

ah

AH

1

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OPHTHALMIC DEVICES PANEL

Ninety-third Meeting

OPEN SESSION

Thursday, October 22, 1998

1:47 p.m.

Lincoln Ballroom  
Silver Spring Holiday Inn  
Silver Spring, Maryland

C O N T E N T S

AGENDA ITEM:	PAGE
<b>Call to Order</b>	
James P. McCulley, M.D., Chair	3
<b>Introductory Remarks</b>	
Sara M. Thornton, Executive Secretary	3
<b>Open Public Hearing</b>	8
<b>Presentation</b>	
Guy M. Kezirian, M.D.	
CRS Clinical Research, Inc.	
SurgiVision Consultants, Inc.	9
<b>Year 2000 Date Problem Update</b>	
Thomas B. Shope, Ph.D.	
Center for Devices & Radiologic Health	27
<b>Division Update</b>	
A. Ralph Rosenthal, M.D.	
Director, Division of Ophthalmic Devices	44
<b>Branch Update</b>	
James F. Saviola, O.D.	
Chief, Vitreoretinal & Extraocular Devices Branch	45
<b>Branch Update</b>	
Morris Waxler, Ph.D.	
Chief, Diagnostic & Surgical Devices Branch	51
<b>Introduction of Issues for Excimer Laser Guidance Discussion</b>	
Morris Waxler, Ph.D. & Malvina B. Eydelman, M.D.	54
<b>Panel Discussion</b>	
Report of Michael W. Belin, M.D.	56
Report of Mark A. Bullimore, McOptom, Ph.D.	92
Report of Walter J. Stark, M.D.	114
<b>Adjournment</b>	153

1                   P R O C E E D I N G S

2                   **Call to Order**

3                   DR. McCULLEY: I'd like to call to order the  
4 Ophthalmic Devices Panel Open Session, and at this point  
5 would like to turn the floor to Sara Thornton for  
6 introductory remarks.

7                   Sara?

8                   **Introductory Remarks**

9                   MS. THORNTON: Good morning. I'd like to welcome  
10 the FDA staff, the public and the panel, and the panel back  
11 to the table, hopefully, after a very good lunch.

12                   Before I proceed with today's agenda, I have a few  
13 short announcements. Messages for panel members and FDA  
14 participants, information or special needs should be  
15 directed through Ms. Ann Marie Williams or Ms. Theresa  
16 Lewis, who will be available at the registration table just  
17 outside the room.

18                   I'd like to ask all meeting participants, panel  
19 and public to please identify yourselves before speaking  
20 clearly into the microphone. We have turned the microphones  
21 up a bit since this morning's session, and I hope that will  
22 help, but we still need your identification for the  
23 transcriber.

24                   At this time, I'd like to extend a special welcome  
25 and introduce to the public three panel participants who

1 have recently joined the Ophthalmic Devices Advisory  
2 Committee and are panel participants for the first time.

3           On my left, Dr. Michael Grimmett, panel  
4 consultant, is Associate Professor of Ophthalmology at the  
5 Bascom Palmer Eye Institute of the University of Miami  
6 School of Medicine in Miami, Florida. He is a specialist in  
7 corneal and external disease and a recognized expert on the  
8 medical/legal/ethical issues associated with refractive  
9 surgery.

10           Also on my left, Dr. Alice Matoba is Associate  
11 Professor of Ophthalmology at the Baylor College of Medicine  
12 in Houston, Texas and a specialist in corneal and external  
13 disease and anterior segment surgery. She is recognized  
14 internationally for her presentations on many clinical  
15 aspects of infectious corneal diseases, contact lenses,  
16 intraocular lenses and corneal transplants.

17           On my right, Dr. Ming Wang is an Assistant  
18 Professor of Ophthalmology and Visual Sciences at Vanderbilt  
19 University School of Medicine in Nashville, Tennessee and a  
20 corneal and external disease specialist. He holds a Ph.D.  
21 in physical chemistry and has completed postdoctoral  
22 fellowships in laser spectroscopy, molecular biology and  
23 ocular genetics. He is currently researching laser  
24 refractive surgery and the molecular biology of corneal  
25 wound healing.

1 To continue, will the remaining panel members  
2 please introduce themselves, beginning with Dr. Frederick  
3 Ferris?

4 DR. FERRIS: Dr. Frederick Ferris, Director,  
5 Division of Biometry and Epidemiology, National Eye  
6 Institute, NIH.

7 DR. RUBIN: Gary Rubin, Associate Professor of  
8 Ophthalmology, Wilmer Eye Institute, Baltimore.

9 DR. BELIN: Michael Belin, Professor of  
10 Ophthalmology, Albany Medical College.

11 DR. PULIDO: Jose Pulido, Professor and Head,  
12 Department of Ophthalmology, University of Illinois.

13 DR. HIGGINBOTHAM: Eve Higginbotham, Professor and  
14 Chair, Department of Ophthalmology, University of Maryland  
15 in Baltimore.

16 DR. McCULLEY: Jim McCulley, Professor and  
17 Chairman, Department of Ophthalmology, University of Texas  
18 Southwestern Medical School.

19 DR. SUGAR: Joel Sugar, Professor of  
20 Ophthalmology, University of Illinois at Chicago.

21 DR. BULLIMORE: Mark Bullimore, the number one-  
22 ranked Ohio State University College of Optometry.

23 DR. JURKUS: Jan Jurkus, Professor of Optometry,  
24 Illinois college of Optometry in Chicago.

25 DR. MACSAI: Marian Macsai, Professor of

1 Ophthalmology, West Virginia University School of Medicine.

2 DR. STARK: Walter Stark, Professor of  
3 Ophthalmology, Wilmer Eye Institute, Johns Hopkins.

4 DR. BRADLEY: Arthur Bradley, Associate Professor  
5 of Optometry and Visual Science, Indiana University.

6 DR. VAN METER: Woodford Van Meter, private  
7 practice of ophthalmology in Lexington, Kentucky.

8 MS. MORRIS: Lynn Morris, Communications  
9 Coordinator at University of California San Francisco, and I  
10 am a consumer member of the panel.

11 DR. YAROSS: Marcia Yaross, Director, Worldwide  
12 Regulatory Affairs at Alergan in Irvine, California, an  
13 industry representative to the panel.

14 MS. THORNTON: Thank you.

15 Also with us at the panel today is Dr. Ralph  
16 Rosenthal, who is Director of the Division of Ophthalmic  
17 Devices at FDA.

18 I'd like to also note that the allotted hour for  
19 the open public hearing presentation, because this is a 2-  
20 day meeting, has been split into two 30-minute periods to be  
21 held at the beginning of each day of the open session.

22 During the meeting today and also tomorrow, there  
23 will be opportunities for public comment interspersed with  
24 the panel discussion on particular issues that were just  
25 discussed, and the Chair, Dr. McCulley, will recognize those

1 who wish to comment and will determine the duration of the  
2 comment period based on the time that we have for the full  
3 panel discussion and the number of people who wish to speak.

4 I have one more thing. I'd like to read the  
5 Conflict of Interest Statement for today's meeting. The  
6 following announcement address conflict of interest issues  
7 associated with this meeting and is made part of the record  
8 to preclude even the appearance of impropriety. To  
9 determine if any conflict existed, the agency reviewed the  
10 submitted agenda and all financial interests reported by  
11 committee participants. The conflict of interest statutes  
12 prohibit Special Government Employees from participating in  
13 matters that could affect their or their employers'  
14 financial interests. However, the agency has determined  
15 that participation of certain members and consultants, the  
16 need for whose services outweigh the potential conflict of  
17 interest involved, is in the best interest of the  
18 Government.

19 A waiver is on file for Dr. Michael Belin for his  
20 financial interest in firms at issue that could potentially  
21 be affected by the Committee's deliberations. The waiver  
22 allows this individual to participate fully in today's  
23 deliberations. A copy of this waiver may be obtained from  
24 the agency's Freedom of Information Office, Room 12A-25 of  
25 the Parklawn Building.

1           We would like to not for the record that the  
2 agency took into consideration other matters regarding Drs.  
3 Arthur Bradley, Frederick Ferris, Michael Grimmatt and  
4 Janice Jurkus. These panelists reported past and current  
5 involvements in firms at issue but in matters not related to  
6 today's agenda. Since their interests are unrelated, the  
7 agency has determined that they may participate in the  
8 Committee's deliberations.

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

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

19           Thank you, Dr. McCulley. I'll now turn the  
20 meeting over to you to open the open public hearing portion.

21                           **Open Public Hearing**

22           DR. McCULLEY: We'll now begin the open public  
23 hearing. We have only one scheduled speaker. I'll remind  
24 both Dr. Kezirian as well as others who wish to speak that  
25 you have 10 minutes for presentation. The only person or

1 people who may query the presenter are panel members and  
2 consultants at the conclusion of the presentation.

3 I'd like to ask Dr. Guy Kezirian to come forward  
4 and remind everyone that in your packet that was at your  
5 place today, there is a handout from Dr. Kezirian.

6 **Presentation of Guy M. Kezirian, M.D.**

7 **CRS Clinical Research, Inc.**

8 **SurgiVision Consultants, Inc.**

9 DR. KEZIRIAN: Thank you, Dr. McCulley. It's a  
10 great pleasure to be here before the panel once again and to  
11 have a chance to share what we have learned about LASIK in  
12 the CRS LASIK studies and to, hopefully, allow you to  
13 consider those comments in your design of your new  
14 guidelines.

15 [Slide.]

16 We in the CRS LASIK study have administered  
17 several protocols now, both IDE and non-IDE studies, and we  
18 have about 250 physician participants in our overall  
19 project.

20 The entire project is funded by physicians--we  
21 haven't taken industry money for the studies--and it is done  
22 as an independent study of these physicians, however, with  
23 open enrollment. We allow anyone who is interested as a  
24 physician to enroll.

25 We are in the process of applying for PMA

1 relabeling of the existing approvals for the lasers using  
2 our data with both the Summit and the VISX companies.

3 [Slide.]

4 One of the things that has been unusual about our  
5 study is that we have this moniker that Morris Waxler and  
6 Charles Caseberg [ph.] coined called the "PRIDE" format.  
7 The concept behind the "practical reality" IDE is to match  
8 the study with practice conventions so that examinations,  
9 examination internals and examination content, procedures  
10 and the entire design of the protocol attempt to match the  
11 standard of care practice of the procedure in the ophthalmic  
12 community.

13 As a result, we feel that we are gathering  
14 information that will reflect the actual performance of the  
15 laser and of the procedure after any approval is reached  
16 with it.

17 [Slide.]

18 These are some of the elements that make up the  
19 PRIDE format that make it a little bit different than some  
20 of the conventional IDEs, and we can say without  
21 qualification that we feel that the process has been very  
22 effective and allowed us to gather a large amount of  
23 information which we feel directly reflects on how the  
24 procedure actually performs.

25 [Slide.]

1           Through that, I want to share with you some of our  
2 conclusions about LASIK and implore that you consider some  
3 of these as you create your guidelines.

4           We recognize that LASIK presents some increased  
5 risks and some decreased risks compared to PRK, and I have  
6 attempted to itemize them here, and I'd like to go through  
7 some of these to enumerate just how frequent they are and  
8 whether or not it's something that needs to be considered as  
9 a separate reportable event.

10           We found that operative complications are unusual,  
11 that despite the press surrounding keratomes, that keratome-  
12 related events or any events result in less than half a  
13 percent of surgery being aborted.

14           We also find, having carefully tracked this, that  
15 reported intraoperative complications related to the  
16 keratome did not correlate with loss of best corrected  
17 acuity. And while that at first seems like it wouldn't make  
18 sense, it is a part of the protocol design that if any event  
19 occurs with the keratome, surgery is abandoned, the eye is  
20 allowed to heal, and surgery is reattempted at 3 months or  
21 more later on. We have found that that has been very  
22 effective in preventing intraoperative keratoma  
23 complications from causing acuity loss.

24           However, we found that there is a significant  
25 number of postoperative complications related to the

1 keratome, and they are listed, with debris, interface  
2 epithelium, flap wrinkling, stain, et cetera, and they occur  
3 at an incidence of about one percent. However, we have  
4 noticed that most of these are not associated with loss of  
5 best corrected acuity and that, with treatment, they do just  
6 as well as the eyes that did not have the complications.

7           It is a significant event as we talk about  
8 designing guidelines, because to this date, the guidelines  
9 require that those events be qualified as adverse events,  
10 and I don't think that that is appropriate.

11           We were concerned, greatly concerned, at the  
12 beginning of the study about ectasia, especially in the  
13 higher refractive ranges of treatment, and we have had no  
14 ectasias occur. We have over 20,000 cases in our database  
15 at this point, and we have zero ectasias.

16           Now, that again is not magic. It occurs because  
17 we have depth limits. We do not permit surgery to occur  
18 within 250 microns of the endothelium, and we think that  
19 that appears to be sufficient to prevent the occurrence of  
20 ectasia.

21           [Slide.]

22           We have noticed that some of the things which  
23 plagued PRK do not exist in LASIK. We have not seen any  
24 haze in any eye beyond trace. We are finding that stability  
25 occurs very quickly in myopic LASIK. Depending on how you

1 juggle the FDA definition of stability, that's either by one  
2 month or 3 months, depending on whether you take the second  
3 observation as being the beginning of stability or the  
4 first. In my written remarks, I expand quite a bit on those  
5 comments, and I hope you'll have a chance to look at them.

6           Glare and halos occur after LASIK. However, when  
7 you compare them against preoperative levels, they are less  
8 than the preoperative level with glasses or contacts. We  
9 found that very interesting, because in the current  
10 guidelines and in the current PMA charts, it asks for  
11 postoperative glare, halos and other patient symptoms and  
12 doesn't ask you to compare them to preoperative levels. And  
13 I think that taking them out of context unfairly suggests  
14 that the procedure is causing those symptoms, when we find  
15 it actually improves them compared with preoperative levels.

16           [Slide.]

17           So in the creation of your guidelines, I would  
18 suggest that we have learned enough about LASIK to allow us  
19 to eliminate some of the more tedious aspects of doing IDEs  
20 and that, since the procedure will be performed with a given  
21 standard of care after it is released, that we attempt to  
22 make those findings that we make during the IDE process  
23 correlate with those observations which are made by surgeons  
24 after approval. It allows us to make one-to-one comparisons  
25 and not have to extrapolate and translate data that occur

1 under different conditions.

2           We have found that 6-month follow-up gives us  
3 useful information, well enough to establish stability and  
4 well enough to evaluate for adverse events and  
5 complications, and we think that 6 months is enough for  
6 myopic LASIK procedures in terms of follow-up, and we think  
7 that the basic observations that are made clinically are  
8 very descriptive about events that occur. We have not had a  
9 hidden group reported to us of problems with patients that  
10 haven't been reflected in vision refraction, best corrected  
11 acuity or the patient questionnaire. Those tests are  
12 sufficiently sensitive to pick up complications when they  
13 occur.

14           I would suggest--and this has been a great  
15 discussion in some of the Eye Care Technology Forum  
16 meetings--that we try to come up with a common denominator  
17 for safety and that in these procedures, not exclusively but  
18 for the most part, best corrected acuity loss is sufficient;  
19 that keratome flap lifts, keratome epithelial ingrowth that  
20 is cleaned, and other things that occur should not be rated  
21 as adverse events if they are not accompanied by best  
22 corrected acuity loss; and that aborted surgery per se  
23 should not be listed as a complication unless it is  
24 accompanied by a loss of best corrected acuity. We have  
25 found that it hasn't been.

1 [Slide.]

2 I would further suggest that the other events  
3 which occur related to keratomes be tracked sort of as a  
4 sub-study within the IDE. If studies allow the use of  
5 multiple keratomes, track it; look at safety issues and rank  
6 them by keratomes. But don't limit studies to one keratome,  
7 because you aren't going to find out how that device or that  
8 procedure works when it is released and is done with  
9 multiple keratomes. And if you track it as an independent  
10 variable, you can look at the keratome as a separate issue.

11 [Slide.]

12 And for efficacy, at least with myopic results, 6  
13 months seem to be adequate, and that we don't know the  
14 answer yet with hyperopia, and our own studies are going out  
15 at least to a year and some of them to two, because we feel  
16 like hyperopia is more likely to experience regression and  
17 refractive change. Myopia, we have not experienced that,  
18 and I think that that might be considered as you design your  
19 new guidelines.

20 [Slide.]

21 Much more extensive written remarks are available  
22 at the front desk, and I have passed them out to the panel  
23 members, if you care to venture deeper into some of our  
24 experiences and learn more about what we have done.

25 I can also be contacted on line or at CRS, and I

1 would welcome any inquiries that you have.

2 Thanks very much.

3 DR. McCULLEY: Thank you very much.

4 I would commend to each of you to take the  
5 opportunity to read the handout that Dr. Kezirian has  
6 provided to us. I had the opportunity to read it and found  
7 it interesting and useful.

8 Are there questions or comments from the panel for  
9 Dr. Kezirian?

10 Dr. Stark?

11 DR. STARK: Congratulations on such large numbers.  
12 I would like to know how you ensure that every patient who  
13 is entered into the study that should be--for example, is  
14 there a chance that some of the investigators could exclude  
15 complications right off the bat? And then, what is your  
16 follow-up rate on these patients? Which patients would fall  
17 into the 12-month period, and what percentage of them have  
18 follow-up?

19 DR. KEZIRIAN: The protocol establishes entry  
20 guidelines just like any protocol, and we have the criteria  
21 specified. They do exclude at this point prior corneal  
22 surgery and that sort of thing, so is our experience  
23 different from how the procedure might perform when it is  
24 being done without those filters, bringing people in--  
25 perhaps. But I think that that's not inconsistent with what

1 you will be establishing in the guidelines, because the  
2 guidelines do the same thing. We know, for example, that  
3 surface PRK is done in eyes which weren't studied under the  
4 protocols as a practice of medicine issue. I don't see a  
5 conflict there; I think that's okay.

6           The way that we report is on line, and we use the  
7 Datasite system. Once a patient does in, he can't be  
8 removed or changed out of the protocol. And we require the  
9 reporting of the eyes to be done within 48 hours of the  
10 event, whether that was surgery or postoperative exam. So  
11 we have a good count as to how many patients are enrolled.

12           We have, as you noticed, a lot of different  
13 protocols, and the IDE protocols are the ones that we police  
14 the most and the ones I have good data on follow-up with,  
15 and we have, again, a practical reality way of dealing with  
16 this, in that if an investigator becomes noncompliant in  
17 follow-up, we don't allow him to submit any more eyes.

18           So with that very simple carrot and stick, we are  
19 able to keep compliance pretty high, and we run--and any  
20 snapshot, of course is different--we just finished our  
21 approved range IDE, and we are just finishing some of our  
22 other IDEs, and depending on exactly what protocol, it  
23 ranges between 75 and 90 percent. So it depends--it's a  
24 complicated question--but overall, we feel we have been  
25 pretty successful in getting the follow-up in.

1 DR. McCULLEY: Dr. Wang?

2 DR. WANG: As an elective procedure, it is  
3 extremely important in my opinion to be safe and also to  
4 ensure patient satisfaction. I agree with you the best  
5 corrected visual acuity is one of the most important  
6 parameters. You did say "seldom." Do you know, among the  
7 20,000 patients, what percentage have actually lost best  
8 corrected visual acuity?

9 DR. KEZIRIAN: I wish I had brought my recent  
10 annual report with me so I could give you the exact number.  
11 But I know that when you stratify the results according to  
12 preoperative refractive error, and when you consider 2 lines  
13 or greater as being outside the safety zone, we have shown  
14 safety through 12 D with both lasers. We have had less than  
15 the FDA limits on best corrected acuity loss through 12 D.

16 DR. McCULLEY: Dr. Matoba?

17 DR. MATOBA: Did you have any postoperative  
18 infections?

19 DR. KEZIRIAN: We haven't had any postoperative  
20 infections occur yet. Now that you've said it, one will  
21 happen tomorrow, but we haven't had any yet.

22 DR. McCULLEY: Other questions?

23 [No response.]

24 DR. McCULLEY: I'd like to clarify a point with  
25 the FDA, if I may. The charge to us for this afternoon's

1 session is to address the three issues that you have posed  
2 to us with the specific preassignments as opening  
3 presentations, and not for us to review the entire guidance  
4 document.

5 DR. ROSENTHAL: That's correct. We'd like you to  
6 emphasize the three. I think Morris has a fourth one.  
7 There is actually a fourth one on stability. But that  
8 doesn't mean you can't make comments on issues that you  
9 think are of particular import.

10 DR. McCULLEY: Well, the approach is--we can  
11 either target, or if the charge to us--I don't think any of  
12 us came prepared to redo the entire guidance document, and I  
13 think that's almost a dangerous route to go down. So we can  
14 make comments for you if you want.

15 DR. ROSENTHAL: Well, if somebody feels  
16 particularly strong about an issue in the guidance document,  
17 we'd certainly like to hear it.

18 DR. McCULLEY: Okay. Dr. Kezirian has brought up  
19 a number of points that my expectation would be that we  
20 would not address or necessarily discuss; that you can take  
21 his comments under advisement--

22 DR. ROSENTHAL: That's right.

23 DR. McCULLEY: --but the panel is not prepared to  
24 or expected to either agree or disagree with many of the  
25 other issues in the guidance document that could be

1 addressed; that we are going to concentrate on the three,  
2 and if there is a fourth, then a fourth.

3 DR. ROSENTHAL: That's correct.

4 DR. STARK: Jim, could I ask one more question?

5 DR. McCULLEY: Yes. Dr. Stark.

6 DR. STARK: I remember the presentation by Drs.  
7 Waring and Stulting on their submission, and the  
8 presentation at scientific meetings indicated about a 10  
9 percent epithelial ingrowth rate, and some of that might  
10 have been talked about innocuous. Could you give us what is  
11 reported as the epithelial ingrowth rate for the 20,000 or  
12 however many cases you are following, and also, is there any  
13 independent validating of results, review of charts, or is  
14 it just all left up to the investigator? For example, if  
15 someone had some complications and decided not to report  
16 them, are we assured that you are getting the complications  
17 reported?

18 DR. KEZIRIAN: Two separate questions. I can't  
19 report on the 20,000 for epithelial ingrowth. I can report  
20 on 5, because those are the ones that are done in the IDE  
21 studies which we just recently crunched. And the epithelial  
22 ingrowth rate is nowhere near 10 percent. It is in the 2  
23 percent range.

24 There is the distinction that we make in  
25 epithelial ingrowth that is something requiring treatment or

1 not; sometimes, there is a small nest [ph.] that the surgeon  
2 will decide to just leave, and that incidence is about 2  
3 percent, that requires some sort of treatment or  
4 intervention.

