

FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH  
OPHTHALMIC DEVICES PANEL  
Eighty-Eighth Meeting

Thursday,  
July 10, 1997

Ballroom  
Gaithersburg Hilton  
620 Perry Parkway  
Gaithersburg, Maryland

## IN ATTENDANCE:

Voting Panel Members

R. DOYLE STULTING, M.D., Ph.D., Chair  
MARK A. BULLIMORE, MCOptom, Ph.D.  
EVE J. HIGGINBOTHAM, M.D.  
MARIAN S. MACSAI, M.D.  
JAMES P. McCULLEY, M.D.  
RICHARD S. RUIZ, M.D.  
PREM SARITA SONI, O.D., M.S., F.B.C.O., F.A.A.O.

Consultants, Deputized to Vote

ARTHUR BRADLEY, Ph.D.  
KAREN BANDEEN-ROCHE, Ph.D.  
KEVIN A. GREENIDGE, M.D.  
GARY S. RUBIN, Ph.D.  
JOEL SUGAR, M.D.  
WOODFORD S. VAN METER, M.D.

Non-Voting Discussants

FREDERICK FERRIS III, M.D., Liaison, National Eye Institute  
JUDY F. GORDON, D.V.M., Industry Representative  
ELEANOR McCLELLAND, Ph.D., Consumer Representative

Panel Executive Secretary

SARA M. THORNTON

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P R O C E E D I N G S

(8:09 a.m.)

1  
2 DR. STULTING: Good morning. I'm Doyle  
3 Stulting. I'd like to call to order this 88th meeting of  
4 the Ophthalmic Devices Panel.

5 I'd like to turn the floor over to Sara  
6 Thornton for introductory remarks.

7 MS. THORNTON: Good morning and welcome to all  
8 attendees. Before we proceed with today's agenda, I have a  
9 few short announcements to make.

10 During the break this morning, there will be  
11 coffee, tea, and pastries available at the Martingayle's  
12 Restaurant, which is just opposite the lobby of the hotel.  
13 Messages for the panel members and FDA participants,  
14 information or special needs, should be directed through  
15 Ms. Ann Marie Williams or Ms. Christie Wyatt. Ms. Williams  
16 is standing right over here by the door. Please contact  
17 her if you have anything that you need to let us know  
18 about.

19 We'd like to ask all the meeting participants  
20 here today to please speak clearly into the microphone --  
21 don't be afraid of it -- so that the transcriber will have  
22 an accurate record of your comments.

23 Now, at this time I'd like to extend a special  
24 welcome and introduce to the public, the panel, and our FDA

1 staff two panel participants who have recently joined the  
2 Ophthalmic Devices Panel as consultants and are  
3 participating for the first time in the meeting today.

4 Dr. Joel Sugar is professor of ophthalmology  
5 and director of the Corneal Service at the University of  
6 Illinois Eye and Ear Infirmary in Chicago, Illinois, and is  
7 also the medical director of the Illinois Eye Bank.

8 Dr. Karen Bandeen-Roche is an assistant  
9 professor of biostatistics with the Department of  
10 Biostatistics, the Johns Hopkins University School of  
11 Hygiene and Public Health in Baltimore, Maryland.

12 To continue, will the remaining panel members  
13 please introduce themselves, beginning with Dr. Judy  
14 Gordon.

15 DR. GORDON: I'm Judy Gordon and I'm --

16 MS. THORNTON: We can't hear you, Judy. It may  
17 be an issue there with the mike.

18 DR. GORDON: Judy Gordon, vice president of  
19 research and development and regulatory affairs for Chiron  
20 Vision and the industry representative.

21 Could you hear that?

22 MS. THORNTON: No, it's not on yet. Sorry.

23 DR. GORDON: We're going to start all over.

24 Here we go, and hopefully I can remember my name now.

1                   Judy Gordon, and I'm vice president of research  
2 and development and regulatory affairs for Chiron Vision,  
3 and I'm the industry representative for this panel.

4                   DR. McCLELLAND: Eleanor McClelland. I'm from  
5 the University of Iowa College of Nursing. I'm an  
6 associate professor and associate dean for undergraduate  
7 studies and community affairs, and I'm consumer  
8 representative on the panel.

9                   DR. VAN METER: Woodford Van Meter in  
10 Lexington, Kentucky. I'm in private practice in  
11 ophthalmology, practice of corneal and external disease.

12                   DR. MACSAI: Marian Macsai, professor and  
13 director of corneal and external diseases, West Virginia  
14 University.

15                   DR. GREENIDGE: Kevin Greenidge, professor and  
16 chairman, Department of Ophthalmology at the SUNY Health  
17 Science Center at Brooklyn, and a glaucoma specialist.

18                   DR. BULLIMORE: Mark Bullimore. I'm an  
19 assistant professor at the Ohio State University College of  
20 Optometry.

21                   DR. BRADLEY: Arthur Bradley, associate  
22 professor of visual sciences, Indiana University.

23                   DR. STULTING: Doyle Stulting, professor of  
24 ophthalmology, Emory University.

1 DR. McCULLEY: Jim McCulley, professor and  
2 chairman, Department of Ophthalmology, University of Texas  
3 Southwestern Medical School.

4 DR. HIGGINBOTHAM: Eve Higginbotham, professor  
5 and chair, Department of Ophthalmology, University of  
6 Maryland School of Medicine.

7 DR. RUBIN: Gary Rubin, associate professor of  
8 ophthalmology at the Wilmer Eye Institute, Johns Hopkins  
9 University School of Medicine.

10 DR. RUIZ: Richard Ruiz, professor and  
11 chairman, Department of Ophthalmology, University of Texas-  
12 Houston.

13 DR. SONI: Sarita Soni. I'm a professor of  
14 optometry and vision sciences at Indiana University School  
15 of Optometry.

16 DR. ROSENTHAL: Ralph Rosenthal, division  
17 director, Division of Ophthalmic Devices in the Office of  
18 Device Evaluation in the Center for Devices and  
19 Radiological Health at the FDA. I assume you remembered it  
20 all.

21 (Laughter.)

22 DR. STULTING: All right. This begins the open  
23 public hearing portion of this morning's festivities, and  
24 Sara Thornton once again will begin.

1 MS. THORNTON: The speakers who will be making  
2 presentations before the committee are doing so in response  
3 to the panel meeting announcement in the Federal Register.  
4 They are not invited to speak by the FDA, nor are their  
5 comments, data, or products endorsed by the agency.  
6 Scheduled speakers are given a 10-minute limit today.  
7 After they have spoken, the Chair may ask them to remain if  
8 the committee wishes to question them further. Only the  
9 Chair and members of the panel may question the speakers  
10 during the open public hearing portion of the meeting. Dr.  
11 Stulting will recognize unscheduled speakers as time  
12 allows.

13 The scheduled speaker for today's open public  
14 hearing portion is Dr. Spencer Thornton.

15 Dr. Thornton, if you'll come forward at this  
16 time, you may begin your presentation.

17 DR. THORNTON: Thank you, and good morning.  
18 I'm Spencer Thornton. I'm president of the American  
19 Society of Cataract and Refractive Surgery, and I've been  
20 practicing ophthalmology for more than 35 years.

21 The ASCRS is a scientific and educational  
22 organization representing ophthalmic surgeons in the United  
23 States and abroad. Our membership of over 7,000

24 ~~ophthalmologists performs the vast majority of cataract and~~

1 refractive surgery procedures in the United States today.

2 I wanted to take a few minutes first to thank  
3 the panel for its work which so richly benefits not only  
4 the practice of medicine but the quality of life for  
5 ophthalmic patients. ASCRS is especially pleased to be  
6 here and to lend its continued support to the panel, since  
7 so many of the breakthroughs in ophthalmic devices have  
8 occurred not in academic research but in clinical settings.

9 ASCRS has enjoyed positive relationships with  
10 FDA and device manufacturers for many years. Under our  
11 former name, the American Intraocular Lens Implant Society,  
12 we worked closely on the approval and classification of  
13 intraocular lenses, contact lenses, and the early  
14 development of multifocal lenses. We have also had success  
15 working with the device manufacturers in alerting them to  
16 areas of improvement in some products. ASCRS is now  
17 working with FDA in its effort to streamline the approval  
18 process through its draft intraocular lens guidance  
19 document for use in the submission of product development  
20 protocols. We believe that through the continuing  
21 evolution of the document and its incorporation into the  
22 approval process of new lens technologies, that improved  
23 materials and devices will be available on a faster  
24 ~~timeline without jeopardizing patient care or safety.~~

1                   Our organization would like to thank the  
2                   advisory panel for its careful and deliberate consideration  
3                   of the intraocular lens products that are being reviewed  
4                   today. As ophthalmic surgeons and specialists in treating  
5                   eye disease, early regulatory approval of advanced new eye  
6                   surgical products are key elements in our clinical  
7                   practice.

8                   I would like to emphasize the importance to the  
9                   ASCRS membership, the ophthalmic community, and the public,  
10                  that important new technologies move rapidly to the  
11                  marketplace once they have been thoroughly studied and  
12                  their risks and benefits identified and understood. While  
13                  the FDA plays a critical role in the evaluation of new  
14                  technologies for safety and effectiveness, it is of equal  
15                  importance to the public health that no undue burdens be  
16                  placed in the progression of such technologies from the  
17                  investigational stage to general availability via market  
18                  approval. Medical practice must ultimately determine the  
19                  clinical utility of new treatment modalities.

20                  As an example, one only needs to look at the  
21                  vast numbers of IOLs which are approved, but the small  
22                  number which are actually being implanted today. Yes,  
23                  ophthalmologists today could be accused of malpractice by  
24                  ~~their peers if they continued to implant some of the lenses~~

1 which were approved in the early years. To ASCRS, this  
2 evolutionary process represents the purest form of peer  
3 review.

4 All of us who practice medicine have been newly  
5 sensitized in recent years to cost-benefit issues. Today  
6 you will see data regarding a new intraocular lens with the  
7 potential to reduce costs to Medicare while increasing  
8 benefits to our patients by lessening dependency on  
9 spectacles following cataract surgery, currently reimbursed  
10 by Medicare at up to \$270 per patient.

11 While, as an organization, ASCRS takes no  
12 official position with respect to FDA approval of the  
13 multifocal lens products, we would like to draw the  
14 advisory committee's attention to a complementary effort  
15 underway at the Health Care Financing Administration. HCFA  
16 is expected to shortly promulgate specific regulations that  
17 may set a fair reimbursement system for advanced technology  
18 intraocular lens products. ASCRS believes that the HCFA  
19 initiative is critically important. For perhaps the first  
20 time, the Medicare program will go on record in favor of a  
21 new cost-saving medical technology. If we hope to bring  
22 Medicare into the 21st century on a solid financial basis,  
23 we need to reward medical technologies that save the  
24 ~~program actual dollars.~~

1           In considering your approval of new advanced  
2 technology IOLs, ASCRS respectfully requests that FDA  
3 forward the panel's conclusions to HCFA in a timely fashion  
4 so that they may develop regulations for advanced  
5 technologies that parallel the important scientific  
6 judgment of this panel.

7           It is critically important that medical devices  
8 which could vastly improve the quality of life for  
9 ophthalmic patients are not unnecessarily delayed in the  
10 approval process. Over the years, it has seemed that the  
11 United States, at least in ophthalmic advances, has fallen  
12 behind the rest of the world due to restrictions and delays  
13 in the FDA approval process. American physicians and  
14 industry have been faced with falling into a position of  
15 second class to the rest of the world, as we have been  
16 relying on nations in Europe, Asia, and Africa because of  
17 their continual contributions to technological  
18 developments.

19           The barriers and delays faced by the United  
20 States medical community are not as great in other areas of  
21 the world, thus leaving the United States to take a  
22 secondary role in bringing new medical advancements to our  
23 patients. Given our current reliance on the international  
24 ~~community in creating new treatment options, I sincerely~~

1 hope that this panel and the entire FDA will place strong  
2 importance on international data and will utilize such data  
3 to assist in speeding the approval process.

4 The ophthalmic community is very excited by the  
5 innovative changes and advances we've seen in lens  
6 technologies. We are eager to work with the panel in any  
7 way we can, especially in providing clinical review of  
8 multifocal lenses and implantable contact lenses for  
9 approval in the United States.

10 Thank you for this opportunity to speak to you  
11 today.

12 DR. STULTING: Are there any questions from the  
13 panel members?

14 DR. BULLIMORE: I don't know whether this is  
15 appropriate but I'd like to know, with respect to the  
16 products mentioned by the speaker, do you have any conflict  
17 of interest with any of the products you mentioned in your  
18 presentation?

19 DR. THORNTON: No, sir. I do not have any  
20 financial interest in any of these products. I represent  
21 the Society only and its interests.

22 DR. BULLIMORE: Thank you.

23 DR. STULTING: Anyone else?

24 (No response.)

1 DR. STULTING: The open public hearing portion  
2 of the meeting remains open. Is there anyone else who  
3 would like to speak before the panel today?

4 (No response.)

5 DR. STULTING: Seeing no particular interest,  
6 we will close the open public hearing portion of the  
7 meeting at this point and turn the floor over to Dr.  
8 Rosenthal for Division updates.

9 DR. ROSENTHAL: Mr. Chairman, panel members,  
10 ladies and gentlemen, I have two Division updates. One has  
11 to do with personnel, the other has to do with excimer  
12 lasers.

13 With regard to personnel, I have happy news and  
14 sad news. The happy news is in January of 1997, Dr.  
15 Anthony Greer joined us as a medical reviewer. He did his  
16 residency at Howard University Hospital in ophthalmology,  
17 had been in private practice in Annapolis for several  
18 years, and had regulatory experience with the Joint  
19 Commission for Accreditation of Health Care Organizations.  
20 You will have the opportunity to meet him this morning when  
21 he presents PMA No. P960036.

22 The sad news is that on June 17, 1997, Bruce  
23 Mischou, who was a reviewer in the Division of Ophthalmic  
24 Devices, had a sad and untimely death. He was a respected

1 reviewer in DSDB, he was an aerospace engineer who  
2 concentrated his efforts in biomedical engineering, and his  
3 professional talents and personal charm will be sadly  
4 missed by the Division.

5 Secondly, with regard to excimer lasers, this  
6 is an update of the Food and Drug Administration policies  
7 regarding lasers for refractive surgery. It's essentially  
8 a summary of what was sent to every ophthalmologist on June  
9 27, 1997. I wanted to ensure that it was in the public  
10 record and to ensure that all the panel members were aware  
11 of the policies.

