here about the high end of the range, but
14 it seems to me there might be a problem at the low end of
15 that range, the hyperopic range.

16 DR. PETTIT: Well, we have done simulation studies
17 and plastic ablation studies and submitted that to the
18 agency previously about this. The other thing you need to
19 remember--and I'm sure you know this, but, you know, once
20 you put the LASIK flap down, any minor counter-wiggles, if
21 you will, get smoothed out by that flap or the epithelium,
22 in the case of PRK treatment.

23 DR. BRADLEY: I'll ask the question a slightly
24 different way. Have you seen any data to indicate that this
25 is a problem?

1 DR. PETTIT: No, we really haven't.

2 DR. BRADLEY: Okay.

3 DR. PETTIT: The low patients, I'm told, do the
4 best, subjectively.

5 CHAIRMAN McCULLEY: Dr. Matoba?

6 DR. MATOBA: Do you have any data on stability of
7 your retreatment patients beyond 3 months?

8 DR. McDONALD: No, we do not.

9 CHAIRMAN McCULLEY: Simple math clarification.
10 The guidance states stability at two measurements 3 months
11 apart, right? So one cannot state that you have reached
12 stability between 1 and 3 because at least my simple math is
13 that's 2 months, just for a point of clarification.

14 Other questions? I think, Marian, you were--

15 DR. MACSAI: I have two questions for the sponsor.
16 First, I'm a little bit confused by what I see as sort of an
17 inconsistency in the presentation between--you presented
18 satis--in the patient satisfaction and quality of vision
19 data, you present the stratified percentages of unsatisfied
20 and extremely unsatisfied patients, and that's where that 10
21 percent comes from. Yet in presenting patient symptoms,
22 such as dryness, fluctuation of vision, clear halos, you
23 have only presented significantly worse symptoms as opposed
24 to significant--as opposed to worse and significantly worse.
25 And I don't understand that.

1 DR. STEVENS: This is consistent with what has
2 been done in our prior labeling and our prior studies.
3 Significantly worse was considered to be where patients
4 seriously--

5 CHAIRMAN McCULLEY: Identify yourself.

6 DR. STEVENS: Christy Stevens, Autonomous
7 Technologies. Where patients felt that their symptoms
8 affected their quality of vision and their quality of life.

9 DR. MACSAI: Well, there--

10 CHAIRMAN McCULLEY: In some of the other things
11 that was significant, it was worse or significantly worse or
12 some such terms, and here you didn't stratify. It was just
13 if they considered it significant, it was worse--or
14 significantly worse at any degree, that they were lumped.

15 DR. STEVENS: Yes. The data is all in the
16 submission, however. It's all reported.

17 DR. MACSAI: Right. But you chose not to present
18 it, and in your thing you gave us, you say, in addition, the
19 data is more informative to patients when the significantly
20 worse symptoms are displayed separately from the worse
21 category. What is that statement based upon?

22 DR. STEVENS: That's just based on the labeling.
23 If all symptoms are included, worse, significantly worse, I
24 think patients need to know how many actually said it was
25 significantly worse versus worse.

1 DR. MACSAI: So then you do think it's important
2 that both worse and significantly worse be reported to the
3 patient? Or do you think that the patient doesn't need that
4 information?

5 DR. STEVENS: I think we were doing what was
6 consistent with what we'd done in the past, but we'd take
7 the panel's recommendation on that.

8 DR. MACSAI: Okay.

9 CHAIRMAN McCULLEY: Mike?

10 DR. GRIMMETT: Just a quick question on
11 retreatments. Is there any data regarding endothelial cell
12 counts after retreatment?

13 DR. STEVENS: Endothelial cell density was a
14 subgroup study and was only done at a few sites. Since we
15 had so few eyes in the retreatment, post-retreatment
16 category, we don't have any data on post-retreatment. We
17 checked and we didn't go below 250 even after retreatment.

18 CHAIRMAN McCULLEY: Leo?

19 DR. MAGUIRE: One of the things that's striking is
20 that you have a high loss of best corrected vision in the
21 pool group at 1 month, and there's no presentation of data
22 at 1 week. You know, the trend is to do bilateral
23 simultaneous surgery on patients, and the average time
24 missed from work for LASIK for myopia is two-thirds of a
25 day. And here we have people who appear to have at least

1 some loss of visual acuity over--even out at a month, and we
2 also have no stability data from 1 week to 1 month to
3 determine what actually goes on in their life during that
4 initial postoperative period. That might not be an FDA
5 criteria, but I think the consumer person here and the
6 people in the labeling component who are having this
7 procedure done would want to know what to expect in terms of
8 stability and optical quality and induced astigmatism during
9 the first postoperative month.