5 I would emphasize, though, that those events do  
6 not necessarily result in loss of vision, and in fact, they  
7 are infrequently associated with loss of vision; that they  
8 can be successfully treated.

9 As far as the independent validation of data goes,  
10 the answer is yes and no. The "yes" part is that the  
11 investigators are required to maintain a separate file from  
12 the chart of the source documents and the report forms, and  
13 that we have on five or six different occasions sent out  
14 lists looking for the source forms to be submitted as well  
15 as the report documents, so that we then take and compare  
16 those two. So we do have that going on. We do visit all  
17 the sites at the beginning of the study and intermittently  
18 during the study, and we have done some of that.

19 But I think what is most encouraging for us and  
20 most reassuring to us is that we hold meetings several times  
21 a year, and complications are a major focus of the meeting,  
22 and we almost have a zeal to present complications because  
23 they often spark very interesting discussions. I don't  
24 think people are trying to hide complications, but have we  
25 gone and checked every chart--the answer is on.

1 DR. McCULLEY: Let me remind everyone that we have  
2 limited time, so the longer the question, the longer the  
3 answer, and the fewer questions and issues we are going to  
4 be able to address.

5 Dr. Bradley?

6 DR. BRADLEY: Your Item 4 in the written documents  
7 that you provided is essentially the issue of cycloplegic  
8 refractions, and you raise the issue of the dilated pupil  
9 that comes along with the cycloplegia, and you are  
10 suggesting that these evaluations should be done with an  
11 artificial pupil of maybe 3.5 mm placed in front of the eye.

12 I think that given the number of reported  
13 subjective complications from patients occurring primarily  
14 at night and the one report that I know of from Germany of  
15 patients--in that case, I think it was PRK--who were failing  
16 their night driving tests and the optical expectation of  
17 halos with a large pupil and the obvious implications for  
18 retinal image quality, I think it would be important to keep  
19 on top of the impact of a large pupil which is going to  
20 occur under low light conditions with these patients and not  
21 simply record the result that you obtained with the small  
22 pupil, because that would in essence be the best case  
23 scenario. The worst case scenario, which is often driving  
24 patients, the one that we are most concerned about, should  
25 also be recorded.

1           So I think it is worth taking data with a large  
2 pupil.

3           DR. KEZIRIAN: Well, I agree and disagree. I  
4 think that the subject patient question captures some of  
5 that information, and if what you are looking for is large  
6 pupil vision, I think that should be tracked separately and  
7 shouldn't be called a cycloplegic exam, because you are  
8 introducing a lot of things when you dilate the pupil.

9           So if you want to have a nonrefractive exam where  
10 you do cycloplegic for some reason, I think a mask is  
11 appropriate; and if you want to capture information about  
12 what happens when you dilate the pupil, that's another exam.  
13 it's not inappropriate to do--I don't think it has to be  
14 done in everyone.

15           Dr. Rubin has presented a very nice exam to look  
16 at post-refractive surgery, post-excimer procedure vision,  
17 and it includes low-contrast measurements of vision in dim  
18 light and bright conditions, and I think that it might be  
19 appropriate to require some of those measurements to be  
20 made, but I don't think those are going to be so variable on  
21 the patient. I do think those are going to be features that  
22 correlate best with the prophyometry of the ablation. They  
23 are going to be laser characteristics. Those are going to  
24 be ablation characteristics that determine that, and that  
25 could probably be measured just as well in lab as it could

1 be in a patient--and probably more reliably.

2           So I think that less is more when it comes to some  
3 of these clinical studies. If you have a patient  
4 requirement be cyclopleged at 3 months, half of them won't  
5 show up because they don't want to do that.

6           DR. McCULLEY: Part of my motivation before in  
7 saying what I did--Dr. Kezirian has basically gone through  
8 and made comment on many, many things in the guidance  
9 document, and I don't think that it should be our role now  
10 to either agree or disagree or try to argue those points.  
11 We don't have the time. There are things in here that I  
12 agree with, there are things that I disagree with. And I  
13 think what I would say to the FDA is don't take our silence  
14 as being concurrence with everything that is in his very  
15 fine document. And I don't think our role here is to try to  
16 reach consensus relative to all of the issues that Dr.  
17 Kezirian brought up. It is food for thought, and I would  
18 hope you would take it that way, and I think that's what we  
19 should take it as--not necessarily to reach consensus on the  
20 many, many, many items that he brought up in his document.

21           DR. KEZIRIAN: And that's the spirit in which it  
22 was offered--

23           DR. McCULLEY: And we appreciate it.

24           DR. KEZIRIAN: --and I am happy to give you the  
25 last word and step down at this point.

1 Thank you very much for your attention.

2 DR. McCULLEY: Well, I think there were two other  
3 questions that I had seen coming--and I took it as that, and  
4 my comments were not necessarily directed at you.

5 Dr. Belin?

6 DR. BELIN: Mine is a comment, not a question. I  
7 don't expect a response, and I'll just give you a differing  
8 opinion that I disagree that flap complications or aborted  
9 surgery is not a complication.

10 I think an aborted surgery is an ultimate  
11 complication. It may not be an adverse event in that it  
12 doesn't lead eventually to patient morbidity, but it is a  
13 complication.

14 DR. KEZIRIAN: I'll agree with that.

15 DR. BELIN; I think that if we were to look at a  
16 laser, and if the laser failed 20 percent of the time when  
17 we expected to do surgery, that would not be acceptable.

18 If you go in with the intention of completing  
19 surgery, and you do not complete it, that's a complication.

20 DR. McCULLEY: Dr. Ferris?

21 DR. FERRIS: Two comments. One, my view is that a  
22 patient views another surgery as an adverse event even if  
23 the vision is still good at the end of the day, because to  
24 him or her, that means an additional procedure.

25 The second thing is just a question or a point of

1 clarification. You don't like the term "best spectacle  
2 corrected visual acuity." In epidemiologic studies, we have  
3 differentiated "best spectacle corrected" from "spectacle  
4 corrected" to try to make it clear that it wasn't the  
5 glasses you were walking around with but in fact the best  
6 corrected. Spectacle correction to me means what you are  
7 walking around with--you come into the office and read the  
8 chart with the glasses that you own, which may or may not be  
9 appropriate. I think that's the reason for the difference  
10 in those two terms.

11 If there is something else, I think you should  
12 make it clear, because it's not clear to me.

13 DR. McCULLEY: Other questions, comments?

14 [No response.]

15 DR. McCULLEY: Thank you very much. We'll now let  
16 you escape.

17 DR. KEZIRIAN: Thank you very much.

18 DR. McCULLEY: Are there any others in the  
19 audience who wish to come to the podium to make comments?

20 [No response.]

21 DR. McCULLEY: Seeing none, we will now close the  
22 open session.

23 The next item on our agenda is a Year 2000 Date  
24 Problem Update, to be presented by Dr. Thomas Shope.

25 **Year 2000 Date Problem Update**

1                   Thomas B. Shope, Ph.D.

2                   Center for Devices and Radiological Health

3                   DR. SHOPE: The purpose of my coming before the  
4 panel today is to have a brief discussion with you about an  
5 issue that we have been paying a little bit of attention to  
6 at the Center and within FDA. It is more of an opportunity  
7 to air the issue a bit, perhaps provide some impetus or  
8 incentive to get some feedback from the Committee members or  
9 the audience regarding the potential problem of the  
10 interaction of the year 2000 date problem, which I am sure  
11 many of you have heard about.

12                   In fact, National Year 2000 Awareness Week started  
13 the 19th, so this is an appropriate week to brief the  
14 Committee.

15                   [Slide.]

16                   I'll give you the specifics of this in a little  
17 bit, but it has been asked if this is a device problem, is  
18 it a health care problem, or is it really doomsday, and  
19 there are varying opinions on that depending on which of the  
20 internet sites you go to and browse through.

21                   a physician at the Department of Veterans Affairs  
22 coined "the millennium bug syndrome" to talk about the  
23 problems he expected with some of their medical devices.  
24 But the idea here is that there are computerized products,  
25 and there is a potential for problems if we don't pay

1 attention and take the appropriate precautions.

2 [Slide.]

3 This is from a couple of years ago when this  
4 problem was just beginning to make the press, and I have a  
5 couple of ads here that sort of make the point for me.

6 [Slide.]

7 One of the real considerations here is what  
8 happens with your personal computer, your PC that has the  
9 old BIOS [ph.] in it, or the real-time clock that really  
10 didn't think far enough ahead to worry about the year 2000  
11 or beyond in terms of keeping dates internal to the  
12 computer. And since many medical devices either interface  
13 with or are powered by or controlled by PCs, there is a  
14 potential problem here.

15 I have listed just a couple of examples of devices  
16 where this might be the case--it's not that there are  
17 problems with these, but there is a potential here if the  
18 design wasn't done in the proper fashion.

19 An example is a pacemaker controller. This is not  
20 the pacemaker. Nobody with a pacemaker is going to have a  
21 condition at the stroke of midnight. But if the physician  
22 who manages that patient has an older-version pacemaker  
23 controller, the next time he visits the office, there may be  
24 some difficulty in either reprogramming or monitoring that  
25 patient. So it is important that people take note of the

1 kind of equipment they have and what the year 2000 impact  
2 is.

3           Other examples of the kind of problems we could  
4 anticipate--and again, it is a real situation where it  
5 depends on how the design was done and whether the  
6 manufacturer used the 2-digit date format and carried that  
7 through, or if it was done with a 4-digit date. So it is  
8 not an automatic thing that there are going to be problems  
9 with these products, and in fact, from what we are gathering  
10 from discussions with manufacturers and the data that we are  
11 getting, most of the problems with medical devices are going  
12 to be rather minor in nature, and I'll talk a little bit  
13 about that in a minute.

14           Systems that communicate with other devices, where  
15 there is data interchange, and those data records perhaps  
16 have dates associated with them, and there could be a  
17 problem with date format, is an area where particular  
18 attention should probably be paid. Clinical laboratory  
19 systems is probably a good example of that.

20           [Slide.]

21           Another little quote that sort of puts in context  
22 the size of the problem, I kind of liked when I was trying  
23 to convince the FDA staff that we needed to pay a little  
24 attention to this was one of the ads from a company that was  
25 trying to solicit business to help people solve their year

1 2000 problems was making the point that this was the biggest  
2 initiative with regard to computers in history. And of  
3 course, you have also heard that there is a deadline that  
4 can't slip, like most computers projects; there is a fixed  
5 time by which all of this has to be done. And this  
6 particular ad was focusing on the concern about health care  
7 facilities and their data processing and recordkeeping  
8 systems, the big, stand-alone computers that keep track of  
9 billing and records and those kinds of things and that there  
10 was potential, at least, for significant problems there.

11 Many hospitals are actively working to deal with  
12 all these problems. There are probably a few that have yet  
13 to wake up and really come to grips with the problem. So if  
14 nothing else, maybe you can take a little concern about this  
15 issue back to your own institution and check in to see  
16 what's happening there.

17 There are potential problems for medical devices.  
18 There are products that are PC-controlled or microprocessor-  
19 controlled, as I mentioned. There are particularly stand-  
20 alone software applications which don't really involve  
21 hardware, but it is a piece of software that you buy, and  
22 you put it into somebody else's hardware, and the program,  
23 an algorithm, may use dates, and if those dates were not  
24 programmed correctly, you could have a problem.

25 A good example of this, one that came to mind

1 early on in the discussions and has been an example that in  
2 fact did have some problems with certain manufacturers'  
3 products, is radiation treatment planning systems. This is  
4 the software that the oncologists and radiation therapists  
5 use to plan teletherapy or brakiatherapy [ph.], which is  
6 using a radioactive isotope to administer radiation therapy.

7           If the program was not real clear about dates,  
8 there is the potential for the date at which the source was  
9 calibrated compare to the date on which it is going to be  
10 used resulting in an inappropriate calculation of the source  
11 strength and an inappropriate delivery of therapy.

12           Those are real examples. There are products like  
13 that that the manufacturers are going to have to change, and  
14 they are actively doing that.

15           But the point is that we need to look at all of  
16 these issues. Many products that have data interfaces  
17 sending data from one device to another, from a monitor to a  
18 monitoring station where it is displayed or recorded  
19 centrally, and everybody has probably heard the term  
20 "embedded chips," which are the ubiquitous little devices  
21 that either record the dates, display the dates, print the  
22 dates. I think this is the area where there is some concern  
23 and confusion with regard to medical devices. But most of  
24 the problems that we have heard about here are date-related  
25 in the sense that it is a product that either displays the

1 date or prints the date on a paper record, but the device  
2 itself does its normal function okay; it is just the  
3 printing/recording function that may have some problems.

4 This present the question of how significant is  
5 that problem, can it be handled, can there be work-arounds,  
6 and does this rise to the level where FDA would have to get  
7 involved to have a recall. I think each manufacturer is  
8 having to make that decision on its own.

9 [Slide.]

10 The problem, of course, as we all know by now, is  
11 2 digits for the year lead to a potential confusion. "00"  
12 could be interested as "1900" or "2000." If the context is  
13 not clear, this could lead to confusion. In fact, some of  
14 these products don't print "00." The system really gets  
15 confused, and you get some other character there that may  
16 not even be recognizable as a number.

17 [Slide.]

18 FDA has, in discussing this with manufacturers and  
19 establishing the web site that I'll talk about in a second,  
20 come up with a definition of what we mean to say that a  
21 medical device is year 2000-compliant or is basically okay,  
22 and this is based on the Federal Acquisition Reg definition  
23 that we use in contracting as well; it was slightly tailored  
24 here to make a little more sense for medical devices.  
25 Basically, our definition, if a manufacturer tells FDA that

1 my product is compliant using our definition, then all these  
2 things are holding--that is, the product doesn't have  
3 trouble with dates anywhere. Even if the product only  
4 prints "00," we consider that a problem, because you really  
5 cannot tell "2000" from "1900." It may not be that the way  
6 that product is used presents a risk to patients. We still  
7 call that noncompliant--it may be noncompliant, and the  
8 facility may decide they can live with it, but in our  
9 definition that is a problem, because the year is ambiguous.

10 [Slide.]

11 So, why am I here? As I mentioned, I want to  
12 bring this to your attention and tell you a little bit about  
13 some of the things we have been doing.

14 If there are some devices in your particular  
15 clinical area or area of experience that you are aware of  
16 that might have problems that you think we ought to pay  
17 particular close attention to, we would like to have that  
18 kind of feedback.

19 When we started this a year and a half or 2 years  
20 ago, we gathered a group in to sit down and say what  
21 devices could have problems, and we came up with a rather  
22 short list of devices that could have significant problems.  
23 We are not confident that we got everything out there. We  
24 have learned since then that there are a few others that  
25 have potential problems. So we are open to hearing about

1 other areas that we might have overlooked, and we are also  
2 interested in any suggestions or concerns you might have  
3 about how FDA's activities related to this could help the  
4 clinical users of these products to help the health care  
5 organizations.

6 We don't have unlimited resources to put into this  
7 activity, but if there are some focused things that you  
8 think we might be able to do, we would be interested in  
9 hearing about those. And the way to do that is through  
10 feedback either to the Executive Secretary of this  
11 Committee; Dr. Rosenthal I am sure could pass comments on,  
12 or you can contact me directly.

13 [Slide.]

14 One of the things we have done is to establish a  
15 database on the World Wide Web, where manufacturers who have  
16 assessed their products can provide that information to the  
17 FDA, and we display it for the hospital engineers, the  
18 hospital/clinical service people who are in the process of  
19 doing their inventory and finding out what products they  
20 have that are going to be affected. They can go to this web  
21 site, look up a manufacturer's name, find out what products  
22 they have reported as having problems.

23 We don't have 100 percent coverage. We are still  
24 working on encouraging manufacturers to submit information.  
25 We have over 3,000 manufacturers represented there

1 currently.

2 [Slide.]

3 This is just an indication of what the web site  
4 looks like. When you get into the FDA home page, just click  
5 on the part that says "Year 2000," and you can get an  
6 introduction, or you can go to the second bullet and enter a  
7 manufacturer's name, search the database. You can download  
8 the database, or the hospital engineer can get a file copied  
9 and use it to compare to his inventory.

10 The rest of the stuff there is some of the  
11 background document that we have made available through the  
12 web.

13 We did put out a guidance document in June of this  
14 year, addressed to the industry, the manufacturers, and it  
15 presented our expectations of manufacturers with regard to  
16 what they need to do. In a nutshell, it told the  
17 manufacturers that they need to assess all of their  
18 products, both current production and past production, that  
19 might still possibly be in use somewhere for potential year  
20 2000 problems, assess the level of risk, and then, under our  
21 Quality System Regs for manufacturing, they have to take the  
22 appropriate action necessary about whatever risks they have  
23 uncovered. At the minimum, this probably requires notifying  
24 customers in some way about a problem, even if it is a minor  
25 problem. If it is a problem that presents a more serious

1 risk, then FDA is going to be very interested in following  
2 up with the manufacturer and making sure that those actions  
3 are taken.

4 We have, of course, the "stick" to use if it comes  
5 to that--our mandatory recall authority--for problems that  
6 present a significant risk to public health. But normally,  
7 we don't have to do that; the manufacturers are very  
8 responsible and do their voluntary recalls or fixes.

9 We have a couple of other things underway,  
10 including monitoring the situation, trying to pay attention  
11 to what is going on. We are active in a health care  
12 outreach group within the Department, in the Federal  
13 Government, to think about better ways to communicate the  
14 issues and what we have learned and to gather input on other  
15 issues that might be relevant to this problem.

16 The real concern here is, of course, making sure  
17 everybody plans ahead, understands what they've got,  
18 develops some contingency plans in case things do go wrong,  
19 and I'm going to stop at that point in my hurried discussion  
20 and just say this is how you can contact me. It is in the  
21 handouts that you got. The Executive Secretary can also  
22 pass on information.

23 I am not going to stay around for your meeting,  
24 but if you do have a question or two, I'd be glad to handle  
25 those before I leave.

1 DR. McCULLEY: Would you take questions or  
2 comments, if there are any?

3 DR. SHOPE: Yes.

4 DR. McCULLEY: Any questions from the panel?  
5 Dr. Bradley?

6 DR. BRADLEY: Could you just give us a ballpark  
7 estimate on how old the PC has to be to suffer from this  
8 problem?

9 DR. SHOPE: That's not a good answer, because it  
10 depends on when the components in that PC got shipped to the  
11 manufacturer and how long they sat in his factory before  
12 they got put in. I think if you bought something within the  
13 last 6 months, there is a reasonable chance, but I think you  
14 should, as they say, test and verify to make sure that it is  
15 okay.

16 DR. BRADLEY: So you are saying prior to 6 months  
17 ago--

18 DR. SHOPE: There were still products coming out  
19 that way, yes.

20 DR. McCULLEY: Not good news.

21 Dr. Wang?

22 DR. WANG: I think the lesson we learn from the  
23 year 2000 problem is that in the 1940s, the computer  
24 scientists did not have the foresight to know what would  
25 arrive in the ensuing 60 years.

1           How is the solution proposed? Is it going to  
2 include the last three digits--that means the problem will  
3 recur in 1,000 years--or is it going to be some sort of  
4 permanent solution?

5           DR. SHOPE: Well, we haven't had the mandate to  
6 dictate the solution. We want manufacturers to correct  
7 their problems for their products. I think there are  
8 international standards on dates that we would encourage  
9 people to use. There are date formats that include the 4-  
10 digit year. There is the potential for a lot of programs to  
11 have problems in 10,000 years, when there is not a fifth  
12 digit for the year, I suppose, and there are other operating  
13 systems that have years, not 2000, but where their  
14 timekeeping mechanism is either based on number of years  
15 since the program was invented or other measures.

16           There is a well-known problem with the global-  
17 positioning satellite; the software in that thing is based  
18 on the number of weeks that the satellite system has been  
19 working, and the maximum number of weeks is reached, I  
20 believe, sometime next fall, and they'll have to start over.

21           So there are a lot of those kinds of issues. I  
22 don't think there is a good answer to say this is the way to  
23 do it. There are a lot of approaches being taken by  
24 manufacturers to deal with their particular problem,  
25 everything from total rewrite of the software to fixes to

1 work-arounds, and those lead to lots of issues.

2 DR. McCULLEY: Dr. Stark?

3 DR. STARK: I didn't get your last slide, but did  
4 you say you have already reviewed a number of ophthalmic  
5 products, Tom, and that through your web site, which would  
6 be fda.gov, and then click on 2000, we can pick up what  
7 information you know about problems?

8 DR. SHOPE: What we have there is the information  
9 that the manufacturers have provided to us. We have two  
10 types of information--either the manufacturers have given us  
11 a web link that will take you to their own manufacturer's  
12 site, where they have year 2000 status, or we have year 2000  
13 status that has been submitted to us, and we display it.

14 We have three kinds of information there. It is  
15 either a statement from the manufacturer that their products  
16 don't use dates--and we have a large number of those,  
17 because our mailing went out to all manufacturers of any  
18 kind of product, so we have sunglasses manufacturers that  
19 have told us they don't use dates in our products, and  
20 crutch manufacturers--so it is the whole spectrum of "We  
21 don't use dates," and that's good to know, I guess, if you  
22 are doing your hospital inventory and you are comparing.

23 The second kind of comment we have had is  
24 manufacturers are telling us that none of their products,  
25 even though they use dates, are noncompliant. In other

1 words, all our product line is okay based on your definition  
2 of compliance. We have those just by the company name, with  
3 that statement.

4           The third kind of information we have is if a  
5 company has identified some of their products that have a  
6 date noncompliant, that has a problem, they list for us make  
7 and model number, software version number, the type of  
8 problem it is, whether they are going to offer a fix or  
9 something to deal with that problem, or if they don't plan  
10 to--some have claimed that something that is 15 years old is  
11 obsolete, and they are not going to provide a fix--but you  
12 now know that, anyway, and you can deal with it.

13           So we have that kind of information on our web  
14 site. It is not mandatory. This is a voluntary request of  
15 manufacturers. We are doing all we can to encourage  
16 everybody to report.

17           We identified about 2,000 manufacturers that had  
18 high probability, based on the products they make, that  
19 those products could likely be computerized, and we focused  
20 on those in addition to the 13,000 manufacturers of all  
21 types. Of that 2,000 or so manufacturers, we have heard  
22 from about 66 percent so far. So I think manufacturers were  
23 a little slow getting up to steam and doing their own  
24 assessments, and many of them were reluctant to say to us--  
25 they can tell us either "We have a problem" or "We haven't

1 finished our assessment, and we'll do that by a certain  
2 date." I think a lot of them wanted to have a whole answer  
3 before they made it public, so I think that has slowed us  
4 down a little bit in getting the data out. It continues to  
5 grow.

6 So a long answer to a short question--yes, you can  
7 find out about products. We have not focused specifically  
8 on ophthalmic. I can't tell you which of the manufacturers,  
9 but I know some of them are there.