12 We wrote to the ophthalmic community on October  
13 10, 1996, describing two situations in which unapproved  
14 lasers were being operated without FDA approval. The first  
15 were the unapproved lasers manufactured by the owner, by  
16 someone else for the owner, or by a corporate entity; and  
17 the second were the importation of Summit lasers originally  
18 manufactured in the United States and exploited for use  
19 overseas or manufactured overseas before the company had  
20 received FDA approval to market the devices in the United  
21 States.

22 We have uncovered through our own investigation  
23 what appears to be a pattern of serious patient injuries  
24 attributed to the use of some of the first type of lasers,

1 the unapproved lasers manufactured by owner, et cetera.  
2 These injuries from these lasers demonstrate the importance  
3 of evaluating the safety and effectiveness of lasers for  
4 refractive surgery with a limited number of patients under  
5 an FDA-approved investigational device exemption and the  
6 oversight of an institutional review board as required by  
7 the Federal Food, Drug and Cosmetic Act.

8           Secondly, with respect to the imported lasers,  
9 many of the physicians who imported these lasers  
10 communicated their belief to the agency that the lasers  
11 were the same as the approved lasers. FDA attempted, in  
12 the exercise of its enforcement discretion, to resolve the  
13 matter and accommodate these physicians by providing an  
14 opportunity for them to certify that the lasers were  
15 identical in all relevant aspects to approved lasers. The  
16 agency's experience with certification has led us to  
17 conclude that the process described in the October 10th  
18 letter cannot be implemented legally. Hence, all  
19 unapproved lasers used outside of an FDA-approved clinical  
20 trial violate the Act and are subject to regulatory action.

21           Thank you very much.

22           DR. STULTING: Ms. Lochner?

23           MS. LOCHNER: Thank you.

24           I had one update today. I wanted to make the

1 panel aware that as of March 31st of this year, FDA revoked  
2 the IOL IDE regulations. As most of you may be aware, IOLs  
3 had their own investigational device exemption regulations.  
4 They were mainly separated out from other medical devices  
5 because the FDA wanted to allow lenses to remain reasonably  
6 available. Since the 1976 Act, many IOLs have been  
7 approved, and they are basically available. So FDA has  
8 removed the special provision for IOL IDE regulations, and  
9 IOLs will now be regulated under the IDE regulation that's  
10 used for all medical devices.

11 There are a few differences between the two  
12 regulations, and I thought I'd just point out a few of  
13 those. One is that IOL sponsors were required to maintain  
14 records for five years under the IOL IDE reg, and under the  
15 medical device reg, the retention period is two years.  
16 Similarly, the IOL reg had a five working day reporting  
17 timeframe for reporting adverse events during the study.  
18 Under the medical device regulation, there's a 10-day  
19 timeframe for reporting adverse events.

20 There were two provisions under the IOL IDE reg  
21 that were unique to IOLs that we have continued to require  
22 under more general provisions of the medical device IDE  
23 reg, and those are the requirement for the IOL implant  
24 card, which will continue to be required under the medical

1 device IDE regs, and the requirement that the label of the  
2 IOL state the sterility shelf life will continue to be  
3 required.

4 Other requirements that will be imposed because  
5 of the medical device IDE reg relate to sponsors'  
6 responsibility with regard to reporting to the FDA use of  
7 their lens without informed consent when informed consent  
8 had not been received. They're now required to report that  
9 to the FDA. Also, other reporting requirements with regard  
10 to the investigators who are participating in the study.  
11 But basically we feel that by bringing IOLs under the  
12 medical device regulations, we'll ensure consistency  
13 throughout the office in terms of how we regulate IOLs and  
14 other medical devices.

15 If anybody would like to see any of the details  
16 of the differences, please let me know and I'd be happy to  
17 give you those details. Thank you.

18 DR. STULTING: Thank you.

19 For the record, that presentation was by Donna  
20 Lochner, who is the chief of the Intraocular and Corneal  
21 Implants Branch. I didn't do the proper introduction.

22 Now, Dr. Morris Waxler, who is acting chief of  
23 the Diagnostic and Surgical Devices Branch, will present  
24 his update.

1 DR. WAXLER: Thank you.

2 The primary focus of our branch's work is the  
3 scientific and technical evaluation of investigational  
4 device exemption and premarket approval applications for  
5 refractive surgery lasers. Currently, there are eight  
6 manufacturers with FDA-approved IDE clinical trials for PRK  
7 and LASIK for treating a variety of refractive indications.  
8 They are conducting more than 20 studies with their lasers,  
9 some in separate IDEs and others in substudies.

10 We have received 34 IDE sponsor/investigator  
11 IDE applications. Seventeen were submitted for lasers from  
12 manufacturers with approved IDEs or PMAs. Six of these  
13 IDEs were disapproved, 10 were conditionally approved, and  
14 one is under review. Seventeen of these 34 were submitted  
15 by black box or gray box owners, of which nine were  
16 disapproved, six conditionally approved, and two are under  
17 review.

18 In order to obtain FDA approval of their IDE  
19 application, all applicants, sponsor/investigators, and  
20 manufacturers must submit an investigational plan to  
21 conduct a scientifically valid clinical trial, and all  
22 applicants must provide an adequate engineering and  
23 technical description of the laser.

24 ~~Once an IDE application is approved by FDA~~

1 and a conditional approval is considered an approval -- it  
2 must be conducted within the limits and conditions of the  
3 approved IDE. Sponsors of, and investigators on, FDA-  
4 approved IDEs may not treat patients beyond these limits.  
5 Such treatment is in violation of the Federal Food, Drug  
6 and Cosmetic Act and FDA regulations. FDA will not approve  
7 IDE applications if there is evidence that the applicant is  
8 treating patients without an FDA-approved IDE or PMA for  
9 the laser. Such an applicant must cease treating patients  
10 and must state in writing that patients are not and will  
11 not be treated without an FDA-approved IDE.

12 Two PMA applications from sponsor/investigators  
13 have been filed by the agency. We are encouraging IDE  
14 applicants to complete their clinical trials and submit  
15 their data in a PMA application as soon as possible. PMA  
16 submissions must have complete technical and engineering  
17 information on the device, as well as scientifically valid  
18 clinical data.

19 DR. STULTING: Thank you.

20 Next is Dr. Bernard Lepri from the  
21 Vitreoretinal and Extraocular Devices Branch.

22 DR. LEPRI: Good morning. I am happy to be  
23 representing Dr. Saviola today, who could not be present at  
24 all this week, and he prepared this report which I will

1 deliver to you now.

2 Dr. Saviola regrets that he was unable to  
3 attend this session and provide this update. He is just  
4 glad that the following announcement can be made before he  
5 became old enough to retire from government service, which  
6 is still a long way off.

7 (Laughter.)

8 DR. LEPRI: At the July 1995 panel meeting,  
9 there was a presentation of the draft guidance document for  
10 contact lens care products, and while I was not here, I'm  
11 sure you all recall that the following July, at the 1996  
12 panel meeting, there was a presentation of the comments to  
13 the draft guidance document for contact lens care products.

14 At this panel meeting, in July of 1997, there  
15 will not be any presentation, only a long-awaited  
16 announcement. Effective this past Monday, July 7, 1997,  
17 the final rule took effect and contact lens care products  
18 have now been reclassified from Class III to Class II.  
19 This marks the end of a significant era of medical device  
20 regulation for these products, and certainly the beginning  
21 of a new chapter.

22 On May 1, 1997, the final version of the 510(k)  
23 guidance document for contact lens care products was made  
24 ~~available on the CDRII Web site. Following the June 6th~~

1 publication of the final rule, a copy was also mailed to  
2 all manufacturers holding approved PMAs. This May 1, 1997  
3 guidance is the special control for Class II regulation of  
4 these products and supersedes all previous drafts of the  
5 guidance.

6 Through the dedication and persistence of the  
7 Vitreoretinal and Extraocular Devices Branch review staff,  
8 the existing inventory of PMA documents under review was  
9 reduced during the final weeks before reclassification,  
10 thereby minimizing the number of documents to be  
11 transitioned. The branch was able to reduce the number of  
12 transition documents to one care product PMA supplement and  
13 one original PMA which could not be resolved by internal  
14 review before reclassification took effect.

15 There are also three PMA supplements and two  
16 original PMA applications for which review had been  
17 completed by staff, but the firms did not receive GMP  
18 clearance and therefore could not be completed prior to the  
19 official reclassification date.

20 The reviews of two annual PMA reports of  
21 contact lens care products were not completed prior to  
22 reclassification.

23 Since the number of transitional documents  
24 ~~which may require conversion from PMA to 510(k) are so few,~~

1 there will ultimately be a minimal impact on the regulated  
2 industry.

3 The staff of VEDB and DOD who participated in  
4 this project would like to thank the panel, the industries,  
5 and agency members who participated in the reclassification  
6 process for their assistance.

7 As part of the organizational transformation  
8 and reengineering effort currently underway in CDRH, VEDB  
9 was chosen as a pilot branch to participate in a project  
10 with the standards reengineering team. The goal of this  
11 project is to utilize standards in the review process via  
12 acceptance of declarations of conformance to a given  
13 standard. It is projected that applying the principles of  
14 standards review will expedite the review process and  
15 thereby produce a preservation of financial resources as  
16 well.

17 This project involves assessing existing  
18 standards for the products reviewed by our branch and  
19 determining the applicability of these standards to the  
20 review process. Specific device factors related to risk,  
21 performance, and function, which have been identified in  
22 special controls guidance documents, will be utilized in  
23 creating device-specific profiles. The profile will then  
24 be evaluated against an identified standard to determine

1 the standard addressing this specific factor.

2 We are anticipating the development of an  
3 addendum to the May 1 guidance document upon the completion  
4 of the project. The addendum would be published in order  
5 to advise applicants of the identified standards accepted  
6 by the branch and agency to be applied in the declarations  
7 of conformance. As part of this project, VEDB will apply  
8 this process of identification and assessment of standards  
9 to the daily wear contact lens special control guidance  
10 document.

11 Thank you.

12 DR. STULTING: Comments or questions?

13 (No response.)

14 DR. STULTING: The agenda calls for the  
15 beginning of the open committee discussion with a  
16 presentation by Ms. Thornton of remarks and conflict of  
17 interest statements and whatnot. We are at this point  
18 considerably ahead of schedule and it makes more sense that  
19 that is connected to the presentation of the PMAs today.  
20 So I would like to deviate from the published agenda and  
21 ask Dr. Rosenthal if he would at this point present his  
22 comments on the product development protocol program.

23 DR. ROSENTHAL: Thank you, Mr. Chairman.

24 ~~Mr. Chairman, panel members, ladies and~~

1 gentlemen, I should like to present a brief description of  
2 the product development protocol, or PDP, which is an  
3 alternative to the IDE/PMA process for Class III devices  
4 subject to premarket approval. It is included in Section  
5 515(f) of the FDC Act.

6 As I said, it is an alternative process to the  
7 IDE/PMA approval process, and it is a process which will be  
8 hopefully implemented over the next years, and I wanted the  
9 panel to be aware of its existence and its details. It has  
10 not been implemented during the early years of the program  
11 because of the complexities related to it, and because the  
12 agency wished to concentrate on core provisions of the  
13 Medical Device Act of 1976 -- i.e., PMA, IDE, 510(k), GMP,  
14 and problem reporting.

15 The current process of medical device  
16 development for a new Class III product is well known to  
17 you but, if I may, I should like to review it briefly.  
18 First there is a concept, a prototype device, preclinical  
19 evaluation, clinical feasibility, pre-IDE and IDE Food and  
20 Drug Administration evaluation, clinical trial, premarket  
21 submission, FDA evaluation, advisory panel recommendation,  
22 marketing, and postmarket surveillance.

23 The major differences with product development  
24 ~~protocol is that, number one, all of the criteria are~~

1 settled up front, and early advisory panel involvement at  
2 the protocol development phase is required. This is  
3 515(f)2 of the Act.

4 The advantages of product development protocol  
5 are as follows: it will reduce FDA resources for  
6 established products; it will reduce the time to market new  
7 Class III devices; the application is criteria based;  
8 agreed product changes are built into the protocol;  
9 resources are focused on safety and effectiveness issues;  
10 and it includes both IDE and PMA features, as well as  
11 postmarket requirements.

12 As far as the product development protocol is  
13 concerned, certain changes will not happen. The first is  
14 there will continue to be strict evaluation of final  
15 results, the science will not be compromised, we will  
16 continue to monitor assurance of safety and effectiveness,  
17 and a segmented review will continue to be made.

18 A proposed product development protocol must  
19 include the following: a description of the device and any  
20 changes that may be made; a description of any preclinical  
21 trials; a description of any clinical trials; a description  
22 of manufacturing methods, facilities, and controls; and a  
23 description of any applicable performance standards. It  
24 ~~must also include proposed labeling, any other information~~

1 relevant to the subject matter of the protocol thought  
2 necessary by the FDA, and the advisory panel must concur in  
3 the need for this additional information. There is also a  
4 requirement for progress reports to the FDA, and when  
5 completed, records of the trials conducted under the  
6 protocol. This is in the Act 515(f)3.

7 The timeframe is particularly important. A  
8 proposed PDP is to be approved or disapproved by the agency  
9 within 120 days unless the parties agree to an extension of  
10 time. This is in Part 4 of 515. The provision does not  
11 provide that the PDP is deemed approved if the FDA fails to  
12 meet the 120-day timeframe. After approval, at any time,  
13 the PDP holder may submit a notice of completion explaining  
14 how the protocol has been fulfilled and setting forth the  
15 result of the trials required by the protocol. This is in  
16 Part 5 of the 515(f) Act.

17 FDA may revise and approve PDP prior to its  
18 completion (1) if the protocol is not complied with; (2) if  
19 the results of the trials under PDP differ substantially  
20 from required results; and (3) if results of the trial show  
21 the device presents an unreasonable risk to health and  
22 safety. Part (f)6A of the 515 Act.

23 Within 90 days of receipt of the notice of  
24 completion, the FDA must either declare the protocol

1 completed or declare it not completed. Not completed may  
2 be declared only if (1) the protocol is not complied with;  
3 (2) the results of the trials under PDP differ  
4 substantially from required results; and (3) there has not  
5 been an adequate showing that the device is safe and  
6 effective as labeled. Part (f)6B of the 515 Act.