10 Do you want to comment on that, why that data was
11 not presented here?

12 DR. STEVENS: We presented the 3- and 6-month data
13 because those were the two time points of stability.

14 DR. MAGUIRE: Well, I'm not getting to stability.
15 I'm getting to optical quality and best--you have--we'll get
16 to stability in a second. First I'm talking about measures
17 of optical quality. At one 1 month, you have in your pooled
18 data 11 percent of the people have a greater than or equal
19 to two-line loss of visual acuity. What's the data at 1
20 week?

21 DR. STEVENS: I don't have that readily available,
22 but--

23 DR. MAGUIRE: You did measure it, though. It's in
24 the criteria. Can you get us that data?

25 DR. STEVENS: Yes.

1 DR. MAGUIRE: Okay. And the other thing is--
2 that's important because people have to know, certainly as
3 consumers ahead of time, what they can expect to experience
4 in their life during the first month postop, both in terms
5 of the quality of their vision and how it will affect their
6 functional performance, especially in people who have high
7 visual needs in their job. And the other thing is the
8 surgeon who's doing it needs to know in terms of what they
9 can expect in having to manage patients and in terms of
10 optical quality and stability during that very--a month is a
11 long time.

12 CHAIRMAN McCULLEY: I understand Leo's point, and
13 I think it's a very important one from a consumer standpoint
14 to have it in the labeling and for us to know what the
15 informed consent should be. I think that's a very good
16 point.

17 DR. MAGUIRE: A second comment on stability.
18 There's a statement that the refraction stabilizes by 3
19 months. I'm assuming you're basing that based on
20 measurements taken 1 day postop, 1 week postop, 1 month
21 postop, and 3 months postop, and yet there's no provision of
22 stability data between 1 week, which would seem a reasonable
23 time to show it, and 3 months, which is a 3-month period and
24 would be interesting to see.

25 Do you have that information?

1 DR. STEVENS: I don't have it readily available,
2 no.

3 DR. MAGUIRE: Okay. I think the panel should
4 consider having that information available before we make
5 any judgments on stability.

6 The second thing is, when you group stability into
7 the 1- and 3-month period and then 3- to 6-month period and
8 say within those periods there's no change of 1 diopter,
9 what you really want to do is you want to know what
10 happens from a reasonable postop period, let's say 1 week
11 and 9 months. And you don't want to just know the mean,
12 which Marguerite has shown to be very good, but you also
13 want to know the variability within the group. Not
14 everybody is stable, not everybody is unstable. But, again,
15 what can the individual patient expect? And when we look at
16 the data that's presented by Marguerite, there's the mean
17 change in dioptric power 0.12 or 0.02, or whatever it was,
18 but the standard deviation is a half a diopter. And looking
19 through some of these tables in here, at some of the
20 individual patients who have 1-week, 1-month, and 6-month
21 data, there's significant variation among a significant
22 minority, maybe 30 or 40 percent, where you see diopter--at
23 least 1.87--shifts in the mean spherical equivalent over
24 that period of time.

25 I wonder if you could comment on that.

1 CHAIRMAN McCULLEY: Well, there are two stability
2 measures, right? There's one that 95 percent of patients
3 will not change by more than a diopter at two measurements 3
4 months apart. And then the other is the mean that is a half
5 diopter, I believe, that is a looser, not so firmly, I
6 guess, into the document, but I know that we've always
7 talked about it and looked at that. But the percentage of
8 people that change significantly comes into that 95 percent
9 people at a 3-month interval must not show more than diopter
10 of change, and a diopter was picked rather than a half
11 diopter for individuals because of the accuracy of repeated
12 refractions.

13 DR. MAGUIRE: But you could change--you could
14 change an undefined amount between 1 week and 1 month. You
15 could change less than a diopter between 1 month and 3
16 months and then change it less than a diopter again for a
17 cumulative increase and not have it show up in the stability
18 data the way it's displayed here.

19 CHAIRMAN McCULLEY: Right. I think--

20 DR. MAGUIRE: And I think the conclusions made
21 from the methods by which Autonomous has presented this are
22 a little bit misleading. You can't make the conclusion--

23 CHAIRMAN McCULLEY: Well, there are two points
24 here. One is stability over time in terms of the efficacy
25 and stability. The other is if there are changes early on

1 that can affect the individual's life and lifestyle, then
2 that needs to be known for purposes of product labeling and
3 for informing the patient.