10 DR. STARK: I think that is a tremendous service  
11 that you are going to provide, because we are now trying to  
12 check over all our machines at Johns Hopkins, at the Wilmer  
13 Eye Institute, and since you have this information, you  
14 might let hospitals know, ambulatory surgery units, because  
15 you have already done a lot of the work that we are going to  
16 have to do.

17 DR. SHOPE: Yes. We have been in touch with the  
18 American Hospital Association and other groups. We have  
19 sort of a national partnership activity going on to try to  
20 communicate and get input on their needs as well.

21 So there are some discussions going on right now  
22 maybe even of expanding this. Some of the hospitals want us  
23 to list everything that is okay as well. That wasn't the  
24 initial design concept that we had,\* and we didn't think that  
25 was a lot of information that people needed, but we are

1 still talking about that.

2 DR. McCULLEY: Dr. Rubin?

3 DR. RUBIN: Gary Rubin. Your emphasis is  
4 understandably on medical devices, but I would think it  
5 might be of interest, given the scope of this panel,  
6 software that is used, for example, in clinical studies  
7 where, for example, the age of a participant is of critical  
8 interest, and if that is not coded correctly, there could be  
9 errors in that.

10 Does the FDA have some interest in, say,  
11 statistical software packages and other things like that,  
12 that might come into play?

13 DR. SHOPE: Well, that's certainly something that  
14 needs to be looked at. The Center for Drugs has had some  
15 discussions about clinical trial-type software. We at  
16 FDA/CDRH have not focused specifically on that, but I think  
17 part of the message we are trying to get out is if it has  
18 software, and software is being used for whatever process,  
19 it needs to be looked at.

20 We have said the same thing to manufacturers about  
21 their automated manufacturing processes. There are real  
22 concerns about if a manufacturer, who may be the only  
23 manufacturer of a product that a lot of people depend on,  
24 has production problems due to the year 2000 problem and  
25 cannot shift, that's a real concern as well.

1           So there is a myriad of issues here. The truthful  
2 answer is we haven't focused on the clinical trial-type  
3 software specifically, but it is something that needs to be  
4 looked at.

5           DR. McCULLEY: Dr. Grimmett?

6           DR. GRIMMETT: Other than January 1, 2000, it was  
7 my understanding that other dates that are sooner than that  
8 are of concern--September 9, 1999, with four 9's in a row, I  
9 understand was an error code in some computer coding. Will  
10 that be a problem?

11          DR. SHOPE: There is a potential there. Leap years  
12 are a problem in the year 2000. Some people in programming  
13 forgot that that was going to be a leap year, because it is  
14 the third, hardly ever used, rule.

15          As to the "9-9-99" business, it's hard to say that  
16 that is going to be a real problem, but it is a potential,  
17 because that's more how the person doing the program used  
18 that in his programming. Some people would say it may or  
19 may not be, but it has to be looked at.

20          There are other dates--if you are doing things  
21 that look forward 3 months, then your problems may show up  
22 this month next year as opposed to January, because you are  
23 forecasting ahead. A lot of the first early attention to  
24 this problem came out of some of the financial industry when  
25 they were doing mortgages and things like that and realized

1 they were having problems in forecasting years ahead. That  
2 sort of congealed, I think, the problem for a lot of people  
3 as they ran into these things that look ahead some.

4 Leap years, the first, the 99th day in the year  
5 1999 may be a similar thing as opposed to September 9th. So  
6 there are a number of those kinds of dates. When people do  
7 this testing, they have a long list of dates they want to  
8 check to make sure things roll over and work correctly.

9 DR. McCULLEY: Thank you very much. We appreciate  
10 it.

11 We are going to move on now to Division Updates,  
12 and Dr. Ralph Rosenthal, Director, Division of Ophthalmic  
13 Devices.

14 Ralph?

15 **Division Update**

16 **A. Ralph Rosenthal, M.D.**

17 **Director, Division of Ophthalmic Devices**

18 DR. ROSENTHAL: Dr. McCulley, I just have one  
19 update, and that is to introduce you to a new Medical  
20 Officer who joined us in September, Dr. Sheryl Berman, who  
21 did her residency at Washington Hospital Center and has been  
22 working in the Washington area for the past several years  
23 and has now elected to come and work with us. She has an  
24 insightful mind and will provide a great opportunity for us  
25 to expand our Medical Officer Reviews.

1 DR. McCULLEY: You won't have to do primary  
2 reviews anymore--Medical Officer Reviews?

3 DR. ROSENTHAL: I have asked her to get up to  
4 snuff within 6 weeks so that--I don't know. We'll see.

5 Other than that, we have had a very productive  
6 year, and I think the panel should be aware of the enormous  
7 amount of work that has been done by this very small  
8 Division over the year and to whom I am eternally grateful  
9 for their diligence and high performance.

10 DR. McCULLEY: Well, certainly, the reviews that  
11 have come to us have been excellent, so from our standpoint,  
12 we appreciate the work.

13 Jim Saviola, Chief, Vitreoretinal and Extraocular  
14 Devices Branch, for an update.

15 **Branch Update**

16 **James F. Saviola, O.D.**

17 **Chief, Vitreoretinal & Extraocular Devices Branch**

18 DR. SAVIOLA: Good afternoon.

19 We passed out during the break the copy of the  
20 Public Health Notification to the panel dated September  
21 25th, and also an October 13th follow-up sheet. Did  
22 everybody receive that?

23 Okay. My update primarily concerns that  
24 particular notification.

25 It generated quite a bit of interest, and in

1 response, the Branch wrote this one-page, October 13th memo,  
2 and there are copies available at the front of the room for  
3 those who are interested in looking at that.

4 This was mailed to over 40,000 addresses on a  
5 purchased mailing list. The Office of Surveillance and  
6 Biometrics, OSM, coordinated this whole mailing and the  
7 process of issuing the health notification, and Ms. Carol  
8 Herman was the person in that office whom we worked with.

9 If people on the panel did not receive a copy, it  
10 was primarily targeted to eye care practitioners who  
11 dispense contact lenses--and I also did not receive a copy  
12 where I work or at home, so I must not have been on the  
13 right mailing list--but then again, I just fit contact  
14 lenses, I don't necessarily dispense them. A copy is  
15 available on the Center web site at [fda.gov/CDRH](http://fda.gov/CDRH).

16 I want to touch on a couple questions that might  
17 have been in some people's minds in the aftermath of this  
18 notification. The primary response we got back from people  
19 was trying to find out which particular lenses we have  
20 cleared regarding tinted lenses and orthokeratology lenses,  
21 and why did we not include the approved lenses in the  
22 notification.

23 The answer to that was that we did not want to  
24 appear to be promoting any particular firm's products; we  
25 didn't want it to seem like we were advertising in this

1 notification.

2           As we were going through the necessary review to  
3 issue this, there was in fact a second firm that received  
4 clearance for a theatrical tinted or an opaque tinted lens.  
5 This fact demonstrates that we are in a very dynamic  
6 environment with these manufacturers.

7           There is a feeling that having a list of approved  
8 suppliers, rather than a list of illegal firms, is more of a  
9 positive reinforcer, and that maintaining two lists creates  
10 a greater risk of miscommunicating a firm's status at any  
11 given time. If a firm had not received a clearance a week  
12 or a month ago, and we had a nonapproved list, that would  
13 change as we updated the approved list, so we would have  
14 twice as much to manage.

15           We are working with a number of firms to try to  
16 bring them into compliance. While I will refrain from  
17 mentioning any nonapproved firms specifically, I will state  
18 that at the moment, there are not any firms that are  
19 approved illegally marketed or so-called after-market tinted  
20 lenses--those are lenses which are purchased clear and then  
21 sent to a tinting house to have the color added to the lens--  
22 -but I do expect that to change in the next few months.

23           Another question that has been considered by some  
24 is since these products have been out on the market for many  
25 years, why did FDA take action now. Well, this is sort of a

1 tough question to answer, and the answer does have many  
2 parts. Our primary target for this notification was not the  
3 major manufacturing firms. The firms we are interested in  
4 are the firms that advertise over the web and other smaller  
5 firms that provide this after-market tinting service. And  
6 there are a large number of this particular operations.  
7 There are limited resources to investigate and develop  
8 compliance cases against these offenders. That is a big  
9 issue as to why our efforts were hampered in trying to do  
10 this individually.

11           The increase in the number of firms is also an  
12 issue that was factored into our decision to issue a  
13 notification to practitioners and dispensers and notify  
14 them of the potential health risks associated with these  
15 tints.

16           We are also trying to maintain a level playing  
17 field, and that is a continuous effort. When a firm which  
18 has a legally-approved device promotes their product in the  
19 marketplace, and there are unlawful competitive firms that  
20 are also promoting their device but have not received  
21 clearance, then we are somewhat forced to take an action.

22           The follow-up information sheet noted specifically  
23 that the theatrical tinted lenses by Wesley-Justin [ph.],  
24 Wild Eyes, are legally clear to be marketed by FDA. When we  
25 evaluate these types of tinting processes, we look at the

1 manufacturing method that the firm is using to incorporate  
2 the tint into the lens as well as the specific tints that  
3 they are using. After that point, the firms are able to add  
4 additional tints which have been listed as safe to be used  
5 with contact lenses and create different color patterns.

6 The second firm that we cleared was the C.L.  
7 Tinters [ph.] firm out of Finland, and they also market a  
8 theatrical tinted lens called Crazy Lens.

9 Another question that might be in some people's  
10 minds is why combine the orthokeratology issue with tinted  
11 lenses; they seem somewhat separate from each other. The  
12 notification mailing was an efficient and economic vehicle  
13 to inform practitioners and dispensers of two issues which  
14 are very similar from a public health standpoint. In both  
15 the tinted lens and the ortho-k lens case, the agency does  
16 not really have any good data available regarding the actual  
17 injuries associated with these devices, yet the potential  
18 for injury does exist.

19 By raising the general awareness level as to the  
20 potential for injury, we hope to accomplish two things.  
21 First, we hope to receive reports under MedWatch that will  
22 allow us to consider any appropriate follow-up activities  
23 and to gather more data on this issue. Second, we hope to  
24 spur the currently violative firms to take action and to  
25 work with us to become compliant. If doctors have a choice

1 between an approved device and one that is not approved, we  
2 hope they will choose the approved device for their  
3 patients. This is already happening with firms coming to us  
4 and working with us to gain appropriate clearances.

5 I don't want to reread this whole thing, but an  
6 important point to consider in how you can know for sure  
7 whether or not a device you are interested in purchasing is  
8 FDA-approved is to request from the manufacturer a complete  
9 copy of the lens labeling, which includes the package  
10 insert, the practitioner's fitting guide, as well as the  
11 patient information booklet. The information contained in  
12 those documents will give you some idea of whether or not  
13 they are trying to pitch something which may or may not have  
14 a clearance from us.

15 That concludes my remarks. Does anybody have any  
16 questions?

17 DR. McCULLEY: Questions from the panel?

18 Dr. Ferris?

19 DR. FERRIS: Because this is a dynamic, changing  
20 area, have you thought about creating a little web site for  
21 this so that you can update it without having to put out yet  
22 another mailing?

23 DR. SAVIOLA: We haven't explored the possibility  
24 of putting this information up on a web site. I do plan to  
25 update the fax notifications periodically as we get

1 additional firms cleared.

2 DR. McCULLEY: Other questions, comments?

3 [No response.]

4 DR. McCULLEY: Thank you very much.

5 Donna Lochner will report tomorrow in the open  
6 session.

7 Now, for a Branch Update before we go to the  
8 discussion to follow, Morris Waxler, Chief of the Diagnostic  
9 and Surgical Devices Branch, will report.

10 **Branch Update**

11 **Morris Waxler, Ph.D.**

12 **Chief, Diagnostic & Surgical Devices Branch**

13 DR. WAXLER: Good afternoon.

14 First, I want to thank the panel for your presence  
15 here and your help over the last year, and also, I'd like to  
16 thank the Branch, which I introduced to you this morning,  
17 and I would like to quickly introduce them in general,  
18 without reading each of their individual names. They have  
19 done a marvelous job, and you will see that when I give you  
20 the details.

21 In addition, I would like to thank the medical  
22 officers and Dr. Rosenthal as well for all the hard work  
23 that it has taken to get through this particular year.

24 First, I want to give you an update on the status  
25 of the PMAs that were reviewed by the panel previously.

1 P97005 was approved by FDA on July 30, 1998. This PMA is  
2 for the single-unit Kremer excimer laser system, Serial  
3 Number KE940202 for the LASIK correction of primary myopia  
4 ranging between -1 and -15 D with or without astigmatism  
5 ranging from 0 to 5 D. Data on safety and effectiveness  
6 from a multicenter clinical trial will be needed to market  
7 additional units of this laser.

8 P970049 for Autonomous Technologies' refractive  
9 surgery laser unit remains under review.

10 P9300116, Supplement 7, for VISX for hyperopia,  
11 remains under review.

12 P970001, for Emory Vision Correction Center's  
13 laser for LASIK, remains under review.

14 Members of the panel asked FDA a couple of  
15 sessions ago to review the data on the relationship between  
16 hormone replacement therapy and refractive surgery outcomes.  
17 We asked Dr. Rhonda Ballum [ph.] in the Office of the  
18 Commissioner to review the published literature and the data  
19 submitted to the agency in the PMAs. Unfortunately, Dr.  
20 Ballum could not be here today to summarize her review. I  
21 will summarize here conclusion.

22 There appears to be no or minimal effect of HRT--  
23 that is, hormone replacement therapy--on outcome. She  
24 concurs with the conclusion drawn by Serander & Peak [ph.]  
25 that both hormone replacement therapy and oral

1 contraceptives may affect the eye during the period of  
2 dosage determination as the body adapts to an altered  
3 hormonal level. However, once they hormonal levels are  
4 stable, there should not be any further effect on the eye.

5           Due, however, to the lack of available research on  
6 the subject of postmenopausal women on HRT versus those not  
7 on HRT, this continues to be a confounding variable, and one  
8 that is worth of a well-controlled sub-study.

9           An independent statistical review of the data  
10 previously presented by Autonomous Technologies shows that  
11 it is age and desired correction that are highly associated  
12 with outcome, not HRT. We plan to seek your advice at  
13 another meeting of the panel about how to or if we should  
14 incorporate this information into our revised guidance for  
15 refractive surgery lasers.

16           Now to our workload. Well, it has been a busy  
17 year. First, on IDEs, our Branch has reviewed, with the  
18 help of other staff in the Division, 597 submissions, 551 of  
19 which were supplements to FDA-approved IDE clinical trials,  
20 27 of which were submissions of new IDEs, and 19 of which  
21 were amendments to disapproved IDEs. Of the 551  
22 supplements, 229 were submitted by manufacturers, 237 were  
23 submitted by sponsor-investigators, and 85 were submitted by  
24 sponsor-investigators of so-called "black box" lasers.

25           Of the 27 submissions of new IDEs, 5 were

1 submitted by manufacturers, 20 by sponsor-investigators and  
2 2 by "black box" sponsor-investigators.

3 The number of manufacturers submitting IDEs has  
4 not increased from the previous year, and the number of  
5 "black box" applicants has decreased to 5.

6 The number of PMAs and PMA supplements under  
7 review in the last fiscal year was 9. A fiscal year, for  
8 those of you who do not know, is the fiscal year ending on  
9 September 30, 1998.

10 I'll be glad to entertain questions, except on  
11 HRT.

12 DR. McCULLEY: Thank you.

13 Does anyone have any questions or comments for Dr.  
14 Waxler?

15 [No response.]

16 DR. McCULLEY: Okay. Are you ready to stay on the  
17 hot seat?

18 DR. WAXLER; Sure.

19 **Introduction of Issues for**

20 **Excimer Laser Guidance Discussion**

21 **Morris Waxler, Ph.D. and Malvina B. Eydelman, M.D.**

22 DR. McCULLEY: Dr. Waxler is going to introduce  
23 the issues for excimer laser guidance discussion. We have  
24 three that have been provided to us in writing, and I  
25 understand there is a fourth.

1 DR. WAXLER: Correct--and I agree whole-heartedly,  
2 Dr. McCulley, with your earlier comments about our focus on  
3 these three issues.

4 The fourth issue was brought to my attention in  
5 several ways, and Dr. Rosenthal and I agreed that it was  
6 timely to bring it to your attention. I think it will be  
7 fairly straightforward and will be important to hear your  
8 discussion of that issue.

9 DR. McCULLEY: Can I ask you for some help to get  
10 your guidance--we are scheduled to go until 5:30, and it is  
11 approximately 2:50 now. Do these three issues and the  
12 fourth, time available, require in your estimation, prior to  
13 beginning, equal time? My concern is that we could end up  
14 with very little time for the third issue if we don't try to  
15 allocate the time to the three. We have often done this  
16 with questions in the past; we didn't for this.

17 DR. WAXLER: Well, I'll have to defer to the chair  
18 and to his illustrious control of the panel.

19 DR. McCULLEY: No--that's an illusion.

20 DR. WAXLER: Well, you are a good illusionist. I  
21 don't know what to say. I think a lot depends on what the  
22 member panelists come up with in regard to each of these  
23 issues. I think each one has its own meaty areas; some, in  
24 my estimate, will take a lot shorter. But I am just  
25 guessing myself, so I wouldn't be much help to you.

1 DR. McCULLEY: It would be my guess as well.

2 We'll take them in the order that they are listed-  
3 -Dr. Belin first, Dr. Stark second, Dr. Bullimore, third. I  
4 am not sure how you want to introduce these. Do you want to  
5 introduce the issue and the question and then have the  
6 assigned person give his evaluation, and the panel can  
7 discuss--we'll do them one at a time.

8 DR. WAXLER: Sure. And I wrote a little preamble  
9 to give the context to the panel and the staff and the  
10 audience, that maybe they should hear.

11 DR. McCULLEY: We have to allot time for that,  
12 too.

13 DR. WAXLER: And I spent hours working on these  
14 two paragraphs--

15 DR. McCULLEY: We have to do it, then.

16 [Laughter.]

17 DR. WAXLER: I appreciate it.

18 Essentially, we are asking the panel to discuss  
19 the development of extensions of the guidance for refractive  
20 surgery lasers and to make recommendations to the agency on  
21 clinical outcomes for the determination of safety and  
22 effectiveness. But we want it for the full range of myopia  
23 and hyperopia, so there are three issues.

24 The current guidance is limited, as you know, to  
25 moderate myopia, and does not cover astigmatism; and also,

1 it suggests the 250 micron residual amount of corneal tissue  
2 that should remain. So we asked the three panelists, Dr.  
3 Belin, Dr. Bullimore and Dr. Stark, to talk about those  
4 issues, and if you like, I will introduce the first issue  
5 from here, and then, when you are ready, we can go to the  
6 second one.

7 DR. McCULLEY: Why don't we do that, and let me  
8 just remind everyone that if we are going to end at 5:30,  
9 which I don't particularly care--I am here tomorrow, too--  
10 that we need to try to allot time and address the issues  
11 thoughtfully, but not belabor the obvious.

12 Okay. If you would like to read your first issue.

13 DR. WAXLER: The first issue is: should the  
14 percentages of effectiveness--that is, UCVA, and the percent  
15 of manifest refracted spherical equivalent--be a function of  
16 the diopter intended correction in order to provide  
17 reasonable assurance of effectiveness. If yes, then what  
18 percentages do you suggest?

19 I'll let Dr. Belin take the floor.

20 **Report of Michael W. Belin, M.D.**

21 DR. BELIN: I want to give some background  
22 information. We actually started this discussion almost 3  
23 years ago, when I suggested that the arbitrary breakdown  
24 into low, moderate and high, and having different efficacy  
25 criteria and safety standards did not make a whole lot of

1 sense; that someone who was a 6 D fell into the low to  
2 moderate, and there, we used plus or minus one-half as one  
3 variable, and if they became 6.25, suddenly, they were in  
4 another group.

5 I proposed that we use a percentage of obtained  
6 correction. And partly for the audience, I use a very  
7 similar explanation to my patients when I am explaining  
8 refractive surgery, and I use a politically incorrect  
9 analogy of shooting a rifle at a target--that no matter how  
10 good of a marksman you are, if the target is 100 feet away,  
11 you will have some scatter of the bullets; and if you move  
12 that target 200 feet away, the rifle or the shooter is just  
13 as accurate, but the bullets will have twice the scatter.

14 That's the analogy I give when I discuss low,  
15 moderate and high degrees of correction.

16 In addition, I think those criteria should be the  
17 same regardless of the shooter and regardless of the rifle,  
18 meaning these criteria should apply whether it is PRK,  
19 LASIK, intracorneal ring, corneal implant--if the goal of  
20 the procedure is to hit the bull's-eye, we should meet the  
21 same efficacy and safety criteria. Otherwise, I think we  
22 are personally putting out our own bias by saying we have  
23 different criteria for LASIK than PRK, because we feel one  
24 is better than the other. If one is better than the other,  
25 then the one that is better will have a higher percentage

1 and will have an easier time meeting the efficacy and safety  
2 criteria that we establish.

3           With that in mind, I did not want to put down hard  
4 and fast numbers; I just wanted to give you what my thought  
5 process was. And again, my thought process was to use a  
6 percentage of correction, realizing that there have got to  
7 be some lower limits, that if we decide that you have to be  
8 within 10 percent, and someone is only at 1.0 D, one-tenth  
9 of a diopter is not reasonable.

10           There is also a typo that I want to correct.

11           With that, I'd like to go over what I have. I  
12 have: "The following must be present"--and I purposely left  
13 the percentage. This will be what you decide, what  
14 percentage of patients must meet these efficacy and safety  
15 criteria.

16           There is a typo in the first line. It is supposed  
17 to read "A reduction of 75 percent or more of pre-existing  
18 myopia or hyperopia based on spherical equivalent or within  
19 plus or minus one-half diopter of target."

20           "A reduction of 50 percent or more in the  
21 magnitude of the preoperative cylinder." Again, I was asked  
22 to base some of this on established data, and there is  
23 reasonable data to suggest that the correction of cylinder  
24 is--I don't want to say less accurate--but to a much lower  
25 degree than the correction of spherical component.

1           In addition, while we may target emmetropia for  
2 myopia or hyperopia, there is also a realization that  
3 someone who is, let's say, 6 D, and we use plus or minus  
4 one-half, one-half diopter overcorrection may be a very  
5 reasonable result, but one-half diopter overcorrection of  
6 cylinder results in a 90-degree flip of the axis which may  
7 not be tolerable.

8           So again, I am just throwing out percentages as a  
9 starting point.

10           "Overcorrections no greater than +/- 0.50 D or 15  
11 percent of the preoperative spherical equivalent, whichever  
12 is greater."