7 Now, if I may just go through the proposed  
8 process. There are still a lot of questions to be asked  
9 about the process, and details have to be ironed out, but I  
10 think the process is pretty straightforward and I would  
11 just like to review it for you.

12 First there would be a presubmission where the  
13 applicant consults with the FDA and other parties to  
14 develop this protocol. There is then a filing review in  
15 which the applicant submits the proposed PDP and the FDA  
16 determines whether it appears to be appropriate. The  
17 timeframe of X days is stated because that could vary  
18 tremendously. Then there would be the FDA review, which  
19 would have to be in 120 days that they would perform a  
20 substantive review of this PDP, and it is here that the  
21 advisory panel would be required, their review would be  
22 required and their input sought. The applicant would then  
23 develop preclinical data and report to the FDA as  
24 appropriate.

1                   Sorry, could we go back one? One more? So  
2 this is the preclinical phase, then we would go to the  
3 clinical phase where the applicant would develop their  
4 clinical data and report to FDA as appropriate. As you  
5 see, I've placed on the side GMP and BIMO as a question  
6 mark. These are the details that have to be ironed out,  
7 where they will be performed in the course of the process.  
8 Then there will be a notice of completion where the  
9 applicant would conclude the trials, prepare and submit  
10 this notice, and then in 90 days the FDA decision on the  
11 PDP and the product could go to market.

12                   Now, as far as the Division of Ophthalmic  
13 Devices is concerned, we are currently in the process of  
14 developing generic-type PDPs for established Class III  
15 products with highly detailed, acceptable guidance  
16 documents and/or grids and/or developed standards, in three  
17 areas. One is the area of intraocular lenses, where Ms.  
18 Lochner is working with the industry to develop the issues  
19 related to the intraocular lenses. Two is in the area of  
20 excimer refractive lasers for the treatment of myopia and  
21 probably astigmatism and hyperopia, and Dr. Waxler's group  
22 is working with the Eye Care Technology Forum in developing  
23 the guidance documents for this group of devices. And  
24 ~~finally in the extended wear contact lenses, up to seven~~

1 days wear, where Dr. Saviola and his group will be working  
2 with industry to develop a similar-type guidance document  
3 that could be used up front as the basis for the product  
4 development protocol.

5 It should be noted that the panel will be  
6 required to give their input and opinions relating to all  
7 of these documents, grids, standards, et cetera, when they  
8 are included in the protocol, and hence I present it to you  
9 today to give you a heads-up as to what we hope the future  
10 will bring.

11 Thank you very much.

12 DR. STULTING: Thank you, Dr. Rosenthal. You  
13 don't want the open discussion at this point, do you? Is  
14 that correct?

15 DR. ROSENTHAL: I'm happy to answer big, broad  
16 questions.

17 DR. STULTING: All right. Are there any big,  
18 broad questions?

19 DR. ROSENTHAL: For little detailed questions,  
20 I don't think we have --

21 DR. STULTING: If you have little detailed  
22 questions, you can submit them in writing and I'm sure  
23 we'll have a chance to review this again.

24 ~~Judging from the length of time that it took to~~

1 do the contact lens document, I suspect we'll be seeing  
2 this again maybe in the future at some point.

3 DR. ROSENTHAL: You will be seeing it in the  
4 future, but we hope the near future rather than the far  
5 future.

6 DR. STULTING: Okay. The agenda at this point  
7 calls for a break. The best I can tell, we've been working  
8 less than an hour, so unless there's a screaming need for  
9 that, we'll move on. What I'd like to do is move toward  
10 the presentation and discussion of P960036, and we'll begin  
11 by Ms. Thornton's presentation of conflict of interest  
12 statements and move through the sponsor presentation, and  
13 then at that point we'll make a decision as to whether  
14 that's an appropriate time for a break or not.

15 MS. THORNTON: This is the open committee  
16 discussion portion of the meeting, and to begin I'd like to  
17 read the conflict of interest statement into the record for  
18 today's meeting, July 10, 1997.

19 "The following announcement addresses conflict  
20 of interest issues associated with this meeting and is made  
21 part of the record to preclude even the appearance of  
22 impropriety. To determine if any conflict existed, the  
23 agency reviewed the submitted agenda and all financial  
24 interests reported by the panel participants. The conflict

1 of interest statutes prohibit special government employees  
2 from participating in matters that could affect their or  
3 their employer's financial interests. However, the agency  
4 has determined that participation of certain members and  
5 consultants, the need for whose services outweighs the  
6 potential conflict of interest involved, is in the best  
7 interest of the government.

8 "A limited waiver has been granted for Dr.  
9 Richard Ruiz that allows him to participate in the review  
10 and discussion of the intraocular lens premarket approval  
11 applications but excludes him from voting. Waivers have  
12 been granted for Drs. Kevin Greenidge and Woodford Van  
13 Meter for their interests in intraocular lens firms that  
14 could potentially be affecting the panel's deliberations.  
15 The waivers permit these individuals to participate in all  
16 matters before the panel.

17 "Copies of these waivers may be obtained from  
18 the agency's Freedom of Information Office, Room 12A-15 of  
19 the Parklawn Building.

20 "We would like to note for the record that the  
21 agency took into consideration other matters regarding Drs.  
22 Arthur Bradley, Eve Higginbotham, Marian Macsai, and James  
23 McCulley. The financial interests reported by these  
24 ~~individuals are not related to the matters before the~~

1 panel. Therefore, the agency has determined that they may  
2 participate fully in the panel's deliberations. In the  
3 event that the discussions involve any other products or  
4 firms not already on the agenda for which the FDA  
5 participant has a financial interest, the participant  
6 should excuse themselves from such involvement, and their  
7 exclusion will be noted for the record.

8 "With respect to all other participants, we ask  
9 in the interest of fairness that all persons making  
10 statements or presentations disclose any current or  
11 previous financial involvement with any firm whose products  
12 they may wish to comment upon."

13 Thank you. I would like to now read the  
14 appointment to temporary voting status.

15 "Pursuant to the authority granted under the  
16 Medical Devices Advisory Committee Charter dated October  
17 27, 1990, as amended April 20, 1995, I appoint the  
18 following individuals as voting members of the Ophthalmic  
19 Devices Panel for the duration of this meeting on July 10,  
20 1997: Drs. Arthur Bradley, Kevin Greenidge, Gary Rubin,  
21 Karen Bandeen-Roche, Joel Sugar, and Woodford S. Van Meter.

22 "For the record, these persons are special  
23 government employees and are consultants to this panel, or  
24 ~~consultants or voting members of another panel under the~~

1 Medical Devices Advisory Committee. They have undergone  
2 the customary conflict of interest review and have reviewed  
3 the material to be considered at this meeting."

4 Signed for Dr. D. Bruce Burlington, M.D.,  
5 Elizabeth D. Jacobson, dated 6/18, 1997.

6 Thank you, Doyle.

7 DR. STULTING: We'll turn the floor over to Ms.  
8 Lochner to begin the introductions and the presentation.

9 MS. LOCHNER: Thank you.

10 I would just like to acknowledge the hard work  
11 of the review team for this PMA: Dr. Kesia Alexander, who  
12 is the team leader and performed the chemistry review; Dr.  
13 Anthony Greer, who performed the clinical review; Susan  
14 Gouge, who did microbiology; Susanna Jones, toxicology;  
15 Murty Ponnappalli, who did the statistical review; Carmelina  
16 Gomez-Novoa, who did the engineering review; and I'd also  
17 like to acknowledge technical advice provided by Don  
18 Calogero.

19 With that, I'm going to turn introduction of  
20 the PMA over to Dr. Alexander.

21 DR. ALEXANDER: Good morning members of the  
22 Ophthalmic Devices Advisory Committee, Ms. Thornton, Dr.  
23 Rosenthal, and guests. My name is Kesia Alexander and I am  
24 ~~the team leader for PMA P960036, Mentor's posterior chamber~~

1 intraocular lens, referred to as MemoryLens. MemoryLens is  
2 intended to be used for primary implantation for the visual  
3 correction of aphakia in patients 60 years of age and older  
4 where a cataractous lens has been removed by an  
5 extracapsular cataract extraction method.

6 MemoryLens is an ultraviolet absorbing  
7 posterior intraocular lens made from a cross-linking  
8 hydrogel polymer. This polymer is considered a  
9 thermoplastic which has the ability to change shape when  
10 pressure or heat is applied. The lens consists of a 6  
11 millimeter biconvex optic, with two supporting blue  
12 polypropylene modified C haptics, yielding an overall  
13 diameter of 13 millimeters.

14 Two clinical studies were conducted to  
15 investigate the safety and efficacy of MemoryLens, one with  
16 the lens shipped flat in which the physician rolled the  
17 lens prior to implantation, and one with the lens shipped  
18 pre-rolled.

19 The PMA contains three sets of clinical data,  
20 two analyses of the data from when the lens was shipped  
21 flat and one analysis of the pre-rolled data. One set of  
22 flat data involves a cohort of 523 subjects which were seen  
23 at Form 6 that was defined as 12 months or greater. The  
24 ~~other set of flat data includes a cohort of 360 subjects~~

1 which were seen at Form 6 which was defined as 12 to 14  
2 months. The third set corresponds to one year pre-rolled  
3 MemoryLens IOL, which is the configuration for which the  
4 sponsor is requesting PMA approval.

5 Statistical analysis comparing the various sets  
6 of data was also submitted in the effort to assure  
7 similarity of the data sets and to assure acceptable  
8 accountability of the core population.

9 The primary panel reviewers for P960036 are  
10 Drs. Greenidge and Higginbotham. The FDA clinical reviewer  
11 for this PMA is Dr. Greer, who will present his review of  
12 this application after the sponsor concludes their  
13 presentation.

14 Thank you.

15 DR. STULTING: At this point, we'll move  
16 forward to presentation by the sponsor.

17 While you're coming forward, I'd like to remind  
18 you as you begin your presentations, please introduce  
19 yourselves individually so that the record can be kept  
20 straight by the transcriptionist.

21 I understand that you have about a 30-minute  
22 presentation. Is that correct?

23 MR. FREEMAN: Yes. I think it's closer to 40  
24 minutes.

1 DR. STULTING: Okay. I don't have any problem  
2 with that. As soon as we're technically ready, you may  
3 proceed.

4 MS. THORNTON: Does the sponsor want to use the  
5 center table?

6 MR. FREEMAN: Yes, please.

7 MS. THORNTON: The sponsor is allowed up to an  
8 hour to make their presentation. I'd like to have that in  
9 the record, please.

10 MR. FREEMAN: Good morning. My name is Bill  
11 Freeman, and I am president of Mentor Ophthalmics. We are  
12 here today to present data demonstrating the safety and  
13 effectiveness of MemoryLens to support an approvable  
14 recommendation from the panel representatives.

15 By way of background, Mentor Ophthalmics is a  
16 division of Mentor Corporation. The division manufactures  
17 a wide range of ophthalmic devices. The other divisions of  
18 the company offer urology and plastic and reconstructive  
19 products.

20 The product to be approved is the U940A  
21 MemoryLens, which is a posterior chamber IOL manufactured  
22 of hydrogel material. It is pre-rolled in its unique  
23 delivery system. To clarify how this lens is implanted, I  
24 would like to show a brief one minute video.

1           The lens is delivered to the OR by the nurse.  
2           She depresses the plunger on the lens container to release  
3           the pre-rolled MemoryLens. The lens is now ready for  
4           implantation. Using standard forceps, the surgeon removes  
5           the pre-rolled lens from the jaws of the delivery arms and  
6           in one step begins the implantation. The insertion is  
7           begun by placing the leading edge of the optic into the  
8           incision and allowing the inferior haptic to self-position.  
9           The lens is directed posteriorly in the capsular bag and  
10          positioned. The unfolding time depends upon the  
11          temperature in the eye, which varies with the temperature  
12          of the irrigating BSS used by the surgeon. Here the lens  
13          is fully opened.

14                    Move to the next slide, please.

15           There have been two clinical studies performed  
16          on this lens. Optical Radiation sponsored the original  
17          study. Then, in 1994, Mentor acquired MemoryLens from ORC.  
18          Mentor then sponsored the pre-rolled clinical study. At  
19          the time Mentor filed the PMA in September of 1996, the  
20          MemoryLens had approval for sale in 15 countries. Since  
21          that time, the number has expanded to approximately 50  
22          international companies, and over 61,000 MemoryLenses have  
23          now been implanted in 21 countries. The majority of lenses  
24          were implanted in Europe, where the lens is now CE marked.

1 The company is encouraged by the feedback of the larger  
2 implanters. Although appropriate quality systems are in  
3 place to monitor lens performance, to date the company has  
4 received only one adverse reaction report.

5 We believe this lens represents an improvement  
6 in foldable lens technology. It has a unique delivery  
7 system. It is the only pre-rolled lens available today.  
8 It provides for one-step delivery and is designed for easy  
9 insertion. The surgeon requires no special instrumentation  
10 to implant this lens. The lens unfolds gently and does not  
11 spring open. It also permits the surgeon to rotate and  
12 place the lens in the bag before the lens unfolds fully.

13 In summary, we believe we are able to show that  
14 safety and effectiveness has been demonstrated based upon  
15 clinical and preclinical evaluations. The pre-rolled  
16 design allows for single-step insertion through a small  
17 incision. The material, as will be explained, was chosen  
18 for its biocompatibility and its gentle unfolding  
19 characteristics, which make it a desirable lens for  
20 surgeons.

21 I would now like to introduce the speakers who  
22 will follow. First is Dr. Tom Paul. Dr. Paul is director  
23 of the Material Sciences Group for Mentor Research and  
24 Development. Dr. Paul will be reviewing the device

1 characteristics and significant preclinical tests.

2 Next is Clarke Scherff. Mr. Scherff is vice  
3 president of quality and regulatory assurance for Mentor  
4 Corporation. He will discuss the regulatory path and the  
5 history behind the two clinical studies being reviewed  
6 today.

7 Lastly, Dr. James Memmen, the medical director  
8 for the MemoryLens study, will be discussing the clinical  
9 results from the studies. Dr. Memmen is a principal with  
10 the Green Bay Eye Clinic, attending physician at St.  
11 Vincent and Billing Memorial Hospitals and, among other  
12 affiliations, assistant professor of ophthalmology for the  
13 Uniformed Services University of Health Sciences.

14 In addition to these presenters, we have Dr.  
15 Richard Chiacchierini, vice president of statistical  
16 services for C.L. McIntosh, available to answer questions  
17 related to data analysis.