4 DR. ROSENTHAL: This is Dr. Rosenthal. I think,
5 Dr. Maguire, you have to realize that there has been a
6 consistent pattern on which we have requested issues
7 relating to stability, and the company has followed that
8 consistent pattern, which we've now done for 2 or 3 years,
9 which has been ingrained in the gestalt of refractive
10 surgical evaluation. And we appreciate the comments about
11 early on. We can certainly address those issues early on in
12 the labeling if the panel feels they are important. But I
13 don't think it is fair to criticize the company for not
14 doing it, because it has never been requested before.

15 DR. MAGUIRE: Okay. That is fine.

16 CHAIRMAN McCULLEY: Often, we have seen 1-week
17 data on the graphs that have been presented. I think it is
18 important for product labeling.

19 DR. STEVENS: Your question on the 1-week to 3-
20 month stability, 91 percent of the eyes had a change of less
21 than or equal to 1 diopter spherical equivalent between 1
22 week and 3 months, with a mean difference of 0.14 diopters,
23 standard deviation 0.59, and a 95 percent confidence
24 interval of 0.08 to 0.21.

25 CHAIRMAN McCULLEY: Ms. Newman? Into the mike.

1 MS. NEWMAN: I'd like you to translate this--

2 CHAIRMAN McCULLEY: Microphone.

3 MS. NEWMAN: Your patient information booklet, I'd
4 like it to be more user-friendly, though, and consumer-
5 friendly, because a lot of what the physician brought up was
6 true, is that you have in here 1, I think, to 3 weeks. And
7 you have things such as they are going to probably have
8 blurred vision and all that. What does that mean to them?
9 They are not going to work? I mean, you have some
10 significant problems here the first week after surgery, and
11 I think you need to just be practical because you don't say
12 anything in the physician booklet about that. How do they
13 counsel the patient? Okay? And then you go right away to 1
14 to 6 months. It may become stable after a few weeks. Well,
15 how could you conceptualize? I mean, you know, you have an
16 age group there in their 50s. Are they going to fall? Are
17 they going to have problems with visual--and I think you
18 need to say that. And like you say, depending on their
19 work, what does that mean to them?

20 Then on this previous page, you have down these
21 wonderful charts, but, again, as a consumer, I don't know if
22 they know what the heck that means, the percentage. Does
23 that mean I'm going to wear glasses? Am I going to have to
24 wear contacts? What do these charts mean? Actually, these
25 may be better in the physician booklet, but I don't really

1 feel that your booklet is that user-friendly as far as a
2 consumer.

3 CHAIRMAN McCULLEY: Marian?

4 DR. MACSAI: I'd like to sort of echo those
5 comments. In the communication between the sponsor and the
6 panel, repeatedly, mention has been made that stratified
7 data is not required for approval, and though that may, in
8 fact--I mean, it was even said in the slides. Though that
9 may be the fact, the point is when you are sitting with a
10 patient face to face and they're saying I have 5 diopters a
11 cyl, am I going to be--do I have a 99 percent chance of
12 being 20/20 or better? The physician needs to have that
13 data to give an accurate answer to the patient.

14 So when we repeatedly ask for stratification, it
15 is for that reason. Regardless of what it says in the
16 document, we are talking about patients and patient care.

17 DR. ROSENTHAL: I think the issue the company was
18 trying to make, Dr. Macsai, was that for approval,
19 stratification was not taken into account, that, in fact, it
20 was the range. Certainly the agency has requested and the
21 company has--every company has provided stratified results.

22 DR. MACSAI: Correct.

23 DR. ROSENTHAL: I think the issue is for this
24 company over a certain diopter there was a query whether or
25 not it was satisfactory enough for approval and, therefore,

1 it had to be stratified in order to evaluate that.

2 DR. MACSAI: Correct, and historically that data
3 has been used to set what's approved, the range of approval,
4 even for this sponsor in previous applications.

5 DR. ROSENTHAL: No question that is also true.
6 But the sponsor had their approach, and--

7 DR. MACSAI: Right.

8 DR. ROSENTHAL: --the agency has its approach.
9 But we do look at stratified data, and in some instances, we
10 do cut them off regardless of what the range is, if the
11 range is unapprovable, if we feel that at extremes of those
12 ranges the results are so problematic that it would not
13 warrant approval.