13           DR. McCULLEY: You're changing it? You wrote  
14 "0.75."

15           DR. BELIN: What did I just say?

16           DR. McCULLEY: You said "0.50."

17           DR. BELIN: It's "0.75." Sorry. I just read it  
18 wrong.

19           "Unplanned induced cylinder, determined by vector  
20 analysis, no greater than 1.00 D or 15 percent of the  
21 preoperative spherical equivalent, whichever is greater."

22           The next, 2 and 3, deal with visual acuity. I  
23 will say that these only apply to myopia. I really feel you  
24 can't use the same visual acuity criteria for hyperopia,  
25 because with hyperopia, you are sometimes dealing with

1 subjective criteria. Many of us who are approaching  
2 presbyopia know that we are all J-1-plus for a minute or  
3 two, but the fact that we are J-1-plus for a minute doesn't  
4 mean that we are J-1-plus when we sit down to read a book.  
5 And people who are hyperopic can be 20/20 uncorrected for  
6 distance and have J-1-plus for near, but are highly  
7 subjectively symptomatic. So 2 and 3 really only apply to  
8 myopic corrections.

9 "Ninety percent of subjects should have an  
10 uncorrected visual acuity of 20/40 or better or an increase  
11 of at least 6 lines of vision."

12 And "Fifty percent of subjects should have an  
13 uncorrected visual acuity of 20/25 or better or at least an  
14 8-line increase in vision." Again, this is trying to  
15 utilize the fact that we expect different results with  
16 people who are -3 and -10; also, to try to give patients a  
17 more realistic expectation that the person who is a -10 has  
18 to have different expectations that the person who is -3.

19 Finally, 4 is the safety: "No more than 0.5  
20 percent of patients with the best spectacle corrected visual  
21 acuity below 20/40 and no more than 3.0 percent of patients  
22 with the best spectacle corrected visual acuity below  
23 20/30."

24 Again, these are not meant to be the numbers that  
25 any of us utilize. It is just supposed to be a thought

1 process of how to get away from the arbitrary breakdown into  
2 the low, moderate and high, and to try to have some  
3 guidelines that can be utilized across the board throughout  
4 the refractive errors but also across the board throughout  
5 the different lasers and different procedures, whether they  
6 be laser-based or not.

7           As far as presbyopia goes you can't even begin--we  
8 would need a day just to discuss how to determine safety and  
9 efficacy criteria for presbyopia, because again, uncorrected  
10 visual acuity is really not what you're looking for. And  
11 I'll throw out that what you really probably have to look at  
12 in these patient are near point or accommodated amplitude,  
13 which we have never really looked at. But that would be a  
14 discussion that would be much longer than we have time for.

15           DR. McCULLEY: Is your suggestion, as I understand  
16 it, acceptable to the FDA, if I can restate it, that we  
17 would not address presbyopia in this document?

18           DR. WAXLER: It sounds quite reasonable.

19           DR. McCULLEY: Okay. So we would address myopia  
20 and astigmatism hyperopia.

21           Are there comments at this time?

22           Yes, Dr. Rubin?

23           DR. RUBIN: Gary Rubin.

24           At the risk of going over old ground here, because  
25 I am not familiar with the history by which this particular

1 document was generated, could you please explain to me the  
2 thinking that would lead one to develop a standard which  
3 refers to a percentage of reduction of emmetropia but a  
4 fixed standard in terms of vision?

5 In one case, we are talking about one that is  
6 conditioned on the starting point, and the other is not.

7 DR. BELIN: It is not. They are actually both the  
8 same. What we have done is said that our uncorrected visual  
9 acuity is based on a reduction up to a certain limit. We  
10 accept 20/40 or better as being a desirable, but if you have  
11 a greater correction, we are looking at a certain reduction  
12 6 lines in vision. We are doing the same thing with the  
13 refractive; we are saying +/- 0.50 D of target or a certain  
14 level of correction.

15 Again, what we are doing is saying that if we are  
16 aiming for a bull's-eye, and you are 1,000 feet away or 100  
17 feet away, it is different, but at some point, no system is  
18 going to fall within a tenth diopter. If you are 1.0 D, you  
19 can't expect to fall within a tenth of a diopter plus or  
20 minus. The same thing--if they are 2.0 D or less, not  
21 everyone is going to be 20/20.

22 So there is a degree that we say yes, that's a  
23 good enough result, but if your correction is greater, we  
24 give you a larger target, really.

25 DR. McCULLEY: Dr. Rubin.

1 DR. RUBIN: Gary Rubin.

2 I guess my initial reaction is to be diametrically  
3 opposed to this, but I am open to suggestions.

4 From the patient's point of view, if the goal of  
5 the procedure is to be able to be free of spectacles, I  
6 would assume--correct me if I am wrong--that a person's  
7 tolerance or demand for spectacles would not be conditioned  
8 on their initial amount of myopia or presbyopia.

9 In other words, if I am a high myope, would I be  
10 willing to tolerate more diopters of myopia after the  
11 procedure than if I am a low myope? And maybe I am wrong in  
12 that expectation, but if I am correct in that expectation,  
13 then that would lead you to have standards that did not take  
14 into account the initial stage of refraction.

15 DR. McCULLEY: Dr. Belin?

16 DR. BELIN: I think the answer for most of us who  
17 do refractive surgery--one, we tell your patients that that  
18 is what they need to expect, that there is definitely a  
19 different expectation if they are a -3 or a -12. All the  
20 data suggests that also, and that is partly why we have  
21 established that. And most patients who are -12 come in,  
22 and they are--some of them--many of them, their goal is very  
23 different than the person who is a -3. The person who is a  
24 -3 has a goal of independence from glasses; a person who is  
25 a -12, it is a lifestyle change, the ability to ambulate

1 without glasses.

2           So I think that patients' expectations are  
3 different, but I don't think we should establish guidelines  
4 on the fact that we have generated a population that may  
5 have unrealistic expectations about what we can do.

6           The last comment is purely a comment: 13 of the  
7 20 people on the panel are wearing glasses. That's kind of  
8 an interesting comment.

9           DR. McCULLEY: I'm presbyopic.

10          Dr. Matoba, did you have your hand up?

11          DR. MATOBA: Dr. Belin stated in the beginning  
12 that he felt that all kerato-refractive procedures should  
13 have to meet exactly the same criteria for safety and  
14 efficacy. Is that something that we have all agreed on?

15                 And the second part of the question is if one  
16 procedure is a lot safer than another, should that procedure  
17 have to meet the same degree of efficacy, or is that an area  
18 for which there is some wiggle room?

19          DR. McCULLEY: Dr. Belin?

20          DR. BELIN: I was expecting that question, because  
21 very often, when we look at things, we look at safety and  
22 efficacy as being somewhat interrelated. We are willing to  
23 accept lower efficacy for greater safety. And I think that  
24 that is usually true, but that's the difference between--and  
25 I don't mean this to be funny--between myopia and, let's

1 say, AIDS. For myopia, we have established a very high  
2 safety limit, because it doesn't have morbidity and  
3 mortality to it, so we have established very strict safety  
4 criteria.

5           When we do that, I think we eliminate having to  
6 tie safety and efficacy. We have set very strict safety  
7 standards. That is very different when you are dealing with  
8 a disease that has morbidity and mortality where, yes, if  
9 you have something that is very safe, lower efficacy may be  
10 acceptable, and if you have something that is not very safe  
11 but is otherwise a fatal disease, you would be willing to  
12 accept it. That is not what we are dealing with in myopia,  
13 but I understand--

14           DR. MATOBA: Okay, that's true. But even  
15 comparing PRK to LASIK, the postoperative infection rates I  
16 think are different. I think you have more infections with  
17 PRK.

18           DR. BELIN: There are probably other people who  
19 can speak to that; I don't know that that's true. Again,  
20 you are dealing with the same thing, safety and efficacy.  
21 when you have an infection in LASIK, it is usually more  
22 problematic than when you have it in PRK. So you can't just  
23 look at infection rate; it gets into the same type of thing--  
24 -now it is safety and efficacy. You may have a lower  
25 infection rate but a higher morbidity rate, because your

1 infections tend to be harder to treat in LASIK.

2 DR. McCULLEY: Dr. Pulido?

3 DR. PULIDO: Jose Pulido.

4 Dr. Belin, I assume that you would keep the other  
5 safety endpoints that are already listed in the 1996  
6 document and just modify the ones that you are discussing  
7 here; is that correct?

8 DR. BELIN: That's correct. Again, I just want to  
9 say that these are not meant to be the guidelines. This is  
10 just meant to kind of give you an idea of what my suggestion  
11 was, which is to have something that can be applied across  
12 the refractive spectrum. These are not meant to be the  
13 numbers.

14 DR. McCULLEY: Dr. Pulido?

15 DR. PULIDO: And when we talk about "or an  
16 increase of at least 6 lines of vision," is that Snellin  
17 [ph.] vision--

18 DR. BELIN: Yes, or it could be--again, that is a  
19 general--it's just a thought process that I think you should  
20 come up with rather than having arbitrary breaks into 1 to  
21 3, 3 to 6, 6 and above.

22 DR. McCULLEY: Dr. Pulido?

23 DR. PULIDO: And you don't mention anything about  
24 stability over time. Did you want to add anything about  
25 stability of results, or no?

1 DR. BELIN: You are correct, I did not put  
2 stability in, and I think that needs to be done, but I think  
3 that is already in the document. And different procedures  
4 do--I think we are talking about when the sponsor shows  
5 stability, and that will be different per procedure.

6 DR. McCULLEY: Mike, I'm not sure I quite agree,  
7 although I have not heard the rifle analogy before, and I  
8 would have intuitively thought that, but my experience  
9 doesn't really quite bear that out.

10 Do you really think we need significantly  
11 different criteria? Again, these are guidelines. They are  
12 not absolute. And the guidelines could be tighter, but they  
13 have some play in them. Do you think that with the play that  
14 is in the guidelines as they are now, we really need  
15 different guidelines beyond what we already have? I guess I  
16 am not too sure about that.

17 DR. BELIN: I think that if we applied the initial  
18 guidelines--and again, this was generated almost 3 years  
19 ago, really, in thought--if we applied the initial  
20 guidelines that we originally utilized in the 1 to 6 range  
21 to 10 to 15 D corrections, we would not have many things  
22 pass.

23 DR. McCULLEY: I guess I'm not 100 percent sure  
24 about that.

25 Dr. Wang?

1 DR. WANG: Ming Wang.

2 Again, I think that as an elective procedure, we  
3 should all aspire to do no harm, and best corrected visual  
4 acuity is one of the most important parameters. I was just  
5 wondering how it the 3 percent loss of best 2 lines  
6 achieved, based on what data, perhaps some satisfaction  
7 surveys of patients. And also, should that percentage also  
8 be proportional to the preop degree of myopia? Someone who  
9 was -15, if best corrected ended up being 20/30, could be  
10 very happy, and they could be limited by the technology of  
11 very deep ablation, and someone who is -2 may not be very  
12 happy if best corrected ended up 20/30.

13 DR. McCULLEY: My experience has been that a -12  
14 to -14 is much more forgiving of things not being perfect.  
15 It changes their world so completely that if things aren't  
16 quit right-on--I have a +1.25 right now, which is awful--  
17 that's the last thing I want. It happens to be a young  
18 person who was -14, and he is delighted. But based on that,  
19 I would not recommend changing the guidance. I would think  
20 that when the data is reviewed for a group of -12 to -14s,  
21 that would be taken into consideration, and I think we can  
22 apply intelligence in interpretation to the guidance better  
23 than trying to come up with additional artificial numbers.

24 DR. BELIN: I think what you are saying, though,  
25 is what we are trying to do, that is, you are saying we have

1 patients who are a -12 who end up being a +1 or a little bit  
2 above, that would normally have been listed as a  
3 complication and adverse event, who are very pleased because  
4 they started off as a -12. In that case, that would not  
5 have been listed; that would have been an acceptable result  
6 considering what they started with. And that's what the  
7 whole goal of this is.

8 DR. McCULLEY: Yes. I'm just not sure we can  
9 accomplish that by creating numbers before the fact rather  
10 than intelligently reviewing data that comes in under a  
11 guidance. You know, it is a guidance, it is not an  
12 absolute.

13 DR. BELIN: I think that's all this was meant to  
14 be is a guidance. Again, this is what I was asked to do, so  
15 I was doing it--

16 DR. McCULLEY: Oh, I understand. As best I  
17 remember, you came up sitting at the table with what is now  
18 in the guidance off the top of your head--

19 DR. BELIN: Correct.

20 DR. McCULLEY: --and it was wonderful. I'm just  
21 not sure--maybe that's what caused some of the baldness--

22 DR. BULLIMORE: Objection. Out of order.

23 DR. McCULLEY: --but that's not super.

24 Another hair-challenged person--Dr. Bullimore?

25 Dr. BULLIMORE: I prefer the term "follically-

1 challenged."

2 [Laughter.]

3 DR. BULLIMORE: I have heard the rifle analogy  
4 before, and as somebody who is usually accused of pointing  
5 it at both feet, I find it quite useful.

6 I have just a couple comments. Firstly, we  
7 haven't been asked by the agency to address safety issues.  
8 This was merely an effectiveness question. So if we want to  
9 adhere to our previous agreement, we should probably do so.

10 I think Michael has approached this in good  
11 spirit, and I think it makes good sense. I have a couple of  
12 observations. Rather than saying "a reduction of 85  
13 percent," I think in order to account for under- and  
14 overcorrections, we should say "within plus or minus 15  
15 percent," and change the verbiage to that.

16 The fact that we don't need a plus or minus for  
17 the cylinder and the fact that it should be lower takes into  
18 account the nature of the beast--and I'll talk about that a  
19 little later--so I would agree again, in terms of guidance  
20 and spirit of the document--I think that's a reasonable  
21 approach.

22 Where I start to disagree with Michael is on some  
23 of the issues of an increase of at least 6 lines of vision.  
24 Even using ETDRS charts of Bailey-Lovey [ph.] charts of  
25 similarly constructed charts, we often only have 6 or 8

1 lines above 20/40. So we would need to get into moving the  
2 patient one meter, half a meter, whatever, in order to  
3 rigidly apply that. It just doesn't seem practical, even  
4 though the spirit is clearly well-founded.

5 That's my 2 cents' worth.

6 DR. McCULLEY: You'd have to define the lines  
7 above 2400, I guess, to take that approach.

8 DR. BULLIMORE: Yes.

9 DR. McCULLEY: Dr. Macsai?

10 DR. MACSAI: Michael, my comments about this  
11 jumping-off point would be that there are a number of things  
12 in your suggestions that are perhaps not applicable when you  
13 are dealing with the higher-myope patient. It seems to me  
14 that what we really want to know is what can the device do--  
15 can it do what it says it is going to do--so we really just  
16 want to know the attempted versus achieved outcomes, because  
17 in a -20 D myope, there may be no patients who can see  
18 20/30, ever. So the device would fail simply on the basis  
19 of one of these criteria. So--

20 DR. BELIN: I don't have any absolute criteria of  
21 20/30.

22 DR. MACSAI: Well, Number 4.

23 DR. BELIN: Well, that's a safety. We just said  
24 that we're not going to--and this assumes--4 is a safety.  
25 It's best spectacle corrected visual acuity; it is not

1 uncorrected visual acuity.

2 DR. MACSAI: Well, if we're going to just talk  
3 about efficacy, we want to know if it is effective--does it  
4 do what it says it is going to do--and why don't we just  
5 stick with attempted versus achieved; and then you have to  
6 measure it in a cycloplegic manner to find out what it truly  
7 achieves and be done with it.

8 DR. BELIN: Okay, but your comment that no patient  
9 who is a -20 may get 20/30 is exactly the point of this,  
10 that we are setting up different criteria for the -20 than  
11 we are for the -3.

12 DR. MACSAI: But if we go by attempted versus  
13 achieved, we don't have to change the criteria based on the  
14 preexisting myopia that the patient is treated for--or their  
15 best potential vision.

16 DR. BELIN: Excuse me?

17 DR. MACSAI: We don't have to even deal with their  
18 best potential vision or their preoperative myopia.

19 DR. BELIN: But if you are doing attempted versus  
20 achieved, you are either going to have a fixed number, or  
21 you are going to have a percentage of what you started with.

22 DR. MACSAI: Right. That's what I would  
23 recommend.

24 DR. BELIN: Then, we're just dealing with--that's  
25 fine. I'm just saying--it's the same thing--we're dealing

1 with a percentage of the correction that you are able to  
2 obtain.

3 DR. MACSAI: Right. And I want to know why you  
4 picked 85 instead of 90 percent.

5 DR. BELIN: For absolutely no reason. That's why  
6 I said I didn't want to put in any number, and the one that  
7 I really didn't want to put in is the first line, which is  
8 "The following must be present in--blank--percent."

9 I kind of used the 85 because everywhere else, I  
10 really used plus or minus 15 percent. And I kind of looked  
11 over some data, some of which was summarized in one of the  
12 recent survey articles. But you can say 90, you can say 85.  
13 The studies are somewhat nebulous, and when you get to the  
14 higher corrections, the patient populations are not very  
15 large. So I purposely started off by saying that I don't  
16 mean to have these numbers as the numbers. It's a thought  
17 process. If people want 88 percent, 93 percent--that's  
18 something you have to decide on. But I agree that--what  
19 you're saying is really what I am saying, that it is a  
20 percentage of the attempted correction. That's really all  
21 I'm trying to say.

22 DR. MACSAI: The other thing is the reduction--in  
23 the old guidance document, we talk about induced manifest  
24 refractive astigmatism of greater than 2.0 D should occur in  
25 less than 5 percent of subjects. And I like the idea that

1 we reduce that 2.0 D. That's ridiculous. That's way to  
2 high. We shouldn't be inducing astigmatism.

3 DR. McCULLEY: Let me ask a point of clarification  
4 from the FDA. You have uncorrected visual acuity, which is  
5 an effectiveness measure. "MRSE," you wrote here. Do you  
6 mean best spectacle corrected visual acuity--that's manifest  
7 refractive spectacle acuity.

8 DR. MACSAI: No. It's spherical equivalent.

9 DR. McCULLEY: Spherical equivalent. Okay. So  
10 that gets into predictability, so we are getting into two  
11 issues here--one is effectiveness, and one is  
12 predictability--right?

13 Dr. Van Meter?

14 DR. VAN METER: Woody Van Meter.

15 One thing that needs to be pointed out to this  
16 comment is that attempted versus achieved is important, and  
17 that's one of the things that we're looking at; but in the  
18 past, I believe we have used uncorrected acuity as sort of a  
19 quality standard because the shape of the ablation, the  
20 quality of the cut, how fast it resurfaces, the quality of  
21 the epithelium afterward, the amount of haze, is not  
22 measured this way. The best way of determining the quality  
23 of the procedure is really how they see without glasses  
24 afterward.

25 So I wouldn't throw out best corrected acuity. I

1 think that that's important. And I wouldn't throw out  
2 uncorrected acuity.

3 DR. McCULLEY: As I understand it, those were  
4 standing as is; we were not considering those. It was  
5 really effectiveness and predictability that we were  
6 addressing.

7 DR. MACSAI: Right.

8 DR. McCULLEY: Effectiveness is measured by  
9 uncorrected visual acuity--which we already know that we may  
10 not be targeting plano for distance--and then, the spherical  
11 equivalent is the predictability +/-1.0 D or +/-0.50 D, that  
12 we have in the guidance already.

13 DR. VAN METER: But I believe that best corrected  
14 spectacle acuity and uncorrected acuity are issues that are  
15 not necessarily safety; they can be efficacy issues, too.

16 DR. McCULLEY: Best spectacle, they are not being  
17 asked to address any change from what exists in the guidance  
18 document. They would stand as they are. They are not  
19 suggesting to us that we would change those, but they are  
20 also, by not asking us to address them, suggesting they are  
21 going to delete them. They would still be there.

22 Marcia, you had your hand up first.

23 DR. YAROSS: Marcia Yaross. A couple of quick  
24 points.

25 First of all, I think the concept of a sliding

1 scale, if that is the way that the data will be evaluated by  
2 the panel and by the agency, I think it is very helpful for  
3 sponsors to have that expressed in the guidance document to  
4 help them know what kind of criteria will be used in the  
5 evaluation. So I think that is a benefit to having a  
6 percent reduction addressed if that is in fact one of the  
7 things that will be looked at in determining if the  
8 statutory threshold of the probable risks being outweighed  
9 by the probable benefits is met.

10 The second point, if we do start looking at  
11 specific numbers, I think it is important to recognize that  
12 in Dr. Belin's document, the first statement is that it  
13 assumes entrance criteria of 20/20, and in the existing  
14 guidance, it talks about entrance criteria of 20/40 or  
15 better. So in comparing numbers, if we are comparing the  
16 ones that are put up as a straw man in this document, there  
17 does appear to be a difference in the underlying  
18 assumptions, and those may need to be addressed.

19 DR. McCULLEY: I think these would be safety  
20 issues relative to a person with preexisting 20/20.

21 DR. BELIN: Right.

22 DR. McCULLEY: I don't think that's discontinent.

23 Dr. Bradley?

24 DR. BRADLEY: It seems to me there are two ideas  
25 here. One is that you correct to within a certain

1 percentage of the original refractive error or to within a  
2 certain dioptric range of, let's say, emmetropia. And it  
3 seems to me two factors will lead to errors here. One will  
4 be the mean effect of your procedure, and one will be the  
5 underlying variance of your procedure.

6 In the discussion so far, we have not separated  
7 those two factors out, and I think that what Dr. Macsai was  
8 talking about, separating out the idea of, let's say,  
9 emmetropia being a de facto standard if one uses the  
10 targeted final refraction, you can use that targeted final  
11 refraction to effectively factor out errors of the mean--  
12 that is, if your instrument can only produce 10 D of  
13 refractive change, and you have a 12 D myope, you  
14 effectively let them know that you are targeting them to be  
15 2 D myopic at the end. That is not an error at this point;  
16 it is only the variance in the procedure that produces the  
17 errors, then.

18 So I think that if you use targeted as part of the  
19 criteria that you are setting up, then you effectively can  
20 remove the mean error, and you can only deal with the  
21 variance, which is where I think we should be.

22 DR. BELIN: When I reread the first part under 1,  
23 I did say "of target." It was "A reduction of 85 percent or  
24 more of preexisting myopia or hyperopia based on spherical  
25 equivalent or within +/-0.50." but it was of target; the

1 target applies to whatever you are--let me just make one  
2 other comment. The reason I purposely left off any  
3 percentage in the first statement, "The following must be  
4 present in--blank--percentage" is because I was asked to try  
5 to base this on some data, but if you change, which we are  
6 definitely going to do, the numbers below, then I didn't  
7 want to put 90 percent in and say 85 percent, or +/- 15, and  
8 have that then change to +/- 10 percent, and not go back and  
9 say that 90 percent really doesn't apply any longer--maybe  
10 now it's only 85 percent.