18 I would now like to turn the discussion over to  
19 Dr. Tom Paul.

20 DR. PAUL: Good morning. My name is Thomas  
21 Paul. I am the director of R&D materials science at Mentor  
22 Corporation. This morning I would like to review with you  
23 the composition of MemoryLens and relate that composition  
24 to its properties as a foldable small incision lens.

1           As part of this review, I will first discuss  
2 the characteristics of the model U940A MemoryLens as a  
3 lens, and then review how it is delivered from the pre-  
4 rolled delivery system. Finally, I will summarize the  
5 preclinical testing of MemoryLens.

6           As seen from the photograph on the left, the  
7 U940A MemoryLens has a lens design that is very similar to  
8 that of conventional IOLs. The lens has a 6 millimeter  
9 diameter optic, and haptics that are 13 millimeters in  
10 overall diameter. In general, this is a lens configuration  
11 that has proved very successful for hard IOLs. As a result  
12 of its conventional design, the mechanical properties of  
13 MemoryLens are very similar to those of conventional IOLs.

14           Since the start of the MemoryLens clinical  
15 trial in 1989, the MemoryLens has evolved as surgical  
16 trends developed. The first MemoryLens was the model  
17 U780A. The present MemoryLens is the model U940A. In the  
18 clinical trials of MemoryLens, the first lens to be  
19 implanted was the U780A. As seen from the table, the U780A  
20 is essentially a larger version of the U940A. The only  
21 differences are that the U780A has a 1 millimeter larger  
22 optic and a 1 millimeter larger haptic than the U940A.  
23 Both models are made of the same optic material and of the  
24 same haptic material. Both designs are very similar to

1 conventional IOLs.

2           The MemoryLens is different from conventional  
3 IOLs in that it has a hydrogel optic. The hydrogel optic  
4 allows MemoryLens to be rolled. Compositionally,  
5 MemoryLens is a hydrogel because its optic is 20 percent  
6 water and 80 percent polymer. The MemoryLenses used in all  
7 preclinical testing and in both clinical trials was the  
8 same, the 20 percent hydrogel material.

9           The polymer portion of MemoryLens hydrogel is  
10 based on substituted variations of the acrylic monomer. In  
11 order of quantity, the monomers that compose MemoryLens are  
12 hydroxyethylmethacrylate, HEMA; methylmethacrylate, MMA; 4-  
13 methacryloxy 2-hydroxybenzophenone, MOBP, the UV absorber;  
14 and ethylene glycol dimethacrylate, EGDMA, the cross-  
15 linker. In general, all of these polymers are well known  
16 and have been widely used in medical devices. HEMA and  
17 EGDMA have been used in contact lenses and IOLs. MMA, of  
18 course, is the basis of most hard IOLs. The MOBP is a  
19 member of the class of UV absorbers that have been used in  
20 IOLs since the first UV absorbers were put into IOLs.

21           The uniqueness of the MemoryLens composition,  
22 however, is not only in the type of monomers used but in  
23 the stoichiometry of those monomers. The stoichiometry of  
24 the MemoryLens optic allows the lens to be a foldable lens,

1 and also gives it its unique and advantageous properties.  
2 One of the unique properties of MemoryLens is its hardness.  
3 Although it is a foldable lens, MemoryLens is very firm and  
4 stiff at high temperature. This is exemplified by the fact  
5 that MemoryLens is too stiff to be rolled at room  
6 temperature or at eye temperature. This hardness, we  
7 believe, is a desirable attribute.

8           The refractive index of MemoryLens optic is  
9 1.473, which is relatively high for a foldable IOL. This  
10 allows the MemoryLens to have a relatively thin optic.  
11 Additionally, the MemoryLens optic material is extensively  
12 extracted during its manufacturing process. This results  
13 in an IOL that has a very low level of extractables and  
14 allows the hydrogel biocompatibility of the material to  
15 exhibit itself. From the outset, biocompatibility of the  
16 MemoryLens was expected to be high, both because of its  
17 hydrogel composition and because of its low level of  
18 residual monomer.

19           In compliance with the FDA guidelines, Mentor  
20 has tested MemoryLens with the full battery of in vitro and  
21 in vivo testing listed, including the one-year implantation  
22 in rabbit. MemoryLens passed each of these studies, and  
23 its qualities of a biomaterial were demonstrated.

24 ~~The most unique aspect of MemoryLens material~~

1 is the placement of its glass transition temperature. The  
2 glass transition temperature of MemoryLens is centered at  
3 about 27 degrees Centigrade. Twenty-seven degrees is a  
4 temperature that is above room temperature and below eye  
5 temperature. This allows the lens to remain rolled at room  
6 temperature, as seen from the photograph on the left.  
7 Since MemoryLens stays rolled by itself, no special  
8 instruments are needed to manipulate the lens.  
9 Additionally, the incision size required by MemoryLens is  
10 minimized by not needing an additional instrument or  
11 shooter to hold it folded during insertion into the eye.  
12 Once in the eye, MemoryLens opens spontaneously and gently  
13 from the heat of the eye.

14           Because the stoichiometry of MemoryLens  
15 composition is very carefully controlled during  
16 manufacturing, the opening speed and recovery times of  
17 MemoryLens are very consistent and predictable. In  
18 laboratory testing of MemoryLens, it was found that the  
19 lens opens very consistently and predictably within about  
20 50 seconds at the assumed eye temperature of 35 degrees  
21 Celsius. The opening speed of the lens shows no  
22 significant variation as a function of diopter. Upon  
23 unrolling, the MemoryLens regains its initial optical  
24 ~~properties within the first day, and MemoryLens does not~~

1 appear to have any significant inherent or induced  
2 astigmatism after it is unrolled.

3 In the clinical trial of MemoryLens, the  
4 original clinical trial of MemoryLens, the lens was rolled  
5 by the surgeon. Although this gave good results, the  
6 process of rolling the lens required far too much time and  
7 effort on behalf of the surgeon. Because of its unique  
8 material properties, however, MemoryLens can be pre-rolled  
9 during the manufacture of the lens and delivered to the  
10 surgeon in its rolled state.

11 This slide shows the delivery system that  
12 contains the pre-rolled MemoryLens. This is the delivery  
13 system that you saw demonstrated in the video. To recap  
14 its use, in the delivery system, the rolled MemoryLens is  
15 held between the jaws of the roller retainer. The jaws of  
16 the roller retainer are the bulges on the lower portion of  
17 the white roller retainer arms and are marked by the red  
18 arrow. In this photograph, the rolled lens cannot be seen,  
19 but the haptics protruding from the roller retainer jaws  
20 identify the position of the rolled lens.

21 The rolled lens is presented for use by pushing  
22 the white button at the top of the delivery system and then  
23 removing the glass vial BSS. After presentation, the  
24 rolled MemoryLens is lightly held between the open jaws of

1 the delivery system. A surgical forceps or other  
2 instrument can then be used to grasp the lens by the optic  
3 and remove it for insertion into the eye. After removal  
4 from the delivery system, the lens can be directly  
5 implanted. No further manipulation of the lens is required  
6 to prepare it for implantation.

7           Previously it was discussed that because of  
8 careful control of stoichiometry, the MemoryLens opens and  
9 regains its optical properties in a very predictable  
10 manner. This consistent opening and recovery behavior also  
11 applies to the pre-rolled, stored MemoryLens. Laboratory  
12 testing has shown that the properties of the MemoryLens do  
13 not change as a result of storage in the delivery system  
14 for up to one year. The lens opening times and optical  
15 recovery times are unchanged. There is no residual  
16 astigmatism in the lens as a result of storage in the  
17 rolled state. Slit lamp examination of stored lenses has  
18 revealed no evidence of haze or discoloration of the lens.

19           As expected, the MemoryLens has an extensive  
20 history of preclinical testing. In the next several  
21 slides, the majority of these tests are listed. While the  
22 tests are too numerous to review individually, they can be  
23 summarized as being consistent with the battery of  
24 ~~preclinical testing that fulfills the requirements of FDA~~

1 guidance and is consistent with ANSI and ISO guidelines.

2 This slide lists the physical testing of  
3 MemoryLens. Highlighted is the UV visible transmittance  
4 curve of MemoryLens. This transmittance curve shown in the  
5 right panel is essentially identical to that of MemoryLens  
6 Mentor's PMMA lenses.

7 Listed on this slide is the MemoryLens  
8 preclinical toxicology testing. As reviewed on the  
9 previous slide, MemoryLens performed well on these tests.  
10 Also listed here is the preclinical toxicology studies done  
11 on the MemoryLens delivery system. This testing  
12 demonstrates that the components of the MemoryLens delivery  
13 system meet all of the requirements of the USP Class 6  
14 plastic both initially, after sterilization, and after one  
15 year of storage.

16 Listed on this slide is the mechanical testing  
17 of MemoryLens. This testing was done in compliance with  
18 the ISO mechanical testing guidelines. The results of  
19 these tests indicate that MemoryLens meets the requirements  
20 of the ISO guidelines. Of particular interest is the  
21 compression force test. Although MemoryLens has  
22 polypropylene haptics, they are the thicker 4.0 prolene  
23 instead of the usual thinner 5.0 prolene. This gives  
24 MemoryLens good mechanical properties initially and after

1 compression decay.

2 This slide lists the chemical and YAG testing  
3 of MemoryLens. As seen from the list, MemoryLens has been  
4 thoroughly analyzed chemically. MemoryLens has also been  
5 analyzed for its resistance to YAG laser damage. The right  
6 panel of this slide shows a typical MemoryLens response to  
7 YAG laser at 5 millijoules. As seen, the laser defect is  
8 small and confined, with rounded edges. This is a very  
9 good response to YAG laser and is a result of the  
10 composition and stoichiometry of MemoryLens.

11 In conclusion, we believe that the preclinical  
12 testing of MemoryLens demonstrates that MemoryLens is safe  
13 for use as an intraocular lens. Additionally, we believe  
14 that the pre-rolled delivery system provides a simple and  
15 effective method for delivering MemoryLens for phaco  
16 cataract surgery.

17 Now I would like to turn the presentation over  
18 to Mr. Clarke Scherff for a review of MemoryLens'  
19 regulatory pathway and an overview of the clinical trials.

20 MR. SCHERFF: Good morning. My name is Clarke  
21 Scherff. I'm vice president for quality and regulatory  
22 assurance for Mentor Corporation. I would like to  
23 delineate the regulatory path Mentor has taken to assure  
24 that MemoryLens is safe and effective. I will also be

1 giving you a breakdown of the two clinical studies that  
2 substantiate the safety and effectiveness of MemoryLens.  
3 The actual data will be presented to you by Dr. Memmen.

4 First, the product we are requesting approval  
5 for is the U940A MemoryLens, presented to the doctor pre-  
6 rolled in a unique delivery system. The characteristics of  
7 the lens shown here have been previously presented to you  
8 by Dr. Paul. This slide shows the delivery system that  
9 presents the lens to the doctor pre-rolled. As Dr. Paul  
10 explained, besides the lens, it contains the roller, the  
11 plunger, and vial with balanced salt solution. The system  
12 is stored refrigerated between 2 degrees to 10 degrees  
13 Celsius. We currently have a one-year shelf life on the  
14 lens in its pre-rolled package configuration.

15 The indication for use for MemoryLens is for  
16 the primary implantation for the visual correction of  
17 aphakia in patients 60 years of age and older. The lens is  
18 intended to be placed in the capsular bag.

19 On September 30, 1996, Mentor Corporation  
20 submitted an original PMA application for MemoryLens. The  
21 PMA contained clinical data from two clinical studies. The  
22 original core study where patients were followed up to  
23 three years contained one-year and later data on patients  
24 to prove safety and efficacy. The second study, the pre

1 rolled clinical study, contained six-month data on patients  
2 in the original submission.

3 Mentor Corporation subsequently received a  
4 letter from FDA on November 14, indicating the PMA  
5 application was fileable. In December, Mentor met with FDA  
6 to discuss questions regarding presentation of the clinical  
7 data, which will be explained in two flow charts later.

8 On February 20, Mentor amended the PMA with a  
9 report of the one-year follow-up data from the pre-rolled  
10 MemoryLens study. Therefore, we have two separate clinical  
11 studies on the MemoryLens with one-year or later data. The  
12 one-year data will be presented to you today.

13 In early May, FDA provided Mentor with a list  
14 of questions resulting from FDA's review of the clinical  
15 data. Mentor responded in an amendment on May 20, 1997.  
16 This amendment contained a revised summary of safety and  
17 effectiveness, and the labeling, which you have been given  
18 copies of. All questions and amendments requested by FDA  
19 have been addressed to date.

20 In addition to the various amendments provided  
21 to FDA, Mentor has performed audits of the 35 clinical  
22 sites comprising 36 investigators from the original study,  
23 and the six clinical sites comprising seven investigators  
24 from the pre rolled study. The purpose of these audits was

1 to determine if we had all the data available for each  
2 patient and if the data that had been provided was accurate  
3 by auditing the clinical records at the site against the  
4 case report forms received and entered into the databases  
5 by the companies.

6 As indicated previously, there have been two  
7 clinical studies performed for MemoryLens. Optical  
8 Radiation Corporation sponsored the original study. The  
9 purpose of this clinical study was to assess the safety and  
10 effectiveness of the new lens material and its rolling  
11 characteristics as an IOL. In October 1994, Mentor  
12 Corporation purchased the intraocular lens division of  
13 Optical Radiation Corporation. This purchase included the  
14 MemoryLens. Mentor Corporation sponsored the second  
15 clinical study which evaluated the new packaging system for  
16 the lens. The packaging system presents the lens to the  
17 doctor pre-rolled.

18 The original study performed by Optical  
19 Radiation had a total of 616 patients, with an extended  
20 cohort of 523 patients, and 93 patients who did not meet  
21 cohort requirements. The extended cohort of 523 patients  
22 includes two sets of patients. It includes 360 cohort  
23 patients that have all the required forms through Form 6,  
24 ~~plus 163 patients who have all the appropriate forms except~~

1 Form 6, but have later forms -- Form 7, 8, 9, or 10. Based  
2 on a request by FDA, we have based the clinical performance  
3 of MemoryLens in the original study on the 360 patient  
4 population. Therefore, the label values for visual acuity  
5 and complication rates are based on this population.

6 In this study, the lens was rolled in the  
7 doctor's surgical suite. This proved to be a difficult  
8 process and time-consuming for the physician.