14 CHAIRMAN McCULLEY: Janice?

15 DR. JURKUS: In the patient information booklet,
16 when you are describing to the patient the percentage of
17 patients who were satisfied or extremely satisfied, it was a
18 nice high number. Then in there it went on to state that
19 the number that was quoted for the unsatisfied patients were
20 only those that were significantly worse. I think for
21 consistency's sake, if you're going to include the
22 information of satisfied and extremely satisfied, you should
23 have unsatisfied and extremely unsatisfied or worse and
24 extremely worse, so that the patient will get a better and
25 more total understanding of what to expect.

1 CHAIRMAN McCULLEY: Well, you presented that in
2 your data, and presumably that will be in the patient
3 information brochure.

4 MS. NEWMAN: No, they didn't present it.

5 CHAIRMAN McCULLEY: It's not in there now? The
6 unsatisfied is not--well, that's inappropriate.

7 MS. NEWMAN: But, again, be careful. I deal in
8 other areas where--

9 MS. THORNTON: Ms. Newman, could you please use
10 the microphone?

11 MS. NEWMAN: I'm sorry. I would like you to put
12 those into words they understand. Again, dealing with
13 incontinence, people don't want to be dry. Fifty percent is
14 great for me, so that could be what we define as very
15 significantly unsatisfied.

16 You know, you need to conceptualize that and what
17 does that mean to an individual depending on their vision,
18 and I really want to stress that because reading this to me
19 it's just so unfriendly and, you know, and then, again, like
20 you say, the physician can counsel the patient. Put it into
21 terminology that's understandable because I think, you know,
22 if you see some kind of statistic with significantly worse,
23 I don't know what that means. You know what I mean? Either
24 put it in words of what that means--and you must have that
25 data in your studies. Similar to what you were saying about

1 when I see patients, it's X, they like this, you have to
2 have that data in there in some kind of terminology that can
3 be user-friendly.

4 CHAIRMAN McCULLEY: Other questions? Dr. Pulido?

5 DR. PULIDO: For the 5 to 6 diopter cylinder--

6 MS. THORNTON: Can you use the microphone?

7 DR. PULIDO: Jose Pulido. For the 5 to 6 diopter
8 cylinder, data for UCVA and MRSE falls below the FDA
9 guidelines, yet you feel that it's sufficiently good enough
10 to warrant approval. Why is that?

11 DR. SALZ: Well, I think it's like other
12 procedures. The efficacy is going to fall off in the higher
13 ranges. It doesn't mean the patient will be necessarily
14 unsatisfied. They're just more likely to need a subsequent
15 treatment. And when I counsel them, I tell them, look,
16 you've got 5.5 diopters of astigmatism. It's very difficult
17 to correct that. You're probably not going to be in this
18 group that gets 90 percent efficacy.

19 And I think it's just addressed in the labeling,
20 as it has been in other applications, that that's a
21 difficult group to treat. I don't think that necessarily
22 means we shouldn't try to treat them because they're going
23 to go out and try other things that may be even more risky.

24 DR. PULIDO: Thank you.

25 CHAIRMAN McCULLEY: Dr. Rosenthal?

1 DR. ROSENTHAL: Dr. Pulido, there are two
2 approaches the agency has taken. The first is to not allow
3 them to treat beyond a certain point. The approved
4 indication stops at a point, and they can't treat beyond it.
5 The other approach has been to approve it to a certain point
6 but allow the treatment with a flagged warning saying the
7 results aren't so good, but--or we have no results at all
8 because they are in the extremes. If we feel there are
9 safety issues, we will stop it. If we feel there are no
10 safety issues, we will allow it with what we call a flagged
11 lockout.

12 So it has been a bit of a controversy within, you
13 know, the area but we have adopted that, and so, therefore,
14 the approval may stop at a certain point, but it will still
15 be allowed with a flagged information.

16 CHAIRMAN McCULLEY: Dr. Pulido?

17 DR. PULIDO: Thank you for the clarification, Dr.
18 Rosenthal. What are the results of the retreatments for
19 that group from 5 to 6?

20 DR. STEVENS: I haven't pulled out the 5 to 6
21 eyes. The majority of the retreatments did have a high
22 sphere or high cylinder, if you look at them, but we only
23 had 14 eyes at 3 months in the submission. So I haven't
24 pulled out the 5 to 6 of those 14 eyes 3 months later.

25 DR. PULIDO: Okay. So it would be a very small

1 number, so we really don't know how they would do even with
2 retreatment. Am I correct to say that?

3 DR. STEVENS: We can look at it, but we haven't--

4 CHAIRMAN McCULLEY: The other thing, just
5 institutional memory is that the FDA has asked the panel in
6 the past to consider adjusting specifically the guidance
7 document for the higher ranges of myopia and for hyperopia,
8 and the panel, I think, in its good sense said we don't want
9 to do that because we don't have numbers. What we want to
10 do is use the guidance document as it is and apply reason
11 and some flexibility when looking at the higher ranges of
12 correction and not to apply it as a policy but as a guidance
13 rather than trying to create numbers for the higher ranges
14 of myopia and specifically for hyperopia.