11 So I kind of purposely left it blank.

12 DR. McCULLEY: I don't follow why you would really  
13 want to have a percent in the beginning if we are setting  
14 percentages below.

15 DR. BELIN: You have to have--

16 DR. BULLIMORE: I think it's useful to focus on  
17 what the FDA or Morris has asked us to look at. If you turn  
18 to page 8 of the guidance document, under Section B, this is  
19 really what we are addressing. The sponsor has asked to  
20 report the proportion of eyes that achieve predictability of  
21 the manifest refraction spherical equivalent of +/- 1.0 D  
22 and +/- 0.50. And then, as part of the guidance document,  
23 it says "for myopes under 7 D, minimum of 75 percent of  
24 subjects should be within 1.0 D, and at least 50 percent  
25 should be within 0.50 D."

1           What Mike was proposing is that we replace the  
2 percentage and the +/- with two percentages. So, assuming  
3 we are still talking for under 7 D for the moment, let's  
4 take the midpoint, 4 D, so without changing our guidelines  
5 or without renegotiating our lines in the sand, we would  
6 rewrite this to say "minimum of 75 percent of subjects  
7 within 25 percent," 25 percent being +/- 1.0 D for a 4 D  
8 myope, "and at least 50 percent of the subjects within 12.5  
9 percent."

10           So we replace a percentage and a confidence  
11 internal in diopters with two percentages, and that's the  
12 thing that I think we're having a little difficulty with in  
13 terms of whether that's going to be any easier to interpret.

14           I think the spirit of Michael's suggestion is a  
15 good one. It is the implementation and recrafting of a  
16 guidance document that becomes a little more hazardous.

17           DR. McCULLEY: Dr. Ferris?

18           DR. FERRIS: Rick Ferris.

19           I find these lines in the sand curious to start  
20 with. Is the purpose of the line in the sand to say that if  
21 you don't get to this proportion, you need not apply, in  
22 which case, the people doing the trial will, I think,  
23 inevitably try to limit the number of extreme patients, -18,  
24 -20, because they are going to affect their proportion?  
25 These fixed numbers will, I think, result in our getting

1 less information rather than more.

2 I think the point that Michael has made is a good  
3 one, and I think we have talked about this before, that is,  
4 that as the severity of the disease gets higher, our  
5 threshold for saying this was an effective procedure ought  
6 to be flexible. And I'm not sure that it isn't enough in  
7 the guidance to say for higher degrees of myopia, less rigid  
8 success is necessary, and leave it at that. The bar will be  
9 set by the first one that comes in and gets this committee  
10 to say we approve this as good enough; then the next group  
11 is going to have to come in and have something at least  
12 equivalent. It seems to me that that's enough.

13 DR. McCULLEY: You've said it much better and  
14 maybe more acceptably. That is what I was trying to say  
15 before, and how that needs to be worded--again, these are  
16 guidelines. They have a title: Guidelines.

17 Dr. Stark?

18 DR. STARK: I'll echo what Rick said. refractive  
19 surgeons will tell you that when you correct the -8 to -10 D  
20 patient, you get one eye plano and the other eye -1. They  
21 now have the expectations of the 1 D myope, so they will get  
22 reoperated; they will get that flap raised 3 or 4 months  
23 later.

24 So those are data that we can collect, and as long  
25 as the patients are adequately informed, I think that's the

1 most important thing. But I think the flexibility, as  
2 pointed out by Rick, would be appropriate.

3 DR. McCULLEY: Dr. Bullimore?

4 DR. BULLIMORE: I just wanted to remind my panel  
5 colleagues of two issues. One is that we are frequently  
6 forbidden to discuss previous PMAs when evaluating a new  
7 PMA; and also, the FDA's Modernization Act, I guess, is  
8 encouraging the development of PDPs, Product Development  
9 Protocols, so we will have to set a line in the sand at some  
10 stage in the future--or, sorry--we may have to set a line in  
11 the sand at some stage in the future if a manufacturer  
12 chooses to go that route.

13 DR. McCULLEY: Dr. Rosenthal?

14 DR. ROSENTHAL: There is a sense that obviously,  
15 at the higher myopic range, you are willing to accept less.  
16 What I don't get is about how much less. And I know that's  
17 sort of putting you on the spot a little bit to draw some  
18 line, but you know, it is very difficult to say "less." I  
19 mean, is "less" one percent? Is "less" 5 percent? Is  
20 "less" 45 percent?

21 So there are a couple of major, major guidelines,  
22 parameters, that we use: UCVA 20/20 or better, UCVA 20/40  
23 or better; intended versus achieved; +/- .50; intended  
24 versus achieved +/- 1.0. And it would really just, from my  
25 standpoint, having had to review documents, give me some

1 idea of what the panel would feel is acceptable. We know it  
2 is acceptable from zero to 6. We know less is acceptable  
3 from 6 to 12. But approximately how much less? That is an  
4 idea I would like to get from this discussion.

5 DR. McCULLEY: Do you want an idea, or do you want  
6 a number to put in the guidance?

7 DR. ROSENTHAL: Sorry?

8 DR. McCULLEY: Do you want an idea, or do you want  
9 a number that you could add to the guidance?

10 DR. ROSENTHAL: Well, whatever you feel  
11 comfortable providing.

12 DR. McCULLEY: Dr. Belin?

13 DR. BELIN: I think that just what you worded is  
14 exactly my motivation for this. We are not accepting less.  
15 We are accepting exactly the same, whether it is 1, 2, 8 or  
16 12 D. That is, we are expecting a certain degree of  
17 efficacy percentage correction.

18 I'll use a drug analysis. When we look at  
19 antibiotics, we look at a 90 percent reduction in bacterial  
20 load. Whether there was a million bacteria or 10 million  
21 bacteria, it's a 90 percent reduction. That's what we look  
22 at. We don't say you reduce the bacteria by a million.  
23 Well, if you have 10, then 9 is not an acceptable result.  
24 It's a percentage reduction. We are not accepting less. We  
25 are expecting the same, but we are trying to go 10 times

1 further. That's the whole motivation behind this.

2 DR. McCULLEY: I'm not sure--and maybe I didn't  
3 understand--but my impression as a treating physician is  
4 that my patients accept much broader range if they are a  
5 high myope than my low to moderate myopes accept, which has  
6 a lot to do with I accept. And a -12 who is made a +1  
7 or a -1 is in general a happy camper. I mean, there are the  
8 younger people who maybe end up -1 who didn't want to be  
9 retreated, but if they are 45, they love it. So I'm not  
10 sure.

11 Dr. Pulido wanted to jump in on this?

12 DR. PULIDO: No, I--

13 DR. McCULLEY: Do you want to de-jump?

14 DR. PULIDO: Well, I go ahead and say I think the  
15 85 percent number that Dr. Belin gave isn't so bad. It  
16 turns out that for a 20 D myope, you have to be at least -3  
17 D afterward. So that's not a bad number. A -10 would be -  
18 1.50. I think it's very reasonable. Those would be happy  
19 patients.

20 DR. McCULLEY: Dr. Rosenthal?

21 DR. ROSENTHAL: I am particularly interested in  
22 Dr. Macsai's comment about the intended versus achieved,  
23 because that is really--the laser says it purports to do  
24 something, and does it do it as it purports to do it. Does  
25 it do it less well at -10, or does it do less well at -12,

1 or should it do the same all the way?

2 Now, the UCVA might be a little different for  
3 other factors, but the intended versus achieved is the  
4 accuracy of the laser in doing what it says it does, and  
5 that is primarily what we, I think, are here to evaluate.

6 DR. McCULLEY: And there is going to be a limit to  
7 what we can do in the cornea. I doubt very seriously that  
8 we can do 20 in the cornea, but then, with setting these  
9 guidelines, they can then be translated over to other  
10 things--

11 DR. ROSENTHAL: But if you have 20, you don't try  
12 to do 20; you try to do 14 or whatever, and you say: I  
13 tried to do 14, and I got to 13.75, or something like that.

14 DR. McCULLEY: Dr. Macsai?

15 DR. MACSAI: Dr. Rosenthal, I agree, I think, that  
16 the consumer, the physician, the patient want to know if the  
17 device can do what it says it does. So if you are a -20  
18 myope, you know, corneal refractive surgery may not be the  
19 procedure for you. It may be one of those intraocular  
20 lenses, it may be--who knows what? But the point is if it  
21 says it corrects 20 D of myopia, it should correct 20 D of  
22 myopia 90 percent of the time. That's what I would consider  
23 an efficacious device.

24 DR. McCULLEY: Dr. Waxler?

25 DR. WAXLER: With great hazard, I enter this

1 controversy. I think that what I was asked to point out was  
2 that we were trying to be fair in our assessment of what is  
3 reasonable assurance of effectiveness. We don't want to  
4 ride on the back of a particular applicant. So when we have  
5 a sense of the community what would be acceptable, as  
6 several of you have said, what would be acceptable to you  
7 with the patient population you would treat, would you find  
8 it acceptable. So make some rough guesses about what  
9 percentages would be acceptable. It seems to me that's what  
10 we are trying to get from you, so we can have some  
11 independent target that is not linked to one particular  
12 manufacturer we happen to know at the moment.

13 That's the quandary we get into. So this  
14 discussion is actually very helpful, regardless of your  
15 having a specific recommendation.

16 DR. McCULLEY: One of the problems with the  
17 percentage is that--let's go back to the 75 percent--a -4  
18 who is left a -1 is not happy; a -12 who is left a -3 is  
19 probably not happy, either; a -12 who is left a -1 may be  
20 happy. Then, percentages end up being problematic in my  
21 mind to a degree, too--I'm going to get corrected--well,  
22 wait a minute. Dr. Wang had his hand up first.

23 DR. WANG: I am hearing pros and cons on whether  
24 to set a line in the sand on both sides, and I also  
25 recognize that these points that Michael put up have both

1 efficacy and safety features in there.

2           Is it possible we dissect the issue into two  
3 parts--safety, for which we set stricter guidelines, because  
4 again, elective procedure, do no harm; and efficacy, set  
5 more flexible, and therefore, based on Dr. Macsai's  
6 suggestion in principle, can laser do what it intends to do.  
7 Therefore, we would set two different types of criteria at  
8 the onset, stricter, with more numbers on the safety side,  
9 and more flexible on the efficacy side.

10           DR. McCULLEY: Point of clarification. We are  
11 talking not about safety in this at all; we are talking  
12 about efficacy and predictability.

13           DR. WANG: But Number 4 is a safety feature.

14           DR. McCULLEY: No--that was something he  
15 introduced himself, and he withdrew, realizing that it was  
16 not requested to be addressed.

17           Dr. Ferris?

18           DR. FERRIS: Rick Ferris.

19           I guess I would like to go back to, I think, what  
20 is probably more important--and maybe I am missing  
21 something--but it seems to me there are lasers out there  
22 now, and this is being done. Whether we like it or not,  
23 it's being done. To the extent that a patient can decide  
24 whether he would like to have it done, it would seem to me  
25 that it would be most useful to know what your equipment

1 does. I would think that if a machine takes you from -20 to  
2 -5, it was effective, it did something. Now, a -20 who is  
3 now a -5 may feel like he died and went to heaven if he can  
4 wear -5 spectacles compared to the -20 spectacles, and  
5 couldn't wear contact lenses.

6 So I wouldn't want to prejudge or preclude that  
7 patient and his doctor from making that determination. What  
8 I would like to say is that if you are going to have a  
9 device that purports to be effective for people with more  
10 than -10 or more than -15, you had better show us the data  
11 that shows what the efficacy rate is.

12 I think Dr. Wang's point was a good one. I don't  
13 want to relax the safety side of this, and we have said that  
14 it has to be this safe or we are not going to allow it on  
15 the market. You had better show me that it does something,  
16 but I am not sure that correcting 15 D of myopia in some  
17 circumstances might not be sufficient. What I'd rather see  
18 is--show me a good spectrum of each of them, and we'll let  
19 the physician decide whether that degree of correction is  
20 worth doing in a patient, because maybe it is and maybe it  
21 isn't, depending on the patient.

22 I think what you are saying is show me what your  
23 machine does.

24 DR. ROSENTHAL: That's exactly what I would like.  
25 It's fairly obvious that if a machine says it can get to

1 +.50--I forget what the--50 percent of the time--+/- .50, 50  
2 percent of the time, you re willing to accept that from -1  
3 to -6, and 75 percent of the--I keep forgetting--

4 DR. FERRIS: That's right.

5 DR. ROSENTHAL: --75 percent of the time at +/-1--  
6 is this acceptable--is this exactly what you would expect at  
7 the higher level, or would you expect a little less? You  
8 say you would expect a little less.

9 DR. McCULLEY: No. It's not saying 100 percent.  
10 Neither one of them says 100 percent. Yes, I personally  
11 would say 50 for +/- .50 and 75 for +/-1, yes, I think  
12 that's fine pu and down the range that we are talking about,  
13 personally.

14 DR. ROSENTHAL: The whole range.

15 DR. McCULLEY: Yes.

16 DR. ROSENTHAL: Good.

17 DR. McCULLEY: Of target, of target.

18 DR. ROSENTHAL: Yes, yes, of target--not of--

19 DR. McCULLEY: Not of emmetropia, but of target,  
20 yes.

21 DR. ROSENTHAL: --right--of what they decide they  
22 want to do in that case.

23 DR. McCULLEY: Yes. I still think that's fine.

24 Dr. Belin?

25 DR. BELIN: I think we're all saying the same

1 thing. We're just fighting about how to word it. You're  
2 asking for targeted. If you want to say a laser is able to  
3 obtain 85 percent of targeted correction 90 percent of the  
4 time, with a maximal correction of 15 D, that's really the  
5 same thing. It's just wording it differently. Granted, it  
6 doesn't matter what you start off with; there is a maximum  
7 you can obtain, otherwise, you won't meet that criteria. We  
8 are able to obtain 85 percent of targeted correction 90  
9 percent of the time--and don't use these numbers--

10 DR. ROSENTHAL: No, no; I know.

11 DR. BELIN: --90 percent of the time, with a  
12 maximal correction of 15 D. That's really exactly the same  
13 thing we have; we're just wording it differently.

14 DR. McCULLEY: But you don't want to put 15 D. It  
15 depends on the thickness of the cornea and the procedure.

16 DR. BELIN: Well, no--the total, the maximal  
17 correction if procedure and instrument dependent. We're not  
18 talking about a laser.

19 DR. McCULLEY: Dr. Waxler?

20 DR. WAXLER: Just a comment. You had asked me  
21 earlier about my advice about time. I would just point out  
22 that we are at 3:45. You are the chair, and I just wanted  
23 to point that out.

24 DR. McCULLEY: Thank you. I'm going to let Dr.  
25 Macsai have a word, and then what I'd like to do--let me ask

1 out loud, since I can't otherwise--I'd like to allow about 5  
2 minutes if anyone from industry would like to jump in if  
3 they have a completely different perspective from where we  
4 are, or if they agree--but don't feel the need to take 5  
5 minutes to say "We agree," but if you disagree, to tell us  
6 why.

7 Dr. Macsai?

8 DR. MACSAI: Michael, it might be that I'm feeble-  
9 brained, and it's too complicated with two percents, but I  
10 just think it's very useful to know if a device, no matter  
11 what it is--a batter, a laser, whatever--does what it says  
12 it's going to do. But as far as the guidance document  
13 revisions--and we weren't supposed to talk about safety--but  
14 what about the astigmatism issue that Michael brought up?

15 DR. McCULLEY: That's safety. Induced astigmatism  
16 or--

17 DR. MACSAI: Inducing a stigmatism is going to be-  
18 -

19 DR. McCULLEY: --correcting astigmatism? Two  
20 issues. Inducing is safety, and percent of correcting, Mike  
21 brought into this, which fits into the same--

22 DR. MACSAI: Well, is overcorrection going to be  
23 considered efficacy or safety?

24 DR. McCULLEY: If you induce astigmatism greater  
25 than 2 D, it's a safety issue as the document is written.

1 Have we provided you with enough food for thought?  
2 Do you have any questions for us?

3 DR. WAXLER: No, I don't.

4 DR. McCULLEY: Okay. I am not going to retire the  
5 panel yet on this question, but at this point, I'd like to  
6 ask if anyone from industry would like to make a comment.

7 [No response.]

8 DR. McCULLEY: Seeing none, can we--we don't vote  
9 on these things, guys--do we want to take a break, or do we  
10 just want to go straight through? Okay, we'll go right on  
11 through.

12 Dr. Waxler?

13 DR. WAXLER: Thank you.

14 The next question, for Dr. Bullimore: What  
15 aspects of astigmatism should be reported? What values of  
16 astigmatic change would provide a reasonable assurance of  
17 safety or effectiveness? What methods of vector analysis  
18 should be used, and what aspects of the vector analysis  
19 should be reported? What vector changes after laser  
20 refractive surgery would provide reasonable assurance of  
21 safety and effectiveness?

22 **Report of Mark A. Bullimore, Ph.D.**

23 DR. BULLIMORE: On relatively short notice, I was  
24 provided with blank overhead sheets and a pen, just in case  
25 they were needed.

1 I really do want to speak just to the questions  
2 raised by Morris and talk about what aspects of astigmatism  
3 I personally believe should be reported. Must like  
4 spherical corrections, in my mind, the most important thing  
5 is the percentage of the cylinder that is corrected, so in  
6 my mind, the most important thing will be to give the  
7 preoperative mean astigmatism and the postoperative mean  
8 astigmatism, and compare the two. That is based on past  
9 experience, which I am not allowed to talk about; that's  
10 what the panel seems to have based their judgments on.

11 So what do we need to do beyond that? Well, there  
12 are some concerns about, I think, vector analysis, and  
13 vector analysis is just a tool that helps us understand not  
14 so much the way the laser or other device worked, but  
15 perhaps the way it didn't work, and there are good reasons  
16 for also including some vector analysis in the summary data.

17 Let's just take an individual patient, and  
18 ignoring axis for the moment, if a person is +2.00 D of  
19 cylinder before and +.50 afterwards, I think we'd all agree  
20 that the reduction in astigmatism is 1.50 D, and comparing  
21 the post as a function of the pre, we've got a 1.50 D  
22 correction, and that's 75 percent of what they started with.  
23 That is important information to go in the PMA, and that's  
24 what I want to see.

25 Now, because we don't have axis information, we

1 don't know what has really gone on here. For example, had  
2 this been axis 90 before and axis 90 afterward, obviously,  
3 then, without the need for vectors, we figure out that +1.50  
4 is the change. But if the axis before is 90, and the axis  
5 afterward is 180, clearly, the total refractive change  
6 induced by the laser is +2.50.

7           What is those axis are not so nicely aligned at 90  
8 or at 180--that's when we need vectors. And I think it is  
9 useful to include vector analysis to actually determine the  
10 amount of surgically induced refractive cylinder. And  
11 really, the surgically induced refractive cylinder is  
12 defined by the agency and maintained in what I put down in  
13 my notes is really the vector difference between these two  
14 cylinders.

15           Now, I don't want to lecture for 10 minutes on  
16 vectors, so I am going to sit down and quit while I am  
17 ahead.

18           What else do you want to know?

19           DR. McCULLEY: Is everyone comfortable with the  
20 issues of vector analysis and the calculation of the  
21 surgically induced correction--is that the agency's  
22 definition? SIRC is vector difference?

23           DR. WAXLER: Yes.

24           DR. McCULLEY: That's correct. And you are  
25 leaving it to the sponsor to use whatever program or

1 formula--presumably, whatever program one uses, the  
2 difference between the vectors is a real number, but there  
3 may be different software packages to get there. But that  
4 really isn't the issue, or shouldn't be the issue. The  
5 difference is what is the issue.

6 DR. WAXLER: I think I'll try without Malvina  
7 here, but that may be hazardous also. I think one of the  
8 issues is--well, what you have already addressed--but the  
9 other issue is, again, is there a line, is there an  
10 acceptable amount, is there an amount of inducement that is  
11 acceptable or not, because we have to make actual decisions  
12 on particular documents. We can't dither around. We have  
13 documents in there, and it has certain numbers. Is there an  
14 amount of change that is beyond the pale that, clinically,  
15 you would find unacceptable?

16 DR. BULLIMORE: Again, in my report to you,  
17 Morris, I did a very cursory review of the recent literature  
18 just to see what was being reported out there, and of the 7  
19 studies that I could readily access on the National Library  
20 of Medicine database, the average percentage reduction in  
21 cylinder--that's just ignoring vectors, ignoring everything,  
22 just taking the average pre and the average post--you come  
23 up with 70 percent. That, if you like, is the standard of  
24 care that people are reporting or at least getting  
25 published. Maybe the people who report 30 percent reduction

1 don't get published, so there may be some inherent bias in  
2 the literature.

3           Again, we can't talk about specific PMAs, but in  
4 my Table 1 in my notes, the data I used there, if you like,  
5 percentage of efficacy was 79 percent. That's a pretty  
6 impressive number. I would be happy to entertain a number  
7 of 70 percent or lower to go in the guidance documents.

8           One thing that is important to remember is when  
9 you are correcting astigmatism, you have, if you like, two  
10 degrees of freedom--what the laser or device does and how  
11 accurately it is aligned. And when you start playing around  
12 with vectors, you find that if you are off by 10 degrees,  
13 even if you make the appropriate cylindrical correction or  
14 the appropriate astigmatic correction, you lose a third of  
15 your effectiveness or efficacy. You are down to 66-point-  
16 whatever percent just by being 10 degrees off. If you are  
17 off by 5 degrees, you are still only just batting above 83  
18 percent.

19           And if you think about what is involved, there  
20 measurement of the preoperative cylinder, alignment of the  
21 patient, and then alignment of the device. There are three  
22 sources of error, and if those combine in a destructive way,  
23 and you end up with 10 percent, which is not unreasonable,  
24 you are only going to correct two-thirds of the astigmatism.

25           So when you see numbers in the literature of 70

1 percent, they are believable. When you see numbers like 79  
2 percent, they are very impressive, very impressive, and I  
3 don't think we should necessarily put the bar too high.

4 DR. McCULLEY: Would you have CMD/IRC and SIRC/IRC  
5 percentage the same, or different percentages?

6 DR. BULLIMORE: No. They should be very  
7 different. I think that in terms of our primary evaluation  
8 of--did everybody get this; I know the panel got them--the  
9 numbers I wrote down, I'll write them down again. The preop  
10 was 1.42--these are means--the postop was 0.30, so the CMD,  
11 which is the--this is FDA language--cylinder magnitude  
12 difference, was 1.12. That's just simple arithmetic there.  
13 And then, the percentage, CMD/IRC, assuming that the IRC,  
14 the intended refractive cylinder, was the same as the preop,  
15 it's just this as a percentage of this. And in the data  
16 that I used in my example, that was 79 percent.