9 Consequently, the new package and delivery system was  
10 designed to deliver the lens pre-rolled to the physician.  
11 The pre-rolled clinical study had a total of 226 patients;  
12 190 are cohorts, and 36 did not meet cohort status. The  
13 only difference between this and the original study is that  
14 the lenses were pre-rolled for the doctor. Therefore, the  
15 clinical study data we will present is from the 360  
16 population of patients in the original study where the lens  
17 was rolled by the surgeon, and the 190 patients from the  
18 pre-rolled study. Even though Mentor has not combined the  
19 data from these two populations of patients, these  
20 populations represent 550 implant patients with MemoryLens  
21 implants. Both studies have been compared to the clinical  
22 values of the Stark grid that recognize standard for  
23 comparison.

24 ~~I would now like to turn the remainder of the~~

1 presentation over to Dr. Memmen, who will review the  
2 clinical data results.

3 DR. MEMMEN: Good morning, ladies and  
4 gentlemen. I am James Memmen, and I am an ophthalmologist  
5 practicing in Green Bay, Wisconsin. I've been involved in  
6 the MemoryLens as a clinical investigator since 1989 and as  
7 a medical director for the pre-rolled MemoryLens clinical  
8 study since 1996. I am a paid consultant to Mentor  
9 Corporation and a minor stockholder.

10 As mentioned previously with regard to the  
11 clinical trials, there have been two trials to date. These  
12 studies were multisite, prospective clinical trials, and my  
13 presentation today will substantiate the safety and  
14 effectiveness of the U940A lens. I will primarily present  
15 to the panel those parameters and data which are relevant  
16 to the clinical performance of the lens.

17 First I would like to review the objectives of  
18 the clinical study, followed by the clinical study results.  
19 The clinical study results I will be discussing include  
20 patient demographics, overall best case and worst case  
21 visual acuity, cumulative and persistent sight-threatening  
22 complications, and other complications and adverse  
23 reactions. I will then present the conclusions from the  
24 study.

1           The objective of the original core study was to  
2 evaluate the safety and effectiveness of MemoryLens, with  
3 particular attention to the clinical performance of the  
4 hydrogel material and its rolling and optical  
5 characteristics. The objective of the pre-rolled  
6 MemoryLens study was to evaluate the safety and  
7 effectiveness of the MemoryLens when delivered to the  
8 surgeon pre-rolled in the current packaging and delivery  
9 system.

10           This table compares the patient demographics  
11 from the two studies, and essentially they were identical.  
12 The average age of patients was approximately 73 years.  
13 There was a higher percent of females than males enrolled  
14 in the study. However, analysis of the clinical data show  
15 that results for males and females were similar, and  
16 therefore there was no significant gender bias. The  
17 majority of patients enrolled in each study were Caucasian.

18           The next series of tables cover the visual  
19 acuity findings for MemoryLens. The overall percentage of  
20 patients with a visual acuity of 20/40 or better at Form 6,  
21 by age, is shown here. In the original study, a total of  
22 93.2 percent of patients achieved a visual acuity of 20/40  
23 or better at Form 6. In the pre-rolled study, 98.4 percent  
24 of patients achieved a visual acuity of 20/40 or better at

1 Form 6.

2 In the original study, the visual acuities  
3 exceeded FDA grids at all ages, and younger patients tended  
4 to achieve somewhat better results than older patients.

5 This corresponds to the expected decrease with age, as  
6 reflected in the grid which is shown for comparison over on  
7 the right. In the pre-rolled study, the visual acuities  
8 also exceeded FDA grids in all age categories, with both  
9 younger and older patients achieving very good results.

10 The overall visual acuities at Form 6 for the  
11 patients in the original study are presented here by age,  
12 with a breakdown. It can be seen that 43.7 percent of  
13 patients achieved a visual acuity of 20/20 or better, and  
14 again younger patients tend to achieve better visual  
15 acuities than older patients. The percentages of patients  
16 with visual acuities worse than 20/40 were very low. The  
17 overall visual acuity results at Form 6 in the pre-rolled  
18 study were similar: 55.8 percent of patients achieved  
19 visual acuity of 20/40 or better.

20 The percentage of patients with visual acuities  
21 worse than 20/40 were very small, at 0.7 percent. Also  
22 note that the two patients with a poor visual acuity in the  
23 60-69 year group here -- this represents one patient in  
24 each section -- one patient had a corneal transplant, and

1 one patient required a retinal detachment repair.

2 The percentage of best case patients who  
3 achieved visual acuity of 20/40 or better at Form 6, by  
4 age, are shown here for both studies. Best case analysis  
5 excludes any patients who had preoperative ocular pathology  
6 or postoperative macular degeneration. 97.6 percent of  
7 patients, best case patients in the original study, were  
8 20/40 or better, and 99.3 percent of best case patients in  
9 the pre-rolled study achieved 20/40 or better acuity at  
10 Form 6. All of these results exceed the grid, which is  
11 noted on the right.

12 Visual acuity results by age at Form 6 for best  
13 case patients in the original study showed that 51 percent  
14 of patients achieved a visual acuity of 20/20 or better,  
15 and only 2.4 percent had visual acuities worse than 20/40.

16 For visual acuity results at Form 6, the best  
17 case patients in the pre-rolled study showed that 57.7  
18 percent of patients achieved a visual acuity of 20/20 or  
19 better, and again only 0.7 percent had visual acuities  
20 worse than 20/40.

21 Worst case analysis includes patients who had  
22 preoperative pathology or postoperative macular  
23 degeneration. The visual acuities of worst case patients  
24 in both studies show that the majority of worst case

1 patients achieved a visual acuity of 20/40 or better. A  
2 total of 24 patients in the original study and three  
3 patients in the pre-rolled study had visual acuities worse  
4 than 20/40. Of the 24 patients in the original study, 10  
5 had macular degeneration. The reasons for the reduced  
6 visual acuity in the remaining 14 were varied. Of the  
7 three patients in the pre-rolled study, one had a retinal  
8 detachment, one had a corneal transplant, and one had  
9 diabetic retinopathy.

10 The following set of tables cover the various  
11 complication categories for the two clinical studies. The  
12 cumulative rates of sight-threatening complications which  
13 occurred during the clinical studies are listed in this  
14 slide. All of the complications occurred below FDA grid  
15 rates, with the exception of cumulative hyphema in the  
16 original study, and we also want you to note the comparison  
17 of that in the pre-rolled study.

18 Fourteen patients in the original study were  
19 reported to have hyphema. All the reports of hyphema  
20 occurred at Form 1. Twelve of the reported cases resolved  
21 by Form 2, and two patients not seen at Form 2 had resolved  
22 by Form 3. Thirteen of the 14 patients achieved a visual  
23 acuity of 20/40 or better at Form 6. The remaining patient  
24 had a visual acuity of 20/60 at Form 6 due to posterior

1 capsular haze, and the patient's visual acuity improved to  
2 20/25 after YAG capsulotomy.

3 The rates of persistent sight-threatening  
4 complications occurring during the clinical studies are  
5 shown in this table. All the complications occurred below  
6 FDA grid rates with the exception of persistent secondary  
7 glaucoma in the original study, and once again also please  
8 compare that to the results in the pre-rolled cohort.

9 Five patients in the original study reported  
10 secondary glaucoma at Form 6. Of these five patients, four  
11 had Orcolon, an investigational viscoelastic known to  
12 increase intraocular pressure, used during surgery. If the  
13 data from these four patients are excluded from the  
14 analysis, the rate of persistent secondary glaucoma is 0.3  
15 percent, which is below FDA grid rate.

16 Other complications at Form 6 which occurred  
17 during clinical studies were reported in low rates, with  
18 the exception of posterior capsular haze, and 15.56 percent  
19 of patients in the original study and 51.58 percent of  
20 patients in the pre-rolled study reported posterior  
21 capsular haze at Form 6. I would like to call the panel's  
22 attention to the fact that patients with any degree of  
23 posterior capsular haze were reported.

24 ~~In evaluating posterior capsular haze, there~~

1 are two critical objective pieces of data to consider in  
2 attempting to determine the clinical relevance of PCH  
3 rates. One, YAG capsulotomy rates, and two, visual acuity.  
4 It can be seen from this slide that despite the higher rate  
5 of PCH in the pre-rolled study compared to the original  
6 study, the patients requiring YAG capsulotomy were lower in  
7 the pre-rolled study than in the original study. These  
8 rates compare very favorably to the reported literature  
9 rates of 4.8 percent to 40.6 percent for capsulotomy. From  
10 the perspective of the requirement for capsulotomy, PCH is  
11 less clinically significant in the pre-rolled study than in  
12 the original study.

13 This slide illustrates the visual acuity  
14 profile for patients with PCH at Form 6 for both studies.  
15 These patients had not received a capsulotomy. Ninety-five  
16 percent of patients in the original study and 99 percent of  
17 patients in the pre-rolled study who had PCH achieved a  
18 visual acuity of 20/40 or better. Clearly, these results  
19 indicate that the reported increase in PCH rates for the  
20 pre-rolled lens patients had little effect on visual  
21 acuity.

22 In general, while the reported case rates for  
23 PCH from every lens appear to be high in the pre-rolled  
24 study, the clinical performance of the lens as exhibited by

1 the rate of posterior capsulotomy and visual acuity  
2 indicate a superior clinical performance.

3 The rates of adverse reactions in the two  
4 populations were below FDA grids, with the exception of the  
5 one report of intraocular infection in the original study.  
6 There were no reports of hypopyon, infection, or acute  
7 corneal decompensation in the pre-rolled study.

8 We believe that the clinical data have  
9 demonstrated that the MemoryLens performs in a safe and  
10 effective manner, based on the following. The visual  
11 acuity results meet or exceed grid values in both  
12 population studies. Complication rates were below grid  
13 values in both studies, with the exception of cumulative  
14 hyphema and persistent secondary glaucoma in the original  
15 study, which were not felt to be lens-related. Adverse  
16 reaction rates were below grid with the exception of one  
17 intraocular infection in the original study.

18 In conclusion, based on the data presented  
19 today, we have demonstrated that MemoryLens performs in an  
20 acceptable manner. The clinical data have shown that pre-  
21 rolled MemoryLens, for which we are seeking approval, is  
22 safe and effective when used for its intended application.  
23 We therefore believe that the data support an approval  
24 recommendation from the panel members.

1 Thank you very much.

2 DR. STULTING: The next item on the agenda is  
3 to open discussion on the PMA. Would you like to take a  
4 break now so we don't interrupt that? Okay. We'll have a  
5 15-minute break. Please return to your seats within  
6 fifteen minutes.

7 (Recess.)

8 DR. STULTING: We would like to reconvene the  
9 meeting. We are discussing P960036, the MemoryLens from  
10 Mentor Corporation. The next thing we need to do is the  
11 clinical review, Dr. Anthony Greer.

12 DR. GREER: Good morning again to the members  
13 of the Ophthalmic Devices Advisory Committee, Chairman  
14 Stulting, Dr. Rosenthal, Ms. Thornton, and other guests. I  
15 am Dr. W. Anthony Greer. I served as the principal FDA  
16 clinical reviewer for the PMA we now refer to as  
17 MemoryLens. I will now present the Division of Ophthalmic  
18 Devices team clinical review of the MemoryLens.

19 PMA application for the MemoryLens Posterior  
20 Chamber Intraocular Lens Model U940A is under discussion.  
21 Some of this material was previously covered. Continuing  
22 with the device characteristics, the principal one of  
23 thermoplasticity is of note in that above body temperature  
24 the material softens and can be rolled and folded. The

1 shape sets without being restrained when cooled to room  
2 temperature. This allows the lens to be rolled into a  
3 smaller insertion profile without damage to the lens. The  
4 lens is also fully hydrated in the rolled and set  
5 configuration. The optical material is made up of a  
6 quadpolymer that has ultraviolet-absorbent properties.

7 The lens background. The clinical study of the  
8 MemoryLens Model U780A began in October, 1989, and was  
9 sponsored by the Optical Radiation Corporation. Model  
10 U780A was initially implanted in a flat configuration. The  
11 firm subsequently received FDA approval to implant the lens  
12 in a rolled configuration through a smaller incision.  
13 Model U780A was rolled by the investigator using a lens-  
14 rolling device.

15 Model U940A was added to the study in May,  
16 1991, and followed a similar pathway of initial flat  
17 configuration insertion, with subsequent approval for the  
18 investigator to roll the lens and implant through a small  
19 incision. The U940A, with its smaller profile, allowed  
20 insertion through a smaller incision. Mentor Corporation  
21 purchased ORC in October, 1994.

22 The clinical indications, as has been noted for  
23 the posterior chamber intraocular lens, primary  
24 implantation for the visual correction of aphakia in

1 patients 60 years of age or older, placement into the  
2 capsular bag, designed for use in a small incision,  
3 extracapsular cataract extraction method.

4 Patient inclusion criteria are as follows. For  
5 the IDE inclusion criteria, the patient should be in good  
6 general and ocular health, the patient should have a sight-  
7 reducing cataract, the patient desires an intraocular lens  
8 insertion, the patient should also be willing and able to  
9 complete all required post-operative visits, and the  
10 patient should be a patient who may not be able to tolerate  
11 or manage contact lens, or would otherwise be an unsuitable  
12 candidate for cataract spectacle correction.

13 The firm's IDE exclusion criteria are as  
14 follows. An uncooperative patient or one who does not  
15 desire an intraocular lens, a patient with whom previous  
16 intraocular surgery has been performed, a patient in whom  
17 multiple surgical procedures were scheduled at the time of  
18 cataract extraction, and a patient under 18 years of age.  
19 Also, it's noted, a patient with the following ophthalmic  
20 pathologies.

21 The objectives of the IDE clinical  
22 investigation. Evaluate the safety and efficacy of the  
23 device, determine postoperative visual acuity, compare  
24 appearance of adverse reactions and ocular complications to

1 that of the reported scientific literature, and identify  
2 any subgroups within the study population that are at high  
3 risk for particular complications.

4 The outcome measures are as noted on this  
5 slide. The visual acuity for the pre-rolled MemoryLens  
6 study was reported as corrected, uncorrected, and pinhole  
7 acuity, the better visual acuity of whichever parameter was  
8 used. The best visual acuity outcomes excluded patients  
9 with preoperative ocular pathology or a macular  
10 degeneration diagnosed at any time postoperatively.

11 A brief review of the FDA form visit schedule  
12 is necessary to understand the various cohort groups  
13 analyzed in this PMA application. The usual FDA  
14 intraocular lens review protocol is demonstrated in the  
15 following slides. Of note is the Form 6 visit, from 12 to  
16 14 months postoperatively. The Mentor Corporation  
17 submission deviated from the usual data collection protocol  
18 in that a significant number of subjects did not have a  
19 Form 6. That is, the 12- to 14-month postoperative exam.