15 Dr. Macsai?

16 DR. MACSAI: I have another question for the
17 sponsor, and Dr. Salz highlighted in his presentation
18 something that I found in my review, which is, when you
19 stratify the accuracy of the MRSE by cylinder, the group
20 that's minus 3 to minus 3.99 doesn't do well. There is only
21 40 or 38.5 percent of those patients that are plus or minus
22 a half and 60 percent that are plus or minus 1.

23 How does the sponsor account for this? Because
24 this is unique to the minus 3 to minus 3.99 group. It's not
25 in any of the other groups. What happened to these people?

1 What percent were retreated? What was their satisfaction?
2 And what were their symptoms?

3 DR. STEVENS: I don't have all the data you asked
4 for, but there's a couple of patients in that group that
5 were mixed astigmats below sphere, like a plus half with
6 minus 3 cyl in both eyes. It ended up slightly
7 overcorrected, so they ended up, you know, minus 1, minus--
8 with some cylinder, and so that's why their MRSE is slightly
9 out there, so the overcorrected mixed astigmatic eyes.

10 DR. MACSAI: Well, a couple patients doesn't
11 account for 38 percent when you are talking about the n
12 which you have set. The sponsor set the n. So I'm not
13 comfortable with that. That's more than a labeling issue to
14 me unless you can clarify why this happened to this group.

15 DR. SALZ: I would just say that my comfort level
16 with it is the ones on either side of that--

17 DR. MACSAI: Right, but not that group.

18 DR. SALZ: --did all right, and we can't explain
19 that.

20 DR. STEVENS: There's only 13 eyes from 3 to 3.99,
21 so it is a couple of patients that drops that down
22 significantly.

23 DR. SALZ: The two patients make a 10 percent
24 difference.

25 DR. MACSAI: Well, it's thirty--it's 20 plus 12.

1 That's 32. Unless I--oh, I see. Only 12 are out to 6
2 months. Okay.

3 CHAIRMAN McCULLEY: This is one of the problems
4 that--

5 DR. MACSAI: So perhaps you don't have enough
6 long-term data or the n is too small? Is that what you're
7 saying?

8 DR. STEVENS: Right.

9 DR. MACSAI: So we need to study more patients?

10 CHAIRMAN McCULLEY: Well, they only had--if I
11 remember your presentation, you only have 75 percent
12 accountability at 6 months, right?

13 DR. STEVENS: No, 75 percent of the eyes
14 available, 93 percent accountability--

15 CHAIRMAN McCULLEY: Yes, okay, data on 75 percent
16 of the eyes.

17 DR. STEVENS: Yes.

18 CHAIRMAN McCULLEY: Which is, you know, another
19 issue about--you know, that we'll discuss later.

20 But when you start playing with percentages and
21 means when the n is varying and the n isn't very big from
22 one time point to another, it creates a real problem, and it
23 can confuse the issues tremendously. And we had that
24 problem with the data. We just have to stay aware that the
25 n is not consistent.

1 Dr. Maguire?

2 DR. MAGUIRE: Could someone in the presenting
3 group comment on the high incidence of induced astigmatism
4 in the normal hyperope group, the hyperope that had no
5 astigmatic correction? Tab A.2, page 46. At least as I
6 read that chart, in the group that had no astigmatic
7 correction, 7.5 percent of the group had an induced
8 refractive astigmatism between 1 and 1.5 diopters and then
9 another 19.5 percent had an induced astigmatism of between
10 0.5 and 0.75 for a total of 25 percent induced cylinder over
11 0.5. And 7.5, 1 to 1.5, that's up there for someone who
12 came in with nothing before.

13 I didn't see that discussed in your presentation.
14 I was just wondering if you'd like to comment on that.

15 DR. STEVENS: It's all included in the submission
16 as you see it. We just presented material based on the
17 draft guidance document.

18 DR. MAGUIRE: Okay. So--

19 CHAIRMAN McCULLEY: Whoa, whoa--

20 DR. MAGUIRE: --you have no comment on it? Is
21 that what I'm hearing?

22 CHAIRMAN McCULLEY: I don't find that response a
23 very acceptable response.

24 DR. STEVENS: I'm not saying it's not appropriate.
25 I'm just saying that it's in the submission. We just didn't