17 Now, if you want to now calculate the SIRC, in the  
18 dataset which I had access to, I calculated that to be 1.36  
19 D for a preop or intended refractive correction of 1.42. We  
20 are probably going to judge the device's efficacy based on  
21 this number. We don't need immediately to resort to vector  
22 analysis to help us judge whether this is an effective  
23 device. In the same way, we can make judgments on spherical  
24 correction based on their percentage effectiveness, or the  
25 number of people between +/- 0.50. We can get most of our

1 gut reaction from this.

2           It becomes something of an intellectual exercise  
3 to figure out whether they don't hit 100 percent because of  
4 axis problems or because the laser just doesn't do that  
5 well. And vector analysis can help you figure that out, and  
6 with this dataset that I had access to, when you work out  
7 the spherical-induced refractive change, that's the mean  
8 astigmatic change induced by the device. You've got 1.36,  
9 which is very close to that which was intended.

10           So on average, the device is doing what it  
11 purports to be doing, and either the errors are due to  
12 alignment errors, or there is some inherent variability in  
13 the device such that sometimes it hits a little under,  
14 sometimes it hits a little over.

15           DR. McCULLEY: So your recommendation CMD/IRC  
16 would be 70 percent based on literature--

17           DR. BULLIMORE: Yes.

18           DR. McCULLEY: --and your CIRC/IRC?

19           DR. BULLIMORE: I don't think we need a  
20 recommendation for that. It's an academic issue.

21           DR. McCULLEY: Okay.

22           DR. BULLIMORE: If this is good, let's approve it,  
23 and let's go home.

24           DR. McCULLEY: Okay. So you've heard that--Dr.  
25 Bullimore is saying he doesn't think you need a CIRC/IRC.

1 I'm going to take them in the order in which I saw hands.

2 Dr. Bradley?

3 DR. BRADLEY: It seems to me it depends a lot on  
4 what the FDA really wants from these numbers. You might  
5 think that from the patient's point of view, the bottom line  
6 is how astigmatism do they end up with, and if that's the  
7 case, it's purely the magnitude of the astigmatism, that one  
8 number, that you need.

9 But personally, I think the FDA would be doing  
10 the patient population a huge disservice by not demanding an  
11 appropriate vector analysis, and I'll give you an example of  
12 why. As Dr. Bullimore just pointed out, there are two  
13 reasons you could end up with the wrong result. One, you  
14 corrected too much or too little astigmatism, or two, you  
15 corrected it at the wrong axis.

16 An example he gave is if you were off by 30  
17 degrees--you had the right amount of correction, but you ere  
18 off by 30 degrees--you end up with only half the correction.  
19 One solution could be to just do it again or double the  
20 amount. Well, you end up with a larger error by doing that.  
21 You don't end up--you don't result in the appropriate  
22 correction, but you end up with a worse correction.

23 So I think the only way you are going to know this  
24 is if you do the appropriate vector analysis. You will not  
25 know the source of your error, and therefore you cannot

1 improve the procedure, and ultimately, I think the patient  
2 population needs the procedure to be optimized, and that  
3 cannot be done without vector analysis.

4 DR. McCULLEY: Dr. Bullimore, and then Dr. Belin,  
5 then Dr. Ferris.

6 DR. BULLIMORE: Just a point of clarification. I  
7 agree with everything Dr. Bradley said. I am not suggesting  
8 that vector analysis not be done. I am only suggesting that  
9 in terms of a guidance document, the only number that we  
10 need to give is this--whatever it is called--CMD/IRC value.  
11 They should do the vector analysis. That is important  
12 information for primary reviewers and the public. I am just  
13 suggesting that they don't have to meet a target value for  
14 anything else other than that.

15 DR. McCULLEY: Before we go to Dr. Belin, could  
16 you suggest a target or be thinking about a target, and I'll  
17 come back to you in a minute.

18 Dr. Belin?

19 DR. BELIN: yes. I just want to bring up so that  
20 we all understand--I don't disagree with anything that was  
21 just said, but we have changed the way we are now looking at  
22 the results from what percentage obtains, let's say, 90  
23 percent, gets 90 percent of a correction to just a single  
24 percentage.

25 So we are saying here, whether it's 70 percent or

1 79 percent, if we do the same thing for myopia, we say 90  
2 percent of correction, that means half of them could be 80  
3 and half of them could be 100. So we have changed the way--

4 DR. BULLIMORE: You have got to deal with them  
5 differently, because with myopia, you have undercorrection  
6 and overcorrection. What I am suggesting here is a number  
7 that takes into account both of these.

8 Let's take 70 percent, so that patients on average  
9 get within 30 percent of their cylinder correction. That's  
10 the same as saying +/- 30 percent for sphere. So they're  
11 not entirely different.

12 DR. McCULLEY: If we're doing this for you, and  
13 you're having to talk while we're discussing it, it doesn't  
14 do you much good. Did you hear what was just said--well,  
15 you couldn't have, because you were talking to each other.

16 Do you have a question that you want to interject  
17 here?

18 DR. EYDELMAN: Yes.

19 DR. McCULLEY: Okay.

20 DR. EYDELMAN: Malvina Eydelman, FDA.

21 We perfectly agree internally with Dr. Bullimore's  
22 recommendation of using CMD/IRC as the guideline, but  
23 including vector analysis for additional information without  
24 necessarily adding a specific target for it. We just had  
25 two additional questions within Dr. Bullimore's analysis

1 whenever you are ready.

2 DR. McCULLEY: Okay.

3 Fred--Rick?

4 DR. FERRIS: Rick Ferris.

5 I guess I'd like to make the same comment,  
6 perhaps, or a similar comment to what I made for the overall  
7 myopia guidance. That is, it seems to me that this question  
8 of efficacy, we ought to think of as--it's like approvable  
9 and nonapprovable; it is effective, or it is not effective.  
10 Well, life to me--I guess I live in a world of grays--I  
11 understand that you have to do effective or not effective.  
12 Well, it is clear that any of the devices that we're talking  
13 about, if we're going to talk about a ration of 0.7, it's  
14 doing something, and the real measure of its efficacy is  
15 what it did. Show me what it did, and then I'll know how  
16 effective your machine is.

17 It seems to me--and I recognize you can't talk  
18 about previous data, but we do that all the time, at least  
19 in medical--in new drugs--and that is that it has to be  
20 equivalent to the drug that's on the market. So the  
21 guidance, it seems to me, is going to be a floating  
22 document. Right now, 0.7 is a reasonable goal; people have  
23 shown that you can do that much--if you can't do that much,  
24 don't bring your device to us--but 0.7 10 years from now  
25 might seem laughable.

1           So it seems to me that the guidance ought to  
2 change. For right now, the 0.7 seems perfectly reasonable,  
3 and we want to see how they finally wound up, not just this  
4 fraction, but how did you do compared to how you wanted to  
5 do.

6           And I'd say the same thing for myopia, that the  
7 overall guidelines are there for lower levels. We said,  
8 well, we'll relax it a little bit; show us what you do, and  
9 unless it's ridiculous, we're likely to say, well, that  
10 becomes the new benchmark, and then the guidelines ought to  
11 change on the drug that's available today.

12           DR. McCULLEY: Do you disagree with the 70  
13 percent?

14           DR. FERRIS: No, and I say the reason for the 70  
15 percent is that it's documented, that that is what can be  
16 done, so if you are going to come in with less than that, it  
17 doesn't seem to make a lot of sense.

18           DR. McCULLEY: Okay. Ming, then Gary, and if  
19 anyone else wants to wave their hand, I'll write you name  
20 down and get to you.

21           Ming?

22           DR. WANG: Ming Wang.

23           Food for thought for the panel and for the  
24 audience: Two patients, both with uncorrected vision. One  
25 is minus one plus 2 cylinder 180, the other is minus 6 plus

1 2.

2           The point is should we be thinking about the  
3 amount of residual cylinder after correction if the  
4 corrected cylinder is, say, 0.7 or whatever, in relationship  
5 to the sphere part, giving, for example, the intrinsic  
6 technical difficulty of high degree ablation. Just as  
7 sphere part is more inaccurate, the cylindrical correction  
8 would be also inaccurate.

9           So perhaps conceptually, not talking about  
10 percentages, but conceptually, the cylindrical correction  
11 should also be, say, a total spherical equivalent dependent  
12 concept.

13           DR. McCULLEY: I'm not sure of the answer to that.  
14 I don't know that we've talked about it. Maybe in a moment,  
15 when we have another brief break, industry can make some  
16 comment based on their data and bigger data base.

17           Gary?

18           DR. RUBIN: I wanted to go back to the point that  
19 I must have missed that you raised a minute ago, that if we  
20 are only talking about CMD/IRC, that's different from saying  
21 a certain percentage of people fall within a CMD/IRC of "x".

22           Mark, you said that it isn't different--or, I'm  
23 not sure. Do I make myself clear here?

24           DR. BULLIMORE: Yes.

25           DR. McCULLEY: They would report is in percentage

1 of patients. It would be in the data.

2 DR. BULLIMORE: You could do that, but again, you  
3 are trying to end up with either two percentages or a  
4 percentage and a number. I am a lumpner rather than a  
5 splitter, so I thought overall, if the device reduces 60,  
6 70, 80 percent of astigmatism, that's what I want to know.  
7 Obviously, in terms of reviewing the PMA, looking at the  
8 variance about that is an important consideration, so if  
9 you've got an average 75 percent reduction in cylinder, but  
10 half the patients only get a half reduction, and the other  
11 half get a full reduction, that is important information,  
12 too.

13 We seem to have enough difficulty dealing with  
14 astigmatism to begin with, so taking it to the lowest common  
15 denominator in terms of a single number was the approach I  
16 was proposing--but I am open to changing that, and I am here  
17 to advise, much like everybody else is.

18 DR. McCULLEY: Have you come up with a  
19 recommendation, or leave it soft, as the FDA has now jumped  
20 in and let us know they are happy with it soft?

21 DR. BRADLEY: Two recommendations. First, for  
22 those marginally dyslexic members of the panel like myself,  
23 this acronym-based conversation is very difficult to follow--  
24 --but I have tried to convert acronyms into real world  
25 vectors, and it seems to me it is possible to define the

1 tolerable error in terms of a vector length. I am having  
2 trouble giving a number to that, but I could certainly think  
3 on that a little longer.

4 DR. McCULLEY: I don't think we are going to get  
5 any closer right now, so rather than beat on that dog, why  
6 don't we ask that Dr. Bradley provide that additional  
7 insight to you for you to take under consideration later;  
8 okay?

9 DR. WAXLER: That's good enough. Thanks.

10 DR. McCULLEY: Now, are there other--you had two.  
11 Did that cover both? You were just fussing about the  
12 acronyms; that was number one.

13 DR. BRADLEY: Yes.

14 DR. McCULLEY: Okay. Any other comments from the  
15 panel at this point? We are not necessarily done.

16 Dr. Eydelman?

17 DR. EYDELMAN: I just wanted to clarify whether  
18 this 70 percent CMD/IRC is the panel's recommendation and if  
19 that's applicable regardless of the range of astigmatism in  
20 the application or in the PMA. In the literature, we see  
21 much less accuracy once very small cylinders are trying to  
22 be achieved, so if the population is skewed, you will get  
23 different outcomes.

24 DR. BULLIMORE: Yes. The 70 percent in terms of  
25 changing astigmatism divided by the preoperative--that's in

1 plain English--I think is based on what's out there, and  
2 yes, you are absolutely right, if you are trying to correct  
3 0.50 or 0.75, you're not going to hit that target rate, and  
4 I think it behooves the sponsor to go off the meaningful  
5 levels of astigmatism in order to meet that benchmark and  
6 not be frivolous in a correction of 0.50 D of cylinder.

7           Such a huge proportion of the population has  
8 cylinders of less than 4, and most of those have cylinders  
9 of less than 2, I think there's no reason to lump it into  
10 categories right now. But this is intended as guidance and  
11 not necessarily as a line in the sand.

12           DR. McCULLEY: I think it would be the same thing,  
13 except going the opposite way, as we said with sphere--  
14 become more tolerant as you get into the lower ranges  
15 because it is harder to peg it.

16           You had two things.

17           DR. EYDELMAN: Yes. If I may bring you back to  
18 Point 2 in Dr. Bullimore's review, he was referring to the  
19 table attached on page 24. That table was created due to  
20 your request at the last panel in October in trying to give  
21 the residual astigmatic error some clinical meaning, and we  
22 believe we created what you recommended. At that time, I  
23 believe the idea was that even though some of the cells in  
24 this table will have very little significance, others will  
25 have greater significance, and our hope was that you would

1 attempt at some point to fill in percentages for that table  
2 that would be acceptable.

3 DR. McCULLEY: Dr. Bullimore?

4 DR. BULLIMORE: Basically, what I said in my  
5 review was that this is my least favorite table, in part  
6 because the data I have seen in the past have been difficult  
7 to interpret. And I'll soften that. I think there is  
8 useful information to be gained by this table. The problem  
9 is you've got a table with the order of 25 cells in it, and  
10 if we recall recent PMAs--and I can't remember them, so I'll  
11 think of a number--where we have 100 or so patients, we've  
12 got 4 people in each cell on average. And then, asking us  
13 to come up with an acceptable number is not reasonable.

14 I would be willing to put a gray zone and say  
15 nobody should fall in this area. For example, nobody with a  
16 residual--I can't even think in this--

17 DR. McCULLEY: We need more time to think about  
18 that, I think, and more data to see over time.

19 DR. BULLIMORE: Yes.

20 DR. McCULLEY: I actually kind of like that table.

21 DR. BULLIMORE: I do, too.

22 DR. McCULLEY: It was my favorite table.

23 DR. BULLIMORE: Well, it's yours. You can keep  
24 it.

25 DR. McCULLEY: Any other comments from the panel?

1 [No response.]

2 DR. McCULLEY: Dr. Wang brought up a question  
3 which--let me see if I can restate it--is the accuracy of  
4 correcting a 2 D cylinder dependent on the degree of sphere  
5 being attempted in correction?

6 I have not been aware of that. Is there?

7 Mark?

8 MR. ODRICH: Mark Odrich, VISX. Having conducted  
9 some of these trials, I'd like to suggest that the error of  
10 the measurement begins to get in the way, and when you start  
11 looking at a vector, you begin to realize that the error of  
12 the measurement for the lower amounts of astigmatism is much  
13 more significant than for the higher, so it is actually  
14 counterintuitive. It is Heisenberg [ph.] rolling in his  
15 grave.

16 What actually occurs is that when you have higher  
17 degrees of cylinder, it is more accurately portrayed, and  
18 there is a lower amount of noise. The paper that is always  
19 cited is Zadnik [ph.] in 1992, but the problem with that is  
20 that she limited the people coming into her repeatability of  
21 ocular measurements to somewhere between 5 and 6 D, and I  
22 don't quite remember where, with smaller amounts of  
23 cylinder.

24 But we started to look, as a secondary role  
25 through Columbia University, at repeatability of

1 measurements as you get higher, and in fact this discussion  
2 of myopia and astigmatism, both efficacy criteria are  
3 fraught with problems once you don't take into account the  
4 errors of the measurements.

5           So I think they are actually interrelated issues,  
6 but I think the interesting thing is that actually, the  
7 magnitude is easier to correct as it gets higher, because  
8 your measuring ability is more reproducible, so--

9           DR. McCULLEY: That wasn't the issue, Mark.

10           MR. ODRICH: I'm saying technically, that that  
11 affects our technical ability.

12           DR. McCULLEY: That wasn't the issue. In  
13 correcting the same degree of cylinder--pick a 250 that  
14 should be fairly easy to get the axis--

15           MR. ODRICH: A -6 and a -1.

16           DR. McCULLEY: A -1 plus 2.50, -6 plus 2.50.

17           MR. ODRICH: That would be laser by laser, I would  
18 imagine, but I can tell you for the VISX it is no more  
19 difficult. There is nothing technically more difficult.  
20 But what is more difficult is that measurement, and that's  
21 why I'm saying to you--

22           DR. McCULLEY: What's more difficult is the 0.50  
23 versus the 2.50.

24           MR. ODRICH: It's the quantification as a vector.  
25 That's what the clinicians are doing. So I think it does

1 answer that question.

2 DR. McCULLEY: Okay.

3 Dr. Belin?

4 DR. BELIN: i was going to comment on something  
5 else, but just on that last comment, Mark did imply that  
6 that's going to be laser-dependent, and again, I don't want  
7 to make this laser- or procedure-dependent, but it clearly  
8 will be dependent, because different lasers go to different  
9 ways of correcting cylinder at a certain level. A plano  
10 minus 3 is treated differently than a minus three minus  
11 three the way you correct cylinder. But the fact that a  
12 company for a procedure decides to treat it differently  
13 doesn't mean we are going to set different efficacy  
14 variables for it.

15 I wanted to make a comment earlier that I think  
16 vector analysis--my specialty, you can talk about all day--I  
17 think that when push comes to shove, you are going to end up  
18 finding that at about a 70 percent CMD/IRC is going to turn  
19 out to be roughly the same as about a 50 percent reduction  
20 vector analysis. You will find out that it will be about  
21 the same. I'll let Dr. Bradley do that.

22 DR. BULLIMORE: I think it actually goes the other  
23 way. I think you'll find that the surgically induced  
24 refractive change is actually going to be bigger than the  
25 change in the absolute cylinder values.

1 DR. McCULLEY: It was in your example.

2 DR. BULLIMORE: Yes.

3 DR. McCULLEY: Now that we're all confused again--  
4 so Dr. Bradley is going to work on this more to make further  
5 recommendation to you.

6 Does the panel have any further comments on this  
7 particular item?

8 [No response.]

9 DR. McCULLEY: Do you have any further questions  
10 for us on this item?

11 [No response.]

12 DR. McCULLEY: Then, we can go on to the last  
13 item.

14 Doyle, I'm sorry, I didn't see you. Dr. Stulting.

15 DR. STULTING: Doyle Stulting, Emory University.

16 To address a point that was raised that you asked  
17 about, which was the effect of spherical correction on  
18 astigmatic change, we just completed a multivariate analysis  
19 and in fact submitted the paper to the FDA, but apparently,  
20 it didn't get distributed. And there is an interaction term  
21 of the sphere on the astigmatic correction, so indeed it  
22 does have an effect, at least in our dataset.

23 DR. BULLIMORE: Which way does it go?

24 DR. STULTING: It increases the variability. It  
25 was an ANOVA, analysis of variation, so the sphere increases

1 the variability of the astigmatic correction.

2 DR. McCULLEY: As you go up.

3 DR. STULTING: Yes.

4 DR. McCULLEY: So I guess--we did not have that  
5 data, and it does then support the issue that, at least in  
6 terms of discussions that I remember from the panel, brings  
7 up a new issue.

8 DR. WAXLER: Correct. That paper that Doyle spoke  
9 about came to late for me to distribute to hardly anybody,  
10 actually.

11 DR. McCULLEY: Okay. So that's something that you  
12 will take under consideration and advisement for the future.

13 DR. WAXLER: Your pleasure.

14 DR. McCULLEY: Next point?

15 DR. WAXLER: Are you ready to go to the next  
16 issue?

17 DR. McCULLEY: Yes.

18 DR. WAXLER: The next issue, Dr. Stark will speak  
19 to, and that is can the amount of residual corneal tissue in  
20 refractive surgery be reduced to 250 microns without an  
21 unreasonable risk of endothelial damage--that is,  
22 endothelial cell loss or ectasia. If yes, then, what should  
23 be the new amount of residual tissue that should remain to  
24 provide a reasonable assurance of safety? What precautions  
25 should be taken to minimize compromising endothelial

1 integrity?

2 **Report of Walter J. Stark, M.D.**

3 DR. STARK: Thank you. Could you turn the slides  
4 on for me, please?

5 I enjoyed reviewing this issue, and as a start-off  
6 for the review, I was given the article by Jones et al. from  
7 Emory contributed by--my secretary wrote Stulting et al.,  
8 but it's Jones at all--and contributed by Edelhauser and  
9 Thompson, and Doyle Stulting, all coauthors.

10 The purpose of this study was to assess the effect  
11 of the laser in situ keratomileusis on corneal endothelium,  
12 and it is probably difficult for some of you to read that,  
13 but it is in a handout that was provided at the desk.

14 In effect, they studied the corneal endothelium in  
15 98 eyes of 65 patients, with correction from 2.75 D up to  
16 14.5 D of myopia, 2 weeks and 12 weeks after LASIK. Of  
17 importance, probably, is that 91 percent of the patients or  
18 59 patients had a history of contact lens use.

19 With the analysis of their data, just as a quick  
20 summary, there was no statistically significant change in  
21 the mean endothelial cell density or coefficient of  
22 variation at 12 weeks and at the times postoperatively  
23 comparing to preoperative values, but the percent hexagonal  
24 to cells will decrease by 1 percent at the 12-week visits.

25 So their conclusions were that corneal endothelial

1 cell density and morphology were unchanged 2 and 12 weeks  
2 after LASIK, and so there was no clinically significant  
3 effect on corneal endothelial cell density by cuts down as  
4 deep to the point that they left in their higher myopic  
5 cases a residual corneal bed of 208 microns.

6           The variation in corneal bed depth or thickness at  
7 the end of treatment would have gone down to that 208  
8 microns.

9           One of the problems with this report and most of  
10 the other reports on this field is the calculation and  
11 thickness of the residual stromal bed. There have been  
12 several studies that have shown--they used the Chiron  
13 corneal shaper--but there have been several studies that  
14 have shown the variability in flap thicknesses within +10,  
15 +20 microns, but there have also been a number of studies  
16 that have shown that there are tremendous variabilities in  
17 how thick these corneal shapers or corneal cutters actually  
18 cut. And I told a number of people and spoke with others,  
19 and Eric Donnenfeld has a paper that is submitted--it was  
20 presented to ASCRS--and they used the Chiron automated  
21 corneal shaper with a 160 micron plate.

22           In this study, they measured the corneal thickness  
23 by pachymetry and calculated the corneal thickness of the  
24 flap by subtracting that, and the thickness of the flap  
25 using a 160 micron plate to cut a 160 micron depth ranged

1 between 81.4 microns and 170 microns. That means that this  
2 corneal cutter in their hands was off by up to 60 microns.

3           The only way you can tell this is by measuring the  
4 residual bed by ultrasonic pachymetry after you have made  
5 your corneal flap. And there are several problems with  
6 that--it is a little bit rough, and it doesn't measure quite  
7 as easily. Surgeons are reluctant to hydrate the bed to  
8 give them a better surface to measure the actual thickness,  
9 because that might affect the rate of ablation.