20 The FDA usually requires a three-year follow-up  
21 form called Form 10 for study for the new materials, and a  
22 two-year visit is included, which is the same as Mentor's  
23 Form 8. It is to be noted, in the comparison of the FDA  
24 ~~standard intraocular lens cohort and what was later termed~~

1 the Mentor extended cohort, for the patient populations in  
2 which the Form 6 visit was absent the FDA Form 6 visit was  
3 substituted by a Form 6 or a later visit. That is, a Form  
4 7, 8, 9 or 10 visit.

5 Three sets of clinical data were evaluated in  
6 this PMA. The original PMA was submitted on September  
7 30th, 1996, for model U940A. It had data from 616 subjects  
8 implanted with MemoryLens in a flat configuration or a  
9 configuration rolled by the surgeon, and 224 subjects  
10 implanted with a pre-rolled current delivery system, of  
11 which Mentor is now seeking PMA approval.

12 Three-hundred sixty patients qualified as  
13 standard FDA IOL cohorts out of the 616. Five-hundred  
14 twenty-three subjects of the 616 qualified for the extended  
15 cohort population. That is, they had Form 1, 2 or 3, Form  
16 4 or 5, and an exam after the Form 6 level.

17 It should be also noted, if we can just go back  
18 for a second on the pre-rolled, that 190 of the 224 in the  
19 pre-rolled configuration qualified as standard FDA cohorts.

20 Analysis assessing the pooled data was  
21 performed for key efficacy. It looked at visual acuity,  
22 best corrected visual acuity, and safety measures. That  
23 is, sight-threatening complications.

24 ~~The questions that were asked, are there~~

1 statistically significant differences between the 360  
2 standard cohort population and the 523 extended cohort  
3 population? Statistical analysis performed by Mentor and  
4 reviewed by the FDA statistician confirmed that there were  
5 no statistical differences. The question was also asked,  
6 can the data be pooled, and statistical analysis indicated  
7 that the data could indeed be pooled.

8           Continuing, the second question with regards to  
9 the pooling of data was whether there were statistically  
10 significant differences between the rolled MemoryLens --  
11 that is, the 190 cohort population -- and the 360 standard  
12 cohort, and/or the 523 Mentor extended cohort population.  
13 Various statistical analysis were used to determine that  
14 the Wilcoxon test was statistically significant at a P of  
15 0.0003.

16           We move to reviewing some of the clinical data.  
17 This is a bar chart that demonstrates the pooled data, the  
18 523 extended cohort, the 360 standard cohort, and the 190  
19 pre-rolled cohort. What is of note in this graph is that  
20 the -- excuse me. The pooled data bar chart is absent in  
21 this slide, but we can get a good idea of what ranges the  
22 pooled data bar chart would be by looking at the bars of  
23 the individual groups. With the exception of the 523  
24 expanded cohort in the 59 years of age or less group, the

1 MemoryLens data exceed that of the FDA grid in all  
2 categories.

3 In a combined best case visual acuity of 20/40  
4 or better, again, it can be noted that the MemoryLens data  
5 exceeds the FDA grids in every category. That includes the  
6 pooled, the 523 cohort, the 360, and the 190 cohort  
7 populations.

8 Looking at the adverse reactions in the pooled  
9 data, there were 10 patients. Nine standard MemoryLens and  
10 one pre-rolled MemoryLens experienced at least one adverse  
11 reaction, for a 1.2 percent. The data was the same for  
12 Form 4 and Form 6 lens. Percentage of patients with at  
13 least one occurrence of intraocular infection was 0.2  
14 percent. It was higher than a Stark grid of 0.1 percent,  
15 but equal to that of the previous five FDA silicone and  
16 sulfacritic IOLs approved. Again, looking for adverse  
17 reactions, the MemoryLens rate was lower than that of the  
18 Stark grid.

19 In looking at the cohort population of N360 for  
20 postoperative complications cumulative, there were no cases  
21 of pupillary block, endophthalmitis, reported for the  
22 MemoryLens cohort. What is of note is the cases of  
23 hyphema, in that the MemoryLens has a rate of high  
24 cumulative hyphema of 3.9 percent compared to the grid of 1

1 percent.

2 Of note in this slide in the cohort population  
3 of N360 is the rate of glaucoma, cumulative glaucoma cases.  
4 The MemoryLens had 1.4 percent compared to the grid of 0.5  
5 percent.

6 Moving to the cohort population of 190,  
7 cumulative sight-threatening complications, sight-  
8 threatening complications on or before Form 6 for cohort  
9 190 compared to the FDA grid are noted in this slide.  
10 There are no reported cases of hyphema, endophthalmitis,  
11 pupillary block, lens dislocations, cyclic membrane, or  
12 betritis. They are not noted. Of note would be the  
13 secondary glaucoma rate of 4.74 percent for the MemoryLens.

14 In the cohort population of the 190 pre-rolled,  
15 the persistent sight-threatening complications, there are  
16 no reports of corneal edema, secondary glaucoma, cyclic  
17 membranes, or betritis in Form 6 in that population.

18 Moving to posterior capsule opacification, in  
19 response to an FDA request, Mentor Corporation provided an  
20 analysis of age-adjusted posterior capsular haze rates for  
21 the MemoryLens study. It was noted previously Mentor  
22 believes that the higher incidence of posterior capsule  
23 haze for the pre-rolled -- that is, the 190 population --  
24 is for two reasons. One, patients noted to have a

1 posterior capsular haze at any time and did not undergo a  
2 YAG laser procedure are much higher in the pre-rolled than  
3 in the 523 or the 360 cohort population.

4 The second reason is that investigators in the  
5 pre-rolled reported the incidence of posterior capsular  
6 haze when it was very slight and did not affect visual  
7 acuity. Patients with posterior capsular haze in the pre-  
8 rolled had a higher visual acuity than patients in the 523  
9 or the 360 populations when they were reported.

10 We can move through the next two slides.

11 The questions that the FDA team reviewers had  
12 for the panel are noted in the slide. Question 1. Based  
13 upon the 360 cohort eyes and/or the 523 extended cohort  
14 eyes, has Mentor provided a reasonable insurance of safety  
15 and efficacy in this device for the visual correction of  
16 aphakia in patients 60 years of age or older where a  
17 cataractous lens has been removed by extracapsular cataract  
18 extraction method?

19 Panel question number 2. The cumulative rates  
20 for secondary glaucoma and hyphema of the MemoryLens exceed  
21 the cumulative rates for secondary glaucoma and hyphema  
22 recorded in the FDA Stark grid. Are the explanations of  
23 the increased cumulative rates of the secondary glaucoma  
24 and hyphema provided by the sponsor acceptable?

1 Panel question number 3. The firm is seeking  
2 approval for the pre-rolled configuration only. Do you  
3 believe the clinical data for the pre-rolled configuration  
4 provides adequate assurance of safety and efficacy?

5 The final question. Is there any additional  
6 information that the panel would like to see in the  
7 labeling for this ophthalmic device?

8 Thank you very much.

9 DR. STULTING: Thank you very much.

10 I'd like to move forward with comments from Dr.  
11 Higginbotham, who was one of the primary reviewers for this  
12 PMA.

13 DR. HIGGINBOTHAM: Considering the detail of  
14 the previous presentations, I'll keep my comments rather  
15 brief. I have prepared for the panel a four-page document  
16 and I hope all the panelists have that in front of you.

17 As you've heard, this is a quadpolymer, and  
18 based on the description that was provided by the company  
19 as well as reviewed by staff, this certainly appears to be  
20 very safe, considering that these materials have been used  
21 in ophthalmic products previously.

22 As you know, there are three cohorts that we  
23 are considering, but it's really the last cohort, the 190  
24 pre rolled, that really is the one that is of greatest

1 concern here.

2           Regarding the first cohort, though, I think  
3 it's important to point out that long-term data indicates  
4 that these patients did quite well in general, and I'll  
5 refer you to the bottom of page 2 of my comments, that over  
6 time the percentage of patients with a final visual acuity  
7 of 20/40 or better increased to 97.9 percent. There was  
8 only one adverse reaction not thought to be related to the  
9 lens, and that was dislocation at the time of mydriasis  
10 examination. In that second paragraph, I listed all the  
11 other sight-threatening complications, and you can see that  
12 those percentages are all quite low.

13           Moving on to the second cohort, the 360, I'll  
14 direct your attention to the middle of the page because  
15 there are three issues that we have in front of us of  
16 particular concern. That's the hyphema rate, the glaucoma  
17 rate, as well as the posterior capsule opacification rate.

18           Let's first discuss the hyphema issue. Of the  
19 360 patients, in the second cohort again, 14 were diagnosed  
20 with hyphema. There were several predisposing factors  
21 which were listed in Volume 4 of the stack that we received  
22 in our mail. Three underwent an iridectomy. Three had  
23 complicated surgeries, including rupture of the posterior  
24 capsule. Two patients were diabetic.

1           However, in all 14 cases, as you've heard  
2 previously, the visual acuity after the hyphema resolved  
3 was better than the preoperative acuity, and 13 of the 14  
4 patients achieved an acuity of 20/40 or better.

5           This morning we have heard that there was some  
6 difficulty in rolling that lens and perhaps there could  
7 have been some difficulty related to the insertion of the  
8 lens to account for the hyphema. That's only conjecture,  
9 but nevertheless, we didn't see this rate of hyphema in the  
10 pre-rolled cohort, which is the 190.

11           Moving on to the next paragraph, which is the  
12 long-term follow-up, overall the visual acuity was quite  
13 favorable in the 360 cohort. One patient suffered a  
14 dislocated lens during a dilated exam. The rate of corneal  
15 edema was less than the Stark grid and there was persistent  
16 uveitis that ranged from 0 to 0.28 percent, quite low, as  
17 well as persistent macular edema which is also quite low.  
18 That resolved in all but three patients by Form 10.

19           Now, the glaucoma. There were five patients in  
20 cohort 2 with secondary glaucoma, four of which had the  
21 investigational viscoelastic, which we've heard previously,  
22 Orcolon, which is thought to have contributed to the  
23 increase. If one eliminates those four patients, the rate  
24 of glaucoma drops below the grid. I was quite satisfied

1 with that explanation, knowing that this particular  
2 viscoelastic was known to cause a secondary glaucoma when  
3 it was used by several investigators.

4 Moving on to the cohort 3, and on to page 4,  
5 I'll direct your attention to patients with complications.  
6 Again, of the 190 cohort patients, 166 experienced at least  
7 one sight-threatening complication, and as you'll see  
8 listed, these were all quite low in terms of overall  
9 percentages. Just to also point out, the rate of macular  
10 edema was below the Stark rate.

11 Now, let's end up with the posterior capsular  
12 opacification. In the three cohorts, the rates of  
13 posterior capsular opacification was, in the first cohort  
14 of 523, 18.5 percent. In the second cohort, 360, was 15.8  
15 percent, and the last was 51.58 percent. Considering, as  
16 you've heard, that the final visual acuity of the last  
17 cohort was greater than the other two cohorts, the  
18 difference in the reporting behavior among the  
19 investigators is a possible explanation.

20 Certainly as you saw, the rates of performing  
21 capsulotomy was certainly within the range of acceptable  
22 clinical practice, but in spite of that, we had such a  
23 significant reporting, so it's conceivable that for a  
24 ~~minimal opacification there was a report given to the~~

1 manufacturer that this was opacification that was noted in  
2 clinical exam. Since there are really no controlled  
3 clinical trials examining the rates of posterior capsular  
4 opacification as a function of age and comorbidities, I was  
5 quite satisfied with the reported findings, and I doubt  
6 that there is any causal relationship associated with the  
7 lens.

8           The rate of glaucoma, I didn't see anything in  
9 Volume 5, as I saw with the second cohort, in terms of the  
10 frequency of trabeculectomies. Just to backtrack a bit, in  
11 the 360 patients there were three secondary  
12 trabeculectomies that were done as a result of the use of  
13 that viscoelastic that I alluded to. It's my understanding  
14 that trabeculectomies were not done in the third cohort,  
15 and so I question whether or not this may have been just an  
16 increase in pressure that was called glaucoma, as opposed  
17 to really frank glaucoma that requires surgical  
18 intervention. So again, there may have been an element of  
19 overreporting as relates to the glaucoma.

20           With all these considerations, keeping all  
21 these considerations in mind, I do believe that this is a  
22 safe and effective product and can be considered for visual  
23 correction for those patients undergoing cataract  
24 extraction who are 60 years of age or older.

1 DR. STULTING: Thank you.

2 I'd like to let Kevin have an opportunity to  
3 comment and we'll open the floor for comments, questions,  
4 and discussion.

5 DR. GREENIDGE: Thank you.

6 At this time, I would like to keep my comments  
7 concentrated on safety and efficacy concerns. First, I'd  
8 like to address effectiveness. The postoperative visual  
9 acuity results from this study were comparable or better  
10 than the Stark grid. This was the case when the results  
11 were analyzed by age and at each postoperative period for  
12 all study groups.

13 Postoperative complications. I would like to  
14 concentrate upon the two complications that have received  
15 the most attention, that of hyphema and secondary glaucoma.  
16 All hyphemas were documented in the immediate postoperative  
17 period, with a majority resolving by three weeks. At 12 to  
18 14 months postoperatively, 13 of the 14 patients with  
19 hyphema had a visual acuity of 20/40 or better. The  
20 fourteenth patient was documented to have a visual acuity  
21 of 20/25 following a posterior capsulotomy.

22 After review, the sponsor has stated that the  
23 etiology of the hyphemas were not related to the lens, but  
24 attributable to variables such as complications during

1 surgery, preoperative conditions that may have made the  
2 patient more prone to complications associated with  
3 bleeding, the patients having multiple procedures performed  
4 during cataract surgery, and patients with more surgical  
5 trauma. The sponsors had submitted data to support this  
6 claim.

7 I would like to go on to secondary glaucoma.  
8 The patients studied have a much greater rate of secondary  
9 glaucoma than the Stark grid. This event is of concern  
10 because of it's potential and immediate long-term effect on  
11 visual acuity and visual function. The definition of  
12 secondary glaucoma was not found, nor the levels of  
13 intraocular pressure required to make the diagnosis or  
14 medications utilized in its treatment.