10           But I have also found from other surgeons that  
11 this has been a problem not only with the automated corneal  
12 shaper but the new hansatome [ph.] Several surgeons in our  
13 area have had unexpected thin flaps and buttonholes and have  
14 sent their units back on several occasions. I have just  
15 visited with Lindstrom and Hartan in Minneapolis. They did  
16 a study and calculated that using a 180 micron blade with  
17 the hansatome, they were initially getting cuts of 110  
18 microns, and they sent it back on a couple of occasions, and  
19 now the 180 micron blade seems to be cutting 150 microns.

20           So that's a major problem with any of the studies  
21 that have not measured directly the thickness of the bed or  
22 tried to measure the thickness of the flap. There may be  
23 some ways to get around that. It has been suggested that  
24 one might be able to take high-frequency ultrasound and  
25 measure the actual thickness of the anterior flap by a

1 little reflectant that one can see there, and that would be  
2 a good study for some refractive surgeons.

3           So there are two questions that were asked of me:  
4 Is there short- and long-term damage to the endothelium as  
5 evidenced by specular microscopy, and is there a loss of  
6 integrity of the cornea that can lead to ectasia. I think  
7 these are very important questions because, not shown well  
8 there, but on page 3 of the handout, there is depth versus  
9 the amount of cut. If we are going to try to correct and  
10 leave 250 microns of tissue in the residual corneal bed,  
11 with a 6 mm diameter cut, you can correct about 10 D with  
12 the LASIK procedure. If you want to leave 200 microns, you  
13 can go up to about 14 D. If you make a smaller optical  
14 zone, you can correct more, but one of the problems of LASIK  
15 and high myopia, especially the smaller diameters, is night-  
16 time glare, so that would increase that.

17           If you use the multizone treatment--Figure 2, for  
18 those who have the handout, and I passed out to the panel  
19 the updated one--you can correct up to about 13 D and still  
20 leave 250 microns of tissue in the residual cornea--but  
21 that's assuming your cut is 160 microns, and it is also  
22 assuming an average corneal thickness of about 0.52 microns.

23           The potential mechanisms for laser damage to the  
24 endothelium would include thermal, mechanical damage from  
25 the shock wave, and damage from the ultraviolet light.

1 Also, we have to consider that the different lasers have  
2 different levels of fluence and repetition rates. But  
3 experimental studies on the rabbit and non-human primates  
4 demonstrate that superficial ablation probably doesn't cause  
5 any damage from the laser. But if you get down to cuts that  
6 are within 40 microns of Descemet membrane, there is damage  
7 to the corneal endothelium, as shown by Koch et al. A  
8 recent presentation by the Emory group, Lim, Jeon and  
9 Edelhauser showed that if you get to 175 microns from  
10 endothelium in the rabbit, you are going to cause some  
11 damage to the endothelial barrier function at 175 microns  
12 and also, another aspect of their study, to 150 microns.

13           The clinical studies in general don't show a loss  
14 of corneal endothelium after excimer laser, except  
15 Pallikaris--and I e-mailed him and faxed him, but I have not  
16 gotten a response--reported in 10 eyes a 5.7 percent loss of  
17 endothelial cells at 6 months and a 10.6 percent loss of  
18 endothelial cells at one year, and treatment of -8 to -17 D.

19           An interesting article by Proeme and associates--  
20 and I put some of the references in here--and also by Perez-  
21 Santonja--shows that contact lens use apparently decreases  
22 the central endothelial cell count by about 7 percent. And  
23 if you take those contact lenses off, people will get an  
24 apparent 7 percent increase in corneal endothelial cell  
25 loss. So I can't remember exactly in the Emory article, but

1 the patients may have actually had a loss of 7 percent  
2 endothelial cells, but gained 7 percent because the contact  
3 lenses were taken off, so it's a little difficult to tell if  
4 they are not standardized. So in effect, to show a 10  
5 percent endothelial cell loss, you would have to lose 17  
6 percent endothelial cells.

7 We did show that excimer laser probably does do  
8 something to the endothelium. This was the histology of a  
9 macular corneal dystrophy patient that we reported after a  
10 failed PTK, and you see this electron-dense collagen  
11 deposition in Descemet membrane, and that was shown in non-  
12 human primates in experimental studies, and this was shown  
13 in a clinical case. So the excimer laser tickles the  
14 endothelium--does something--and I asked Dick Green if he  
15 had any more thoughts on it, and he said he didn't, that the  
16 collagen that's migrating up through Descemet membrane is  
17 produced by the endothelium, and he didn't know why, except  
18 that it showed some minor trauma to the endothelium--and  
19 that was a cut of about 300 microns; we were 300 microns  
20 away from the endothelium. So that's just food for thought.

21 The Jones et al. article did not address the issue  
22 of ectasia, and ectasia has not been reported to be a great  
23 problem after excimer laser, except by Seiler and Associates  
24 in the Journal of Refractive Surgery in 1998, this year. He  
25 reported on three cases of ectasia after use of the excimer

1 laser, and these were in corrections from -10 to -13 D.

2 I calculated two of them that I could best  
3 calculate--and I have included this article; I am sure some  
4 of you will want to do the addition again--but one of the  
5 cuts left about 215 microns of tissue, and the other, 175  
6 microns of tissue, again, assuming that the keratome did  
7 what it did, and that's a big assumption.

8 So that would suggest that as you get close to 215  
9 microns, you may increase the risk of ectasia.

10 I talked to Richard Abbott, and he said that he  
11 has now got a case of ectasia in a patient who was referred  
12 to him after three repeat lasers.

13 Lindstrom said that he uses 200 microns as the  
14 minimum amount of residual corneal tissue and has found no  
15 ectasia, and he points out that hyperopic ALK gives no  
16 effect if 200 microns of tissue are left. So you don't get  
17 the bowing-forward effect, again, assuming that the machine  
18 is cutting what it is supposed to cut.

19 While Slade states that he thinks 200 microns of  
20 the tissue residual is okay, he plans for 250, to be  
21 conservative, and this would also allow for some  
22 retreatment. He points out that in MKM, myopic  
23 keratomileusis, which is no longer done, that you can go  
24 down to the 200 microns, and that's a full cut across at 200  
25 microns rather than 200 microns residual thickness only

1 being right in the center, which you would expect with  
2 LASIK, and he said that they did not get any cases of  
3 ectasia.

4           So in summary, I think there appears to be little  
5 evidence from the literature, and in particular, the Jones  
6 paper, even considering that there are some deficiencies in  
7 the paper, about what is the actual corneal thickness left.  
8 There seems to be little evidence of serious loss of  
9 endothelial cell function at 12 weeks, but the limitation of  
10 that study as with others is that it is only 12 weeks'  
11 follow-up, and I think one would have to look at at least a  
12 year follow-up to see if there is any effect from the  
13 endothelium or other long-term problems.

14           Ectasia has not been reported to be a problem,  
15 except that by Seiler. Gary mentioned that--I think he  
16 indicated in his presentation that they have not had any  
17 problems with ectasia, and there is a large number of  
18 studies that they are following. But with Seiler, that one  
19 case did have ectasia with 250 microns of tissue. And I  
20 polled several people, and they are listed here, who are I  
21 guess what you could consider respected refractive surgeons  
22 who have had a moderate experience, and most of them, except  
23 for Lindstrom and Slade, strongly recommended adhering to  
24 the 250 micron limit.

25           So in summary, I think we don't have adequate data

1 to tell us what the minimal safe residual thickness of the  
2 corneal bed after LASIK would be without the risk of ectasia  
3 or corneal endothelial damage. Several surgeons polled have  
4 stressed that we need to have guidelines not only on the  
5 residual corneal bed thickness, but also on the optical zone  
6 profiles and the diameter and thickness of the flap. And I  
7 would add to that that I think the FDA should look at some  
8 way to document good manufacturing practice of the makers of  
9 the keratome--that, even though they are 510k, if people are  
10 getting these keratomes, especially people who might not be  
11 corneal experts or experts in refractive surgery, and go in  
12 and set the machine up right and have a 160 or 180 micron  
13 plate, they should be getting 160 or 180 micron cut, plus or  
14 minus 10 microns, rather than plus or minus 50 or 60  
15 microns.

16 So I think we ought to stick to 250 at this point,  
17 especially with other modalities of refraction becoming  
18 available, maybe the intracorneal or the intraocular lenses,  
19 but I really think we should do something about  
20 standardizing these corneal cutters.

21 DR. McCULLEY: That was outstanding. I agree with  
22 a lot that Walter said. I could restate, but I don't know  
23 how much restating we need to do of what he said. I think  
24 he covered it very thoroughly and brought up at one point or  
25 another throughout his discussion all the major points that

1 I have thought of.

2 One flaw in these LASIK studies that some people  
3 seem to continue to fall into is not to measure the corneal  
4 thickness preop and then make assumptions; it's easy to do.

5 Yes?

6 DR. GRIMMETT; Michael Grimmatt.

7 I thought that was a beautiful presentation by  
8 Walter. I have one comment. I am not sure the data that  
9 underlines Dick Lindstrom's comment regarding hyperopic ALK  
10 doesn't give ectasia of 200 micrometers of tissue are left  
11 posterior to the cut. Perhaps there is some additional data  
12 that I don't know of. In Archives of Ophthalmology in April  
13 of this year, Lyle et al. published a series of hyperopic  
14 ALK in which approximately one in five developed progressive  
15 ectasia, and they analyzed to see whether the depth of the  
16 cut was related to those who developed ectasia, and they did  
17 not find a statistically significant result.

18 Perhaps Lyle's study just points out the fact that  
19 you have discussed, that these keratomes don't cut  
20 accurately, so maybe they were all over the map, and that's  
21 why they couldn't find it. But unless Dick has published  
22 otherwise--I tried to look that up recently and was unable  
23 to find that data.

24 DR. McCULLEY: Dr. Wang?

25 DR. WANG: Ming Wang.

1 I understand the 250 guideline actually came from  
2 mid-air, with the intuitive assumption that the biological  
3 system tends to have a full degeneracy, without any  
4 experimental data. Is that true, to the knowledge of  
5 panelists?

6 DR. McCULLEY: Where did the 250 come from? I  
7 think what we have seen--and Walter alluded to it with the  
8 CRS study--they had no ectasia, but they limited it to 250.  
9 So I think there is a good deal of data to support that 250  
10 undisturbed is safe for endothelium and  
11 structural/anatomical integrity. So whether it came from  
12 the air or not, it seems to be a good number, and the  
13 question is whether we can go deeper or not, and I don't  
14 think we have that information.

15 Something else that Walter brought up that is a  
16 really big point and that Dr. Grimmett also hit on is that  
17 we need to know--and I am surprised--there is variability on  
18 the depth of the cut depending on the intraocular pressure,  
19 so it may vary with the same keratome cutting well, if the  
20 pressure in the eye varies. But there seems to be more to  
21 it than that, that the keratomes don't necessarily always  
22 cut with everything being standardized within a tolerance  
23 limit that we are keratorefractive surgeons would like to  
24 see. And I would agree with the +/- 10 microns. If you  
25 start getting more than that, until we know whether we can

1 go below 250 or not--right now, at 250, if those things cut  
2 20 to 30 microns deeper, we may be approaching 200, and that  
3 may not be safe.

4 DR. WAXLER: Just to comment on Dr. Wang's  
5 comment, the 250 didn't come totally out of thin air.  
6 Basically, it came out of an analysis of what was reported  
7 in the literature with regard to animal work at the time and  
8 also adding some 50 microns. The data that was available at  
9 that time, several years ago, was that somewhere in the  
10 neighborhood of 200 was probably a threshold area. And  
11 then, we knew that the microkeratomes were sloppy, but no  
12 one really knew how sloppy, so we just added 50 microns. So  
13 it was kind of out of air, but not completely. Every now  
14 and then, we revisit that to see if we have any more  
15 information.

16 I appreciate your analysis; it was excellent.

17 DR. McCULLEY: Dr. Bullimore?

18 DR. BULLIMORE: Just a question in terms of the  
19 ectasia. Can you only actually tell it is ectasia when it  
20 is progressive, or may there be some ectasia happening in a  
21 large majority of patients, but you just don't know what is  
22 ectasia and what is the laser not working properly?

23 DR. STARK: I think that's a good point. Many of  
24 these people are doing corneal modeling after surgery. They  
25 do it when the epithelium clears up at 2 or 3 months and

1 then later. And so far, there are only these three cases  
2 reported. Those are the only cases in the literature.  
3 Richard Abbott's case is after three LASIK; that's just bad  
4 surgical mentality, I guess. Those are the only three  
5 reported cases, but they are of concern, because they are  
6 reported by an experienced investigator, Seiler, who I  
7 believe, from reading the article--I can't remember for  
8 sure--but I believe they did the cases, so you would expect  
9 that they had ruled out keratoconus prior to the surgery.

10 DR. McCULLEY: We also don't know how many cases  
11 have been done below the 250, with the 250 being the  
12 guideline. It seems like until we have a series with  
13 significant numbers of patients measuring the thickness of  
14 the flap, knowing how accurate that is, and therefore  
15 exactly how much posterior cornea is left undisturbed, until  
16 we have that data, I don't see how we can get off of the  
17 250. Does anybody else?

18 Mike?

19 DR. BELIN: I was just going to agree with Mark.  
20 We actually don't know if we get ectasias, because what we  
21 are doing is we are using topography, and we are doing pre  
22 and post, but we have flattened--because we are dealing with  
23 higher corrections in LASIK--we are flattening the central  
24 cornea. You would either have to look at patients that  
25 you've done cuts and no ablation, which is never going to

1 happen, or you look at the peripheral cornea, and the  
2 problem with that is we know the reliability of the  
3 topography out there is very, very poor. So it really is an  
4 unanswered questions.

5 Part of the reason we may see regression, which we  
6 are, people admitting in the higher corrections, is we may  
7 be getting a slight ectatic effect. You don't really know.

8 DR. McCULLEY: Other comments?

9 [No response.]

10 DR. McCULLEY: Do you have any further questions?

11 [No response.]

12 DR. McCULLEY: We'll allot 10 minutes for comments  
13 from anyone in the audience who has an additive view or a  
14 differing view.

15 [No response.]

16 DR. McCULLEY: Seeing none, Morris, do you have  
17 anything further?

18 DR. WAXLER: I have one more question that we had  
19 mentioned at the beginning that you have nothing written on,  
20 and I think it is an issue that has come up repeatedly, and  
21 I will address it if this is an appropriate time.

22 DR. McCULLEY: Certainly.

23 DR. WAXLER: Currently, the guidance defines  
24 refractive stability as 95 percent of the eyes reaching a  
25 change of less than or equal to 1.0 diopter of manifest

1 spherical equivalent refraction between two refractions  
2 performed at least 3 months apart.

3           The guidance also suggests confirmation of the  
4 stability estimate with another measure of MRSE 3 months  
5 later. There are two aspects of refractive stability that  
6 we would like you to discuss and make a recommendation to  
7 the agency on: How much change in refraction is reasonable  
8 to expect? A mean difference of zero refraction over a 3-  
9 month interval is ideal, but what is a reasonable change to  
10 expect--0.01 D, 0.10 D, 0.20 D, 0.30 D, 0.50 D?

11           The current guidance implies that the change can  
12 be +/- 1.0 D. Is this reasonable? Should we add a  
13 statistical definition so that the slope of change in  
14 refraction should not be significantly different than zero?  
15 That's the first question; it was a long-winded one, but  
16 that's the first question.

17           Do you want to deal with that one and then go to  
18 the next one?

19           DR. McCULLEY: Why don't you let us know what you  
20 have in store for us?

21           DR. WAXLER: Okay. The second one is if 95  
22 percent of the eyes are within +/- 1.0 D MRSE between two  
23 refractions taken between 3 months and 6 months, then, has  
24 stability been reached at 3 months or 6 months? Should  
25 confirmation of the point of stability be taken at 9 months

1 or earlier?

2 DR. McCULLEY: Okay. We'll go back to your first  
3 question in just a minute. When I re-read the guidance, it  
4 didn't give a time. I had read in the guidance document  
5 itself that between the two intervals, one interpretation of  
6 it was one month apart, two refractions that were the same  
7 one month apart--that was the CRS interpretation of it in  
8 Dr. Kezirian's document. When I read the guidance document,  
9 it said less than 1.0 D of change between two visits. It  
10 didn't say 3 months.

11 DR. WAXLER: Yes, it does.

12 DR. McCULLEY: What page?

13 DR. WAXLER: I don't have the page number with me,  
14 but I'm sure my vast auxiliary staff here will find it.

15 DR. McCULLEY: Okay. I'll look again.

16 DR. WAXLER: I just checked it this morning, and  
17 it said it when I read it this morning.

18 DR. McCULLEY: Okay. I read it in a different  
19 place, and it didn't say 3 months; but here on page 18, it  
20 does. Okay. So it is stated as 3 months. Now that you've  
21 gotten me straightened out--

22 DR. WAXLER: Actually, to make that first question  
23 simpler--

24 DR. McCULLEY: Please.

25 DR. WAXLER: --you have a mean difference between

1 those--you had the 3 months--the guidance only says the 3-  
2 month interval and 95 percent within +/- 1.0 D, but do you  
3 want that curve to be asymptotic [ph.], and at what point do  
4 you want it to be asymptotic? You know, if it changing at  
5 0.3 D, and it is still changing, the person is going to be  
6 back where they started not too long in the future, so the  
7 question is how close to zero do we need to have that  
8 estimate. Again, it's one of these things that you don't  
9 like to deal with, but we have to make a judgment when an  
10 application comes as to whether or not it is asymptotic, and  
11 the change is not unacceptable from a clinical point of  
12 view.

13 DR. McCULLEY: Okay. You said something about  
14 mean. This is 95 percent of individual patients have less  
15 than 1.0 D of change between two visits 3 months apart.

16 DR. WAXLER: Right.

17 DR. McCULLEY: The only way we can judge that  
18 curve other than those two points is to have other points to  
19 know what the slope of that curve is, or what the history of  
20 it is apt to be. So I don't know that we can answer that  
21 from two points.

22 DR. ROSENTHAL: But you have all the points. You  
23 have the mean difference. Not only do you collect the  
24 percentage that has less than or equal to 1.0 D between the  
25 two, but you have the mean difference between the--

1 DR. McCULLEY: The whole group.

2 DR. ROSENTHAL: --no--the mean difference between  
3 the refractions at the two intervals.

4 DR. McCULLEY: Right, and we're saying that 95  
5 percent of the people have to be within 1.0 D difference.

6 DR. ROSENTHAL: That's right, but when you look at  
7 the means, they can--

8 DR. McCULLEY: What means? We're looking at  
9 individual patients in this.

10 DR. ROSENTHAL: The other way to look at it is you  
11 take a mean--

12 DR. McCULLEY: Of the total group. Two different  
13 issues.

14 DR. ROSENTHAL: --a mean of the differences--

15 DR. WAXLER: The mean change.

16 DR. ROSENTHAL: The mean change. Sorry. Thank  
17 you. A mean change, a mean change. That's what I meant to  
18 say.

19 DR. McCULLEY: Okay.

20 DR. ROSENTHAL: And the mean change should get  
21 smaller and smaller as you get closer to stability. Now, if  
22 the mean change of .3--we know if it is .01, it is quite  
23 acceptable, or if it is .05, it is quite acceptable, or even  
24 if it is .1, it is probably acceptable, but--

25 DR. McCULLEY: The mean change is for the total

1 population.

2 DR. ROSENTHAL: Correct.

3 DR. McCULLEY: And we get that data.

4 DR. ROSENTHAL: Yes.

5 DR. McCULLEY: In a different presentation of the  
6 data. So you are saying that to--

7 DR. ROSENTHAL: In the presentation of stability,  
8 we get the issue you first dealt with, and we also get the  
9 mean difference.

10 DR. McCULLEY: The mean change; right. And do we  
11 have a number for mean change?

12 DR. ROSENTHAL: No.

13 DR. McCULLEY: So you're asking should we add to  
14 stability in addition to 95 percent of the patients being  
15 within +/- 1.0 D--or, within 1.0 D 3 months apart--that we  
16 see if we can come up with an acceptable mean change between  
17 two time points to predict stability, which would also  
18 presumably have to coincide with the 95 percent being within  
19 a diopter change.

20 DR. ROSENTHAL: Correct.

21 DR. McCULLEY: Now I understand.

22 Dr. Belin?

23 DR. BELIN: Does it make sense for anyone that we  
24 have a definition of preoperative stability that's so  
25 different from the definition of postoperative stability?

1 The definition preoperatively is 0.50 D or less during the  
2 year prior to baseline exam; the definition postoperatively  
3 is up to 1.0 D over 3 months. To me, that doesn't make any  
4 sense.

5 Now, I don't want to make anyone do a year-long to  
6 show stability, but I think 1.0 D over 3 months is not  
7 stable.

8 DR. MACSAI: Hear, hear. Second.

9 I also would point out that--I know the agency has  
10 access to it, and I didn't know you were going to ask this,  
11 so I didn't bring any of the reprints--but earlier, someone  
12 referred to Carla Zadnik's study on the reproducibility of  
13 refractions, and we do know there is some change in manifest  
14 refraction whether or not you have refractive surgery over  
15 time. So that perhaps a slope of zero may not be within the  
16 nature of the human beast, but perhaps from those two  
17 sources, you could calculate what an appropriate slope would  
18 be.

19 And I would also agree with Dr. Belin's comment  
20 that to have a preoperative acceptability of 0.50 D and  
21 postoperative of 1.0 D is inappropriate.

22 DR. McCULLEY: Now are you sorry?

23 What is the number--I know I have in my mind what  
24 the number is--reproducibility of a refraction, the  
25 spherical component over time?

1 Dr. Bullimore?

2 DR. BULLIMORE: From memory, the 95 percent  
3 confidence intervals from Carla's paper were manifest  
4 subjective refraction with the order, I think, of +/- 0.50  
5 to 0.75--but that's--

6 DR. BELIN: But for the average population, that  
7 doesn't take into--that's an individual variation over time.  
8 The mean population is stable.

9 DR. BULLIMORE: Yes. As was raised from the floor  
10 earlier, we have got to consider two issues here--the  
11 repeatability of our measurement and whether there is an  
12 underlying change in refraction, regression or whatever you  
13 want to call it--creep--and whether there is any inherent  
14 variability induced by the procedure the patient has  
15 undergone.

16 So we are trying to cram all these different  
17 effects into a nice, bite-size number that Morris can go  
18 away and take with him, and it's difficult.

19 DR. McCULLEY: Marian?

20 DR. MACSAI: This is a point at which postmarket  
21 surveillance could answer the question to some degree. I  
22 recall in previous discussions about individual PMAs that we  
23 are not discussing that this issue has come up over and over  
24 again. The postmarket surveillance was done in the PERK  
25 study by looking at the patients 10 years out, and they

1 found some interesting findings.