15 The concern for this complication is based upon  
16 its occurrence rate in four subsets: 3.4 percent in the  
17 U780A lens, 2.7 percent in the U780A lens that was rolled,  
18 5.5 percent in the U940A rolled, and 4.7 percent in the  
19 U940A pre-rolled, compared to the cumulative 1.6 Stark  
20 grid.

21 The variable time of onset was noted at four  
22 weeks, seven months, one year, and in one case greater than  
23 14 months postoperatively. Three patients, as we have  
24 heard, who received an investigational viscoelastic

1 required surgical trabeculectomy. The sponsor states that  
2 the major cause of the secondary glaucoma noted throughout  
3 the study may be this particular viscoelastic, and if these  
4 patients were removed from the data, then the rates of  
5 secondary glaucoma would be comparable to the Stark grid.

6           However, if we're going to use the Stark grid  
7 as the basis of comparison, and I do believe there is --  
8 when you look at the Stark grid, they do differentiate  
9 between persistent sight-threatening complications for  
10 which they had a rate of 0.5 percent and cumulative sight-  
11 threatening complications for which the Stark grid  
12 percentage is 1.6 percent. If you look at all of the  
13 subsets, including the pre-rolled subset, the rate of  
14 glaucoma exceeds both of these rates as set forth by the  
15 Stark grid.

16           It is my impression that this device has been  
17 shown to be effective, in that the visual acuities are  
18 quite satisfactory and meet all known criteria. However,  
19 there is a safety issue regarding the glaucoma. The  
20 question that I would raise is should this safety issue  
21 regarding glaucoma, if we do not hear explanations that may  
22 or may not offset what I've said today, be reflected in the  
23 labeling. Individuals at risk for glaucoma or with  
24 ~~preexisting glaucoma should be aware of this additional~~

1 risk.

2 Thank you.

3 DR. STULTING: The floor is open for comments  
4 and discussion. Dr. Ruiz?

5 DR. RUIZ: We don't have a lot of information  
6 about surgical techniques in terms of the location of the  
7 incision and so on, which I think would have -- and we've  
8 heard some explanation about surgical complications,  
9 peripheral iridectomies and so on, which of course would  
10 have much more implication in terms of hyphema than the  
11 lens. I really don't think the lens has anything to do  
12 with the hyphemas.

13 The capsular haze is an interesting thing.  
14 What were the criteria for haze? At least in my case, I  
15 think it's about 100 percent if you're talking about the  
16 whole posterior capsule. There just aren't any without  
17 some haze. If you're talking about the central 2  
18 millimeters or so, then I think the capsular haze thing is  
19 really not a very important issue here.

20 The viscoelastic sort of intrigues me. Was  
21 this stuff washed out? This new viscoelastic that is  
22 implicated as a cause for some of these glaucoma problems?

23 DR. MEMMEN: The viscoelastic in cases both  
24 here as well as many other reported cases that occurred

1 with Orcolon were all removed as much as possible by the  
2 surgeon according to the usual standard techniques.

3 DR. STULTING: May I remind you, when you  
4 speak, please give your name first because the  
5 transcriptionist can't figure out who it is.

6 DR. MEMMEN: James Memmen.

7 DR. RUIZ: Now, the other thing that interests  
8 me is the U780 lens with the 7 millimeter optic and the 14  
9 millimeter haptics. Is that lens going to be available?

10 DR. MEMMEN: No.

11 DR. RUIZ: What are you doing if you need to  
12 put this lens in the sulcus?

13 DR. MEMMEN: The design of the study was  
14 intended to --

15 DR. RUIZ: For in the bag. If the posterior  
16 capsule breaks -- for example, in some of these cases they  
17 went and inserted the lens anyway, not in the bag.

18 DR. MEMMEN: There were 14 patients in the  
19 study who had sulcus implantation and they did not  
20 decenter. The experience we've had has been that sulcus-  
21 fixated lenses have not decentered, but that was not the  
22 proposed indication for the lens.

23 DR. RUIZ: Right. Do you think it's desirable  
24 to have a 7 millimeter optic and a 14 millimeter haptic

1 available in the event that the capsule ruptures?

2 DR. MEMMEN: My own opinion is yes. The  
3 purpose of the U780A lens was designed in the late 1980s  
4 when people were still considering sulcus fixation as a  
5 viable primary alternative for cataract surgery. It still  
6 is for uncomplicated surgery. Now, in the era of patients  
7 who are having capsulorhexis, it certainly would be a  
8 viable place to put a PCIOL in the case of a capsular  
9 problem.

10 DR. RUIZ: Capsules do rupture.

11 DR. MEMMEN: Yes, sir, they do.

12 DR. RUIZ: Both anterior and posterior, and  
13 there is a need for a backup lens to go in the sulcus. I  
14 was just wondering what the company's plans were in terms  
15 of that.

16 MR. SCHERFF: My name is Clarke Scherff.  
17 Currently, in the new packaging delivery system that the  
18 lens will be delivered in, we do not have a system to work  
19 with the larger lens size. That's something we can  
20 consider down the road, but that's not something that we're  
21 working on today.

22 DR. RUIZ: Obviously, if the 6 millimeter optic  
23 in a 13 millimeter haptic works fine in the sulcus, then  
24 ~~maybe there's no need for it at all, but theoretically the~~

1 bigger one should be better.

2 DR. MACSAI: No. Excuse me, Dr. Ruiz. Are you  
3 talking about theoretically the bigger optic or the  
4 bigger --

5 DR. RUIZ: Haptic.

6 DR. MACSAI: Haptic diameter?

7 DR. RUIZ: Theoretically, the 7 millimeter  
8 optic because it can accommodate for any decentration,  
9 since in the sulcus it's more likely to decentrate slightly  
10 than it is in the bag, and the larger haptics, because of  
11 the larger span necessary.

12 DR. MACSAI: But technically the sulcus is 12.5  
13 millimeters in diameter, so a 13 millimeter haptic diameter  
14 would be more advantageous for sulcus fixation.

15 DR. RUIZ: Than the larger one.

16 DR. MACSAI: Than the larger one. As far as  
17 optic size, I agree, but not haptic size.

18 DR. VAN METER: Woody Van Meter. There is also  
19 some advantage, I guess, to having a 7 millimeter lens if  
20 there's retinal pathology or in diabetic patients, but I  
21 believe the 13 millimeter haptic is acceptable for sulcus  
22 or capsular implantation.

23 DR. STULTING: Go ahead, Marian.

24 DR. MACSAI: Marian Macsai. I have some

1 questions for the sponsors. My understanding is that this  
2 hydrogel optic requires storage or refrigeration from 2 to  
3 10 degrees. Is that correct?

4 DR. PAUL: Tom Paul. Yes, that's correct.

5 DR. MACSAI: So it's not kept on a shelf, but  
6 rather in a refrigerator?

7 DR. PAUL: Yes, it is kept in a refrigerator.

8 DR. MACSAI: Have you done studies in the event  
9 that the refrigerator should drop below 2 degrees? I.e., 0  
10 degrees. What happens to a lens if it freezes? What  
11 happens to the lens if the refrigerator fails? Is  
12 refrigerator monitoring required with a continuous time  
13 monitoring and an alarm system for this lens? Because that  
14 sort of a refrigerator, to my knowledge, is usually  
15 available in blood banks, eye banks, and bone tissue banks,  
16 but not usually available in operating rooms.

17

18 DR. PAUL: Tom Paul. To answer the questions  
19 in order, first, nothing happens to the lens if it freezes.  
20 In laboratory testing, when the lens delivery system and  
21 vial have been frozen, the lens recovers its full optical  
22 properties and is totally unharmed. If the lens freezes,  
23 the lens vial may break, for which you have an obvious  
24 symptom of failure, so there is not a possibility of a lens

1 being damaged and inadvertently being used.

2 With regard to the temperature monitoring, the  
3 temperature monitoring is on the side of the unit box.  
4 There are two temperature dots on the side of the box that  
5 monitor the storage conditions. One is a cumulative dot  
6 that keeps track of time and temperature. The other is a  
7 34 degree dot, which puts a cap on the time and  
8 temperature.

9 So with that dot system to protect the lens,  
10 there is no need to have a recording system on the  
11 refrigerators. Any refrigerator will work.

12 DR. MACSAI: Can you clarify this for me? So a  
13 dot changes color if it reaches higher than 34 degrees?

14 DR. PAUL: Yes. If it reaches higher than 34  
15 degrees, or if it exceeds the time-temperature storing  
16 conditions of the storage temperature, then the dot and  
17 unit box will turn blue, turn color. The lens has been  
18 thoroughly tested to demonstrate that the dot will turn  
19 color before the lens is damaged or altered in any of its  
20 properties.

21 DR. MACSAI: So would that require special  
22 shipping conditions from Mentor to the user?

23 DR. PAUL: Yes. Currently, these are shipped  
24 in foam boxes with blue ice coolant in them. Also, shipped

1 perishable, so it does have a special shipping.

2 DR. RUIZ: What happens to the lens if the  
3 temperature is exceeded? It's being held in this holder  
4 where it can't unroll. What happens to it?

5 DR. PAUL: Well, if the temperature is  
6 exceeded, the time temperature dots will go off so the  
7 lens, you would not use it. You would have to heat it to a  
8 temperature considerably above the 10 degrees for the lens  
9 to be damaged. What will happen is that residual crease  
10 traces will take a longer time to go away. For instance,  
11 if this lens were stored at 104 degrees Fahrenheit for  
12 about a week, what would happen, it would take 11 days for  
13 the last crease trace to go away, and that is a cosmetic  
14 crease trace.

15 DR. RUIZ: But they do go away.

16 DR. PAUL: They do go away. The lens is not  
17 damaged.

18 DR. RUIZ: What if it's kept at room  
19 temperature?

20 DR. PAUL: That has not been validated. The  
21 one-year shelf life of the 2 to 10 degrees is our validated  
22 shelf life. I believe that the lens can be validated for  
23 higher temperatures storage, but it has not.

24 DR. RUIZ: Wouldn't it be a great advantage if

1 you could keep it at room temperature?

2 DR. PAUL: Yes, it would.

3 DR. RUIZ: You didn't investigate that?

4 DR. PAUL: Those studies had been preliminary  
5 investigated. I believe that can happen, but that has not  
6 been validated and approved yet.

7 DR. STULTING: Yes, Dr. Sugar?

8 DR. SUGAR: Have there been any lens fractures  
9 on insertion, or if the lens were to unfold prematurely,  
10 can it be rerolled without heating it? Or if you attempt  
11 to fold it like an acrylic lens, will it fracture?

12 Two, you said that the unfolding time was 50  
13 seconds in a controlled environment. You didn't say what  
14 it was in the clinical circumstance.

15 DR. PAUL: In the pre-rolled study, we have not  
16 seen any broken lenses or any lens artifacts. I believe  
17 that's because we roll the lens or are in control of the  
18 quality of it. In the surgeon-rolled lens, we did see a  
19 number of human-induced failure modes, which having it pre-  
20 rolled in the delivery system corrects.

21 The lens cannot be rolled at room temperature  
22 or eye temperature. So if that lens is prematurely  
23 unrolled, you cannot roll it in the surgical theater.

24 ~~DR. MEMMEN: This is James Memmen again.~~

1 Regarding it unfolding, if it's at room temperature and  
2 room temperature is below certainly 25 degrees Centigrade,  
3 it will not unroll at all. So it really isn't a problem.  
4 It will just sit there. If you are operating in an un-air-  
5 conditioned situation in the tropics where the temperature  
6 -- or Washington, D.C. for that matter, where the  
7 temperature might exceed that, then you might have a  
8 situation where it would very slowly unroll.

9 We have certainly seen and had significant  
10 experience where we have actually placed the lens in the  
11 wound and then watched to see what would happen, because  
12 that was one of my concerns. The lens unrolled so slowly  
13 that you can place it in the room and sit there and watch  
14 it. I wouldn't recommend doing it for extended periods of  
15 time, but you can certainly do it for minutes, and then  
16 place the lens in. It does not unroll while sitting in the  
17 wound.

18 The unrolling time in the usual circumstance is  
19 for it to be -- 80 percent unrolled is really about five  
20 minutes in most cases. That is my experience. I tend to  
21 use chilled balanced salt solution and I was not monitoring  
22 the anterior segment temperature.

23 DR. MACSAI: Did you say eight minutes, sir?

24 DR. MEMMEN: Five minutes.

1 DR. MACSAI: Oh, five minutes.

2 DR. SUGAR: Do you feel you have to sit there  
3 and watch it for those five minutes? At what point do you  
4 feel that it is sufficiently stable where you are not  
5 concerned that you are going to catch capsule or have some  
6 displacement of the position of the lens?

7 DR. MEMMEN: Since the lens is rolled about the  
8 axis of the haptic insertion, once both haptics are in the  
9 bag, you do not have to watch it at all, any longer. The  
10 overall length of the lens will be placed in the bag. It  
11 is folded with the fold underneath, facing the posterior  
12 capsule, so when it unfolds, it unfolds like this.

13 The longitudinal axis is in the bag, so you  
14 don't need to sit and watch it, except for comfort levels  
15 initially when you are putting it in. There is no way that  
16 it can, for instance, grab an anterior capsule leaflet as  
17 it unfolds. It can't engage that because it's unfolding  
18 posterior to anterior direction. So it cannot engage the  
19 anterior capsule leaflet.

20 DR. MACSAI: Are those insertion instructions  
21 clear? I guess I misunderstood. I thought it could be  
22 also inserted, since it's biconvex, this way.

23 DR. MEMMEN: It's 10 degrees posteriorly  
24 angulated.

1 DR. MACSAI: So it's this way.

2 DR. MEMMEN: So it's always inserted this way,  
3 yes.

4 DR. PAUL: Tom Paul. In the pre-rolled  
5 condition, since it is pre-rolled, there is only one way of  
6 inserting it. That's taken care of in the pre-roll.

7 DR. HIGGINBOTHAM: Eve Higginbotham. In Volume  
8 5, you will see the implantation technique.

9 I have two questions, actually. The first  
10 relates somewhat to this last issue. Do you have to have a  
11 perfect capsulorhexis? We know that some lenses  
12 specifically ask you to have a perfect capsulorhexis before  
13 inserting. Is this something that should be added to this  
14 lens, or can you insert it if you have an imperfect  
15 capsulorhexis?