2 DR. McCULLEY: Other comments?

3 Morris?

4 DR. WAXLER: If I could just add to what Marian  
5 said, I think that our immediate issue, though, is in the  
6 premarket, because we have applicants with particular data,  
7 but we want to be fair, and we want also to do a good job  
8 from a public health standpoint--what is a reasonable value  
9 from the standpoint of a group of clinicians. If you had a  
10 group of patients, and you had a certain change of 0.2 or  
11 0.5, would you be comfortable with a laser that had that  
12 kind of mean difference--

13 DR. McCULLEY: Mean change between the two points  
14 of stability as otherwise defined by our somewhat flawed  
15 numbers.

16 DR. WAXLER: Right. Otherwise what happens is we  
17 get into a game where we're saying, well, no, this one looks  
18 good, and that one looks bad, and you hardly have a stable  
19 footing.

20 DR. McCULLEY: Yes. It would have been nice--  
21 considering the way we approached these other questions,  
22 with one person taking the assignment and really searching  
23 the literature, we could probably do a better job for you.

24 DR. WAXLER: Yes, I think so.

25 DR. McCULLEY: I don't get a sense we are heading

1 in any strong direction.

2 Does anyone else have anything? Dr. Wang?

3 DR. WANG: Ming Wang.

4 With regard to the duration postop, I think there  
5 are some clinical observations which would support one year.  
6 In terms of wound healing, the flap is almost impossible to  
7 lift at one year, meaning the stroma really healed quite  
8 well. Second, most of the refractive surgeons in clinical  
9 practice do not follow patients beyond one year, and that  
10 seems to be working very well. Third, to second Michael's  
11 point, to have equal standards postop, since preop, we have  
12 stability of refraction one year, say, 0.50 D, it would be  
13 reasonable to have. So these three all support intuitively  
14 to me one-year follow-up.

15 DR. McCULLEY: Number one, I can raise flaps at a  
16 year. The interface probably never heals. And I have lifted  
17 flaps at a year. it may be a little bit harder than at 3  
18 months, but I don't think the interface probably ever heals.  
19 And from maybe an ideal standpoint, to require a year or two  
20 or even longer, the more comfortable we get--but again, we  
21 start to get into the issue that I mentioned before, that we  
22 start to delve over from ideal science into the world of  
23 commerce, and there are some things where we have to make  
24 some compromises in the scientific ideal and the practical.

25 Any other comments? Dr. Belin?

1 DR. BELIN: I made a point of suggesting that I  
2 don't think we should have one year; I agree with you that  
3 that is not practical. But 1.0 D over 3 months--and again,  
4 this is not going to be just for lasers; we have some  
5 devices, instruments or implants that may be applicable for  
6 only low levels of correct. Let's say we have a device  
7 that's only applicable from -1.0 to -3.0. Let's say it  
8 corrects 250, which for us is +/- 0.50, and that's a perfect  
9 result. That means that at one month, they are 250; at 3 or  
10 4 months, they are -150, and that meets criteria, and that's  
11 stable. It's not. It meets everything that we have est up,  
12 but it's not stable.

13 DR. McCULLEY: So you are back on the point that  
14 within 1.0 D 3 months apart is probably not a good  
15 guideline, and you would suggest it be 0.50.

16 DR. BELIN: I'll just ask does anyone here think a  
17 1.0 D change over 3 months represents stability. Does  
18 anybody--that's all I'll ask.

19 DR. McCULLEY: Okay. Fair question. Straw poll.  
20 I won't try to restate it. Who thinks that a 1.0 D change  
21 over 3 months or less than 1.0 D is an acceptable definition  
22 of stability--anybody?

23 Dr. Ferris?

24 DR. FERRIS: This is Rick Ferris.

25 It's confusing, because--I think we have to be

1 careful with this--5 percent have the 1.0 D change. If you  
2 expect 5 percent to have a 0.50 D change by chance, just  
3 measurement error, and you have a real 0.50 D change in--I  
4 guess you can figure out what proportion you have to have a  
5 real 0.50 D change to then see a 5 percent 1.0 D change--I  
6 guess you would almost have to have 100 percent having a  
7 0.50 D change to get 5 percent having a measured 1.0 D  
8 change.

9           But you can see--the issue has to do with talking  
10 about individual patients, which I think is difficult, but  
11 you have to do it with regard to complications, and then  
12 talking about the group. And when you are talking about  
13 this drift over time, I think you are stuck with talking  
14 about the group. It is very hard to look at individual  
15 patients. It isn't very hard to look at the change over  
16 time, and that statistic, the average change at each visit,  
17 is a relatively simple statistic to create. And if that is,  
18 as Morris suggested, that statistic ought to be flattening.  
19 It shouldn't continue. If you had a 0.25 D average loss in  
20 the first interval and continued to have a 0.25 D average  
21 loss over the next two intervals, that would be much more  
22 concerning to me than even an initial change in the first  
23 interval and then a flattening.

24           And I was trying to think--maybe you could do some  
25 sort of test of the slope, but I am not sure that that's a

1 good thing to do, either, because for one thing, the larger  
2 the study, the more likely you are to have a statistically  
3 significantly different than zero slope, and that's not the  
4 issue here.

5 I think the issue is that you don't want--I don't  
6 know where the 1.0 D came from, and we can argue about the  
7 number--but you don't want to be losing 1.0 D or more of  
8 efficacy of the procedure, at least not without knowing that  
9 it exists.

10 And I did take some exception to a comment that  
11 was made that, oh, we don't follow these people for after a  
12 year, and it works out okay. Well, yes, it works out okay  
13 because we don't know whether it works out okay or not. So  
14 we don't know what's going on later.

15 So at some point, somebody is going to do a long-  
16 term follow-up of these patients, because obviously, from a  
17 public health point of view, that is important. It may be,  
18 though, that looking at the slope of this difference is an  
19 important direction to go to say that you are reaching  
20 stability and that that slope ought to be less than one-  
21 tenth of a diopter, or that slope out to be less than two-  
22 tenths of diopter. If you still have a drop-off of 0.25 D  
23 every three months, that sounds pretty concerning to me.

24 DR. McCULLEY: And I guess that's what Morris was  
25 asking--what would that slope be. But one of the problems

1 with the mean and why we need or wanted the other  
2 information on the individual patient is that the mean can  
3 be screwed up by somebody going a +1.0 and somebody else  
4 going a -1.0.

5 DR. FERRIS: Oh, absolutely. For efficacy, you  
6 absolutely have to look at those individual patients, but  
7 for this question, I think it may be important to look at  
8 the mean to get some idea of whether there is an on-the-  
9 average recovery--the sort of thing that was seen in PERK,  
10 where on the average, there tended to be a drift in one  
11 direction or another--and I think the only way to assess  
12 that is looking at means.

13 DR. McCULLEY: Well, we do that. The question is  
14 how much of a change in mean from one 3-month point to the  
15 next is acceptable or unacceptable--where is the cut-off--  
16 because we do look at the means.

17 DR. FERRIS: I understand.

18 DR. McCULLEY: What would you suggest would be a--

19 DR. FERRIS: Well, I am a little bit concerned  
20 about doing this by the seat of my pants--

21 DR. McCULLEY: Yes, okay.

22 DR. FERRIS: --but someone between one-tenth and  
23 two-tenths of a diopter. If there is still that level of  
24 drop-off over a 3-month period, and it is consistent--it is  
25 different when it is bouncing around--but when you look at

1 these intervals, and there is a consistent drop-off in that  
2 range, that would make me feel much more concerned than if  
3 it were bouncing around, if it went down, and then it went  
4 up, and then it went back down again. That third back down  
5 is probably a combination of errors between the two previous  
6 ones. It is the trend over time, and maybe that's the  
7 issue, that the average trend over time can't be more than  
8 one-tenth or two-tenths of a diopter.

9 DR. McCULLEY: You've got to consider what points  
10 you have on the curve.

11 DR. FERRIS: Yes.

12 DR. McCULLEY: I mean, they are going to have 3  
13 months and 6 months.

14 DR. FERRIS: Well, if you just have 6 months--

15 DR. McCULLEY: Well, no--we may have 12--

16 DR. FERRIS: Yes. I think you need the 12 for  
17 this particular calculation. Even that would be--

18 DR. McCULLEY: Well, we haven't required that in  
19 the past.

20 Dr. Matoba?

21 DR. MATOBA: I may not understand the issue here,  
22 but Dr. Bullimore said that reproducibility of a refraction  
23 is about 0.50 D to 0.75 D, but in that case, it is random,  
24 and it is as likely to go positive as negative; isn't that  
25 correct?

1 DR. BULLIMORE: Yes.

2 DR. MATOBA: So then, that variability is as  
3 likely to cancel out as to add to the postop change in  
4 refraction. So with that effect, Dr. Ferris, your comments?

5 DR. FERRIS: No. For the slope, you are right,  
6 that on average, it averages out, and you have a mean change  
7 of zero. When you are saying you have to have 95 percent  
8 within 1.0 D or 95 percent within 0.50 D, that's when the  
9 random error comes into play, because a certain number of  
10 those are due to chance, not due to treatment effect. So it  
11 depends which one of those two pieces you are looking at,  
12 whether the error is going to be important or not.

13 DR. McCULLEY: Dr. Bullimore?

14 DR. BULLIMORE: I think the data that you want is  
15 out there, Morris, and it's just a matter of whether through  
16 a homework assignment or something--we go to the literature  
17 or look at past PMAs, because you are allowed to do that, we  
18 are not--and see what the standard of care is, and what has  
19 the bar been set at by previous studies and previous  
20 procedures.

21 DR. McCULLEY: I don't think they are allowed to  
22 look at past PMA data in developing guidelines.

23 Dr. Wang?

24 DR. WANG: I just want to bring in one historical  
25 perspective. If you look at the published PERK study, over

1 20 to 25 years, there is expected in the 20th century to be  
2 about a 1.5 to 2.0 D hyperopic shift, so if you divide by 20  
3 years, you have about 0.1 D per year, or 0.05 for 6 months.

4           The point of this is that I understand Jim's point  
5 that it is impractical to look too long, but err on the  
6 conservative side, because as we found out, PRK has much  
7 smaller slope and has been drifting.

8           DR. McCULLEY: Other questions, comments?

9           Dr. Stulting?

10           DR. STULTING: I am sorry to be a little bit out  
11 of order, but you were struggling with some data about  
12 refractive change, and we spent a good bit of time looking  
13 at this, and I have some real data to offer, and I can  
14 present it to you in public forum so you can reference it.

15           The first was from the multivariate study of our  
16 LASIK data. Essentially, what we did was to separate out  
17 the refraction-dependent or the attempted correction-  
18 dependent component of variance from that which was  
19 apparently refractive-independent. In other words, we  
20 looked at the Y intercept. And that number was 0.50 D for  
21 standard deviation.

22           There is another dataset that we looked at as  
23 well, and that was contributed to us by Peterson et al., and  
24 it was from the Nidek study. It was not the operated eyes,  
25 but the unoperated eyes, that were measured 3 to 6 months

1 apart, and that was presented at ARVO.

2 We did a similar analysis on that, looking at the  
3 standard of deviation, and that was 0.4 D.

4 So those are two independent datasets, one on  
5 operated myopic eyes, the other on unoperated myopic eyes,  
6 with similar ranges of refraction, and the numbers for the  
7 standard deviation were in very good agreement, 0.4 and 0.5.  
8 So it turns out that looking at +/- 1.0 D is the 95 percent  
9 confidence interval, roughly, based on both of those  
10 studies. If you look at +/- 0.50 D, that means you are  
11 going to disqualify patients for refractive surgical  
12 studies, a third of them, just based on chance variation in  
13 their refraction alone.

14 Similar numbers that we got for variance in  
15 astigmatic magnitude were 0.3 D standard deviation. So you  
16 may want to consider those numbers for your deliberations.

17 DR. McCULLEY: Is that published now, Doyle?

18 DR. STULTING: The Peterson numbers were not  
19 analyzed by them; we analyzed them with their permission.  
20 And those data have been submitted as well, and they were in  
21 the same information that Morris mentioned, so the FDA got  
22 them a couple of weeks ago.

23 DR. McCULLEY: That is where I was leading.

24 DR. STULTING: Yes, sir.

25 DR. McCULLEY: Thank you.

1           Having reopened the floor to Dr. Stulting, in  
2 fairness, is there anyone else in the audience who would  
3 like to approach the podium for additional comments?

4           [No response.]

5           DR. McCULLEY: Other panelists, questions,  
6 comments?

7           Dr. Belin?

8           DR. BELIN: Just again--I think this is what Dr.  
9 Matoba was mentioning--I believe Dr. Stulting was again  
10 talking about error of individual refractions, not mean  
11 population drift, and those are two different things.

12          DR. McCULLEY: Yes; that was what I understood as  
13 well.

14          Is that correct, Doyle? A nod from the back.  
15 Thank you. Let the record show he nodded.

16          Dr. Ferris?

17          DR. FERRIS: That is that the standard deviation  
18 of 5 percent of these repeat refractions would be more than  
19 a diopter and 5 percent less than a diopter. This isn't  
20 standard error of the mean. This is--

21          DR. McCULLEY: He said standard deviation.

22          DR. FERRIS: I understand. I just want to make  
23 sure. So that's saying that 5 percent would be more than a  
24 diopter.

25          DR. McCULLEY: Correct. That's my understanding,

1 and let the record show Dr. Stulting is nodding again.

2 DR. FERRIS: Or, no--2.5 percent more and 2.5  
3 percent less. Five percent outside--of course, the mean is  
4 going to be stable. But he's saying that by chance, you are  
5 going to find 2.5 percent 1.0 diopter above and 2.5 percent  
6 1.0 diopter below--no?

7 DR. McCULLEY: Dr. Stulting is nodding his head  
8 once again.

9 DR. FERRIS: Well, there is somebody else shaking  
10 their head, so that's--

11 DR. McCULLEY: We were talking about Dr.  
12 Stulting's data.

13 DR. FERRIS: Oh, all right.

14 DR. McCULLEY: Dr. Odrich?

15 DR. ODRICH: Mark Odrich, VISX.

16 That's assuming no cretosis [ph.]; that's assuming  
17 a bell-shaped curve. And that's the point--these are not  
18 always distributed in bell-shaped curves. So there are some  
19 other variables involved. Certainly it is 2.5 above and  
20 below with no cretosis. But again, that's the error ratio.

21 DR. McCULLEY: I could ask him to define  
22 "cretosis," but I think I can assume what it is--I'm not  
23 sure.

24 DR. STARK: Jim, why don't you define it for those  
25 who might not know?

1 DR. McCULLEY: No, no, no. I think that means  
2 that these are not shaped like a bell, that they have a  
3 little, weird squiggly at the end, or an upturn or  
4 something--that would be my guess. That'll teach me to try  
5 to be a smart-alek this late in the day.

6 Any other questions or comments from the panel?

7 [No response.]

8 DR. WAXLER: Are you ready for the second part, or  
9 did you answer the second part?

10 DR. McCULLEY: I'm sorry, I forgot about that. Go  
11 ahead. I just forgot about it.

12 DR. WAXLER: Okay. This has to do with when you--  
13 according to the guidance, where we say you measure at 3  
14 months and you measure again at 6 months, and if you find  
15 that there is no mean difference, you then take that to  
16 understand that the point of stability is at 3 months, or it  
17 is at the middle or it is at 6 months--so I would like to  
18 hear some discussion; that would be helpful to us.

19 DR. McCULLEY: Well, it would be helpful for me to  
20 know from where you are coming with that question. You have  
21 to have the 6-month to define the 3-month. So what is the--

22 DR. BULLIMORE: I think you have to say that  
23 stability has been established at 6 months.

24 DR. McCULLEY: But based on establishing at 6, it  
25 occurred at 3.

1 DR. BULLIMORE: Well, I chose my words very  
2 carefully--you need the 6-month data point to say that, so  
3 stability has been established at 6 months.

4 DR. McCULLEY: Right. And in retrospect, occurred  
5 at 3. What's the point?

6 DR. WAXLER: The point of this exercise--and it  
7 may be pointless--but the point of this exercise is when do  
8 you count the confirmatory next evaluation? Do you start  
9 counting from the 3-month point and get another confirmatory  
10 point, or do you get a point at 7 months or 8 months--

11 DR. McCULLEY: Do you mean if you want to confirm  
12 what you think you have confirmed at 6, when do you have to  
13 do it the next time?

14 DR. WAXLER: Well, the question is do you go to  
15 the next longer time interval. Do you have to go out  
16 another 3 months in order to confirm what you found as no  
17 difference between 3 and 6.

18 DR. McCULLEY: All right. At 6 months, by our  
19 definitions, you have stability established based on the  
20 values at 3 versus 6 months. If you want to confirm that  
21 further, at what point should the next exam take place--  
22 would one more month be acceptable, or would one need to go  
23 to a full 3-month from the 6-month point, in your example?

24 DR. WAXLER: And that issue has come to us, and  
25 that's why I am asking you the question. What do you think?

1 DR. McCULLEY: I guess my question would be why is  
2 it being asked if you've established stability.

3 DR. ROSENTHAL: This is Dr. Rosenthal. I'll tell  
4 you why it's being asked. Firstly, it has a labeling issue,  
5 because in the labeling they say "point of stability." The  
6 other thing is that in many of the tables that we request,  
7 it says "point of stability." That is what we use in the  
8 Summary of Safety and Efficacy, the "point of stability."  
9 And is the point of stability at 3 months, or is the point  
10 of stability at 6 months?

11 I intuitively felt that it was at 6 months, but  
12 they established between 3 and 6, and therefore, the data  
13 should be shown at 6 months--but maybe I am wrong.

14 DR. McCULLEY: I don't know--wasn't it Reagan who  
15 got in trouble for saying "point in time"?

16 DR. SUGAR: But when you define it as a change of  
17 less than 1.0 D between 3 and 6 months, it is therefore  
18 stable in that interval; it became stable at the beginning  
19 of that interval. And if you want to confirm that, you have  
20 to look at another 3 months, because your definition  
21 includes 3 months.

22 DR. MACSAI: Right.

23 DR. McCULLEY: I agree. Stability was reached at  
24 3 months, but you had to have 6 months to establish that it  
25 did.

1 DR. MACSAI: And 9 months to confirm.

2 DR. ROSENTHAL: This is Dr. Rosenthal. So, when  
3 you ask for a table at "point of stability," do you pick 3  
4 months or 6 months?

5 DR. SUGAR: Three months.

6 DR. ROSENTHAL: Pardon?

7 DR. SUGAR: Three months is the point at which it  
8 became stable.

9 DR. McCULLEY: But you don't know that unless you  
10 have 6 months. That's the problem with "point."

11 Dr. Macsai?

12 DR. MACSAI: If you go along with the point that  
13 Morris brought up earlier about the slope, then, it is a  
14 little bit of a moot discussion, because you need the 3, 6,  
15 and 9 to calculate if you are talking about the mean  
16 difference. So if you are going to redefine the terms to be  
17 dependent on the slope of the mean differences, you need at  
18 least two points--in other words, three measuring points, 3,  
19 6, 9--to calculate that slope--and hopefully, longer.

20 DR. McCULLEY: This is a labeling issue. Rather  
21 than begging off the point, to get rid of the point and say  
22 stability was established at 6 months--it wasn't established  
23 until 6 months--Rick, do you have a better play on words?

24 DR. FERRIS: This is Rick Ferris.

25 The stability is driving me crazy, because I

1 think, as Dr. Wang pointed out, it could be inherently  
2 unstable over a 20-year period, and we were not able to  
3 measure it over a one-year period. So to say that you have  
4 established stability seems pretty grandiose. What you have  
5 established is that there isn't any gross instability.

6 DR. McCULLEY: So what you're saying is we should  
7 never have used the word "stability"; we should have said  
8 that it was determined by 6 months that there was no greater  
9 than a "blank" change in refractive error.

10 DR. FERRIS: I'm not sure that labeling change  
11 will fly.

12 DR. McCULLEY: Anyone else?

13 DR. ROSENTHAL: May I just ask the panel,  
14 therefore, you say the stability has been established at 3  
15 months. If you want to look at the day--say you were a  
16 doctor who wanted to look at the data that the agency has  
17 put in the public arena--would you rather see the 3-month  
18 data or the 6-month data if you had your choice to see one  
19 or the other?

20 DR. McCULLEY: The gut response from me is to say  
21 the longer out, the better, but that's gut--that's my gut.

22 DR. ROSENTHAL: Yes, okay. That may be why I  
23 chose 6 months, because my gut response was you want to see  
24 it the further out it is.

25 DR. BELIN: If this is your graph, although over a

1 3- to 6-month period, you may have a slope that you define  
2 as acceptable, you cannot say that at the 3-month period,  
3 that slope is no longer acceptable. You need two points--if  
4 you want to have anything less than the 6-month, then you  
5 have to do an exam at 4 months or at 5 months. Between 3  
6 and 6, you met criteria for whatever you define as  
7 stability, but from 3 to 4, you haven't met it unless you  
8 have a 4-month point.

9 DR. McCULLEY: Okay. Well, I don't know, that  
10 made sense to me. Basically, if you look at that curve, you  
11 are saying that stability was truly reached there, as he  
12 drew it, at 4 months. But you don't know it; so it took the  
13 6-month to know.

14 DR. McCULLEY: Other comments? I hope we haven't  
15 been too helpful.

16 DR. WAXLER: Thank you very much.

17 DR. McCULLEY: Any other questions, comments?  
18 Morris, do you have anything else?

19 DR. WAXLER: No.

20 DR. McCULLEY: Dr. Rosenthal, do you have anything  
21 else?

22 DR. ROSENTHAL: No. Thank you very much.

23 DR. McCULLEY: Let me remind everyone that  
24 tomorrow we begin at 9 a.m. In your packet is material that  
25 has been provided by Dr. Michael Lemp, who is going to speak

1 in the public session. You might want to look it over. It  
2 was in the packet that we got on arrival today. And be sure  
3 to look through the material that Donna provided to us as  
4 well.

5 Sara, do you have anything before we adjourn?

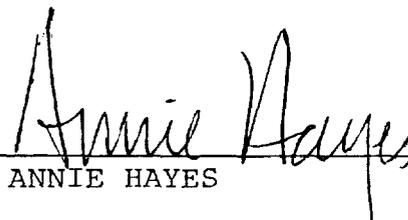
6 MS. THORNTON: I just want to thank the three  
7 presenters who made the gargantuan effort to answer Morris'  
8 questions, and we would like to see you tomorrow, fresh.

9 DR. McCULLEY: We stand adjourned.

10 [Whereupon, at 5:18 p.m., the proceedings were  
11 adjourned, to reconvene on Friday, October 23, 1998, at 9  
12 o'clock a.m.]

*C E R T I F I C A T E*

I, ANNIE HAYES the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

  
ANNIE HAYES