16 DR. MEMMEN: Our experience is that, first of  
17 all, when we were doing this procedure for the original  
18 core study, that was pre-capsulorhexis, or the study  
19 occurred during the development of capsulorhexis. So we  
20 were implanting these lenses in 1989, and certainly  
21 capsulorhexis didn't come into regular use until about '91  
22 or so.

23 So clearly the lens can be inserted in a  
24 ~~patient without a capsulorhexis or an imperfect~~

1 capsulorhexis. We did not have decentration problems in  
2 patients in whom we used can opener capsulotomy.

3 DR. HIGGINBOTHAM: My second issue relates to  
4 the glaucoma. I just would like to explore that just to  
5 make sure that I understood your data correctly in these  
6 five volumes. Now, in the second cohort you have four out  
7 of the five patients that received the experimental  
8 viscoelastic material, is that right?

9 DR. MEMMEN: Yes.

10 DR. HIGGINBOTHAM: And if you eliminate those  
11 four, the rate drops below the Stark grid in terms of the  
12 glaucoma rate.

13 DR. MEMMEN: Yes, ma'am.

14 DR. HIGGINBOTHAM: Now, moving on to the last  
15 group of patients, the 190, can you tell me a little bit  
16 more about the 4.7 percent that had the secondary glaucoma?  
17 Did you have in that last group of patients anyone that  
18 underwent a trabeculectomy?

19 DR. MEMMEN: To my knowledge, no patients in  
20 the second cohort underwent a trabeculectomy. And, in  
21 fact, all of those patients only had increased intraocular  
22 pressure reported, which is any intraocular pressure above  
23 21 millimeters of mercury reported on Form 1, and all of  
24 those patients resolved by Form 2.

1 DR. HIGGINBOTHAM: So the 4.7 percent really  
2 relates to the first two forms. So by Form 6 it was down  
3 to what percentage?

4 DR. MEMMEN: There were no reports of patients  
5 with persistent glaucoma in the pre-rolled 190 cohort.  
6 There was only about 4 percent of the patients who did have  
7 a transient intraocular pressure rise associated with  
8 surgery. They had pressures over 21 at Form 1 and they all  
9 resolved, every single one resolved at Form 2.

10 DR. HIGGINBOTHAM: And do you recall or do you  
11 know if those patients that did develop a transient  
12 increase in intraocular pressure had pre-existing glaucoma?

13 DR. MEMMEN: Excuse me, I have to look for just  
14 a second.

15 DR. RUIZ: Wasn't that one of the criteria for  
16 inclusion in the cohort, that they not have pre-existing  
17 glaucoma?

18 DR. MEMMEN: That was not an exclusion  
19 criteria. They could have medically controlled glaucoma.

20 For the 190 cohort, I don't have the data  
21 available and I don't really believe that we looked at it,  
22 mainly because it was a 4 percent rate of patients who had  
23 an intraocular pressure spike that resolved by Form 2, and  
24 I didn't think it was clinically significant. So I don't

1 recall looking for it. Whether or not they had reports of  
2 elevated intraocular pressure in Form 0 --

3 DR. HIGGINBOTHAM: I think that would be  
4 helpful to know, though I agree with you that since it  
5 resolved, it is not a clinically significant issue but it  
6 would be clinically helpful to practitioners to know that.

7 DR. MEMMEN: If you'll give me a second, we can  
8 try to find that information for you.

9 DR. STULTING: Can you handle it if we move on  
10 to other issues while somebody on your team is looking up  
11 that data? Is that all right with you?

12 DR. MEMMEN: Yes.

13 DR. STULTING: Other questions?

14 Woody?

15 DR. VAN METER: I have three questions that I  
16 would like to ask the sponsors. In the first group of  
17 patients it was noted in both reviews that we saw that  
18 those patients had had one sight-threatening complication  
19 identified, at Form 6 all had a higher percentage of 20/20  
20 vision than those that had no sight-threatening  
21 complications.

22 My question is, if that's the case, then is  
23 this a reasonable way to collect data, or does it make any  
24 ~~difference that they had sight threatening complications if~~

1 they did better than those patients that had no sight-  
2 threatening complications?

3 DR. MEMMEN: James Memmen again. I am not here  
4 to tell the FDA what data they want to collect or not.  
5 Some things are considered sight-threatening complications.  
6 Our corneal edema and any measure of corneal edema after  
7 cataract surgery we certainly see -- in perfect surgery, if  
8 you are sensitive you are going to see some corneal edema.  
9 You are going to see a few cells in flare in perfect  
10 surgery, so you are going to have a report of iritis.  
11 Those are associated with the cataract surgery itself.

12 DR. VAN METER: That's fine. I was interested  
13 in your explanation for that data.

14 The second question I have is that in your  
15 presentation, you mentioned that 61,000 lenses were  
16 implanted in 20 countries. Were all of these the  
17 MemoryLens, or were these just Mentor lenses?

18 MR. SCHERFF: This is Clarke Scherff. All the  
19 lenses were in the pre-rolled lens configuration, and they  
20 were all the MemoryLens U940A model.

21 DR. VAN METER: A second question then is,  
22 since this is shipped in refrigerated capacity, do you have  
23 a guesstimate on the rate of, for lack of a better term,  
24 spoilage, how many are rejected? Does the company replace

1 those at no charge if they, for one reason or another,  
2 exceed the temperature guidelines, or if they can't be  
3 implanted?

4 MR. SCHERFF: Currently, if the issue is with  
5 the shipment that the company is making, then we do replace  
6 those. If it is mistakes that are made by our  
7 distributors, then that's a negotiable issue with those  
8 distributors internationally.

9 DR. VAN METER: Thank you very much.

10 One final question. Is explantation of this  
11 lens performed like you would a standard PMMA lens?

12 DR. MEMMEN: I would assume. This lens is very  
13 far in the eye. So I would assume -- I have never  
14 explanted one, but I would assume that one would want to  
15 bisect the haptics and remove it.

16 DR. VAN METER: Thank you.

17 DR. STULTING: Kevin?

18 DR. GREENIDGE: I have two questions. In your  
19 initial presentation, you mentioned that the lens had very  
20 low extractables. I would just like a further  
21 clarification as to what an extractable is.

22 DR. PAUL: Yes. This is Tom Paul. When the  
23 lens is polymerized with the four monomers for the quad  
24 polymer, some of those monomers are left behind. The

1 polymerization is never 100 percent. In the manufacturing  
2 process the lens is then extracted with acetone and with  
3 water to flush out those residual monomers that are left  
4 from the polymerization.

5 DR. GREENIDGE: So is an extractable something  
6 that has been washed out and is now gone, or is an  
7 extractable something that has been washed and it's left to  
8 come off at a later time?

9 DR. PAUL: No. An extractable is something  
10 that is in the lens that at some time could come out. But  
11 extracting it in the manufacturing process, we make sure it  
12 comes out during the manufacture of the lens. So when the  
13 lens is a final device, there is nothing inside that can be  
14 extracted out.

15 DR. GREENIDGE: So once it gets to the patient,  
16 it's not a very low extractable, it's a zero extractable?

17 DR. PAUL: It's in the level of very few parts  
18 per million.

19 DR. GREENIDGE: The next question I would just  
20 like to review is, and maybe it's because it's something I  
21 spend a lot of time with, is glaucoma. I would just like  
22 to review the data for the U940A rolled. It is my  
23 impression that that is the identical lens as the U940A  
24 pre rolled other than the fact that one is rolled by the

1 physician and the other comes rolled. Is that assumption  
2 correct?

3 DR. MEMMEN: Yes.

4 DR. GREENIDGE: The data that you present as  
5 far as secondary glaucoma in those patients -- and that was  
6 a slightly larger group than the 190, I believe it was a  
7 study group of 260 patients -- I do not believe that this  
8 is the group that received the questionable Orcolon. Is  
9 that correct? This did not receive the investigational  
10 viscoelastic substance.

11 While you are checking that, I would just like  
12 to raise my question and maybe you can answer this for me.  
13 When looking at the various forms which we have seen  
14 correspond to various postoperative periods, on Form 1 we  
15 have a rate, and I would just like to use -- and there are  
16 only two numbers I have for the grid standard. One is a  
17 1.6, which is cumulative, and the other is a 0.5, which I  
18 believe is after one year.

19 So my interpretation is that any rate above 1.6  
20 that's persistent is greater than the cumulative rate. At  
21 Form 1 we have a rate of 4.62 percent. Just moving  
22 forward, Form 3, which is four weeks, we exceed the Stark.  
23 We have a rate of 1.73, and actually the study is a number  
24 of 4. At Form 4, which is seven months, we only have three

1 patients and we are below the Stark rate at 1.43.

2           However, at Form 5, new patients start  
3 appearing and we again go up to and above the Stark rate of  
4 above 3 percent. At Form 6 we are still at above the Stark  
5 rate at 2.6 percent. At one year we are above the Stark  
6 rate at 3 percent. The number of glaucoma patients  
7 persists to Form 10.

8           My question is, in the pre-rolled group for  
9 which you are seeking approval, all of the secondary  
10 glaucomas and the rate was similar to in this group, all of  
11 it resolved in Form 1.

12           I would just like to have a possible  
13 explanation as to why in this large a group with the same  
14 lens, the glaucoma seems to come and go, and throughout  
15 Form 6 into Form 7 you are well above the Stark grid  
16 percentage.

17           DR. MEMMEN: First of all, I'd like to answer  
18 Dr. Higginbotham's question -- this is James Memmen again  
19 -- which is, in the pre-rolled study, of the patients who  
20 had transient pressure spikes, one patient was a glaucoma  
21 suspect prior to surgery. Otherwise they were just normal  
22 patients.

23           Number two, I'm a little confused by this  
24 question, and I guess I would clarify that, first of all,

1 in the pre-rolled study the patients who had transient  
2 intraocular pressure spike, those all resolved by Form 2.  
3 In the U940 patients who were in the original cohort, I am  
4 getting the data mixed up a little bit with what you are  
5 citing, so I am having a little difficulty understanding  
6 the question, but I --

7 DR. GREENIDGE: If someone wants to get it for  
8 you, it's Table 34.5.

9 DR. MEMMEN: Because one thing I would like to  
10 clarify is that my understanding of this is that there is a  
11 Stark grid parameter for secondary glaucoma of 0.5 percent  
12 for persistent glaucoma at Form 6. I may be incorrect, but  
13 I don't believe there is a grid parameter for cumulative  
14 glaucoma.

15 DR. GREENIDGE: But if we use the 0.6, which is  
16 the one-year data of 0.5, at Form 6 your rate is 2.6  
17 percent as opposed to 0.5 percent. At Form 7, which is  
18 subsequent, the rate actually increases to 3 percent.

19 Do you want my form?

20 DR. MEMMEN: You have to understand once again  
21 that while this is a percentage of 2.6 percent of this  
22 group subset of patients, it has to be measured within an  
23 entire cohort of the patients, which was for 523 patients.  
24 So it's very difficult to do that.

1           We have a total basically of four patients here  
2 with the 2.6 percent and five patients at Form 7. I am  
3 going to try to actually address exactly which patients  
4 those were right now, so I can give you a reason. But what  
5 I suspect is that those are, by chance, our Orcolon  
6 patients.

7           Because this was the largest subset, the rolled  
8 940 lens was the largest subset, and those patients were  
9 done at the end of the study -- I am going to get those  
10 patient numbers, but I believe those were --

11           DR. GREENIDGE: Yes, I would like that, because  
12 of that group of five, at least one of those patients of  
13 this data is a new patient that just entered at that point.  
14 It was my impression that of the Orcolon patients, that  
15 three of those four received trabeculectomies.

16           DR. MEMMEN: Early on, right.

17           DR. GREENIDGE: Early on.

18           DR. MEMMEN: There was another patient who --  
19 well, basically of the patients who had secondary glaucoma  
20 in the original study, a substantial number were Orcolon  
21 patients. The other patient was a patient who had received  
22 steroids into the study to treat arteritic ischemic optic  
23 neuropathy and had a pressure rise as a result of that.

24           ~~Actually, there are five patients if you're~~

1 looking at the same grid, there are five patients reported  
2 at Form 5 as well.

3 DR. GREENIDGE: My impression is that the  
4 reason why we used the Stark grid -- and I have seen some  
5 comments made that the date of the study of the Stark grid  
6 was so long ago and techniques have changed so much that  
7 actually common practice is to have complication rates  
8 lower than those in the Stark grid.

9 But my impression is that the reason why we use  
10 that study is because of the extremely large study group  
11 that it reported on and that various occurrences like  
12 arteritis, steroid use, et cetera, would wash out in the  
13 fact that that was such a large study group.

14 My only concern, and I just wanted to hear some  
15 answers, is it seems that when you look at each individual  
16 group -- the 780 flat, the 780A rolled, the 940 rolled --  
17 that the rates exceed the Stark. This was just one. The  
18 explanation that was originally offered was that of the  
19 viscoelastic. I'm not quite sure that, at least in this  
20 table, that -- and I am hearing other responses now as to  
21 what it might be, but that may not be consistent with this  
22 table here.

23 DR. MEMMEN: When you are quoting the different  
24 ~~breakouts of the groups, are you looking at page 2135 on~~

1 Section 6 and Section 5 in Volume 1?

2 DR. GREENIDGE: Actually, it's going through  
3 and picking up the various points. I do not have the exact  
4 page numbers for each one of those rates, but it was in the  
5 data.

6 DR. MEMMEN: Because you have to remember, one,  
7 Stark grid talks about persistent secondary glaucoma, not  
8 about cumulative incidences of glaucoma. So I think when  
9 you break out the different rates here at 3.4 percent for  
10 the U780 flat, 2.7 percent for the U780 rolled, 5.5 percent  
11 for the U940A rolled, those are not persistent reports of  
12 elevated intraocular pressure. Those are cumulative  
13 reports of elevated intraocular pressure, and so they  
14 reflect single incidences. There is no Stark grid for  
15 measuring those. The Stark grid is only for persistent.

16 DR. GREENIDGE: I would just defer to Murty --  
17 I'm sorry, Murty, if I'm mispronouncing your name --  
18 Ponnappalli, who in his report does cite a cumulative Stark  
19 grid percentage of 1.6 percent. I was using that as the  
20 reference point.

21 DR. MACSAI: Marian Macsai. I also was  
22 wondering if you could tell us in these numbers, the five  
23 patients, then four patients, then five patients on the  
24 Forms 5, 6 and 7. Are they the same patients?

1                   And are you just reporting an incidental  
2 pressure measurement of 23 at one visit, or are you  
3 presenting glaucoma as defined by optic nerve changes,  
4 visual field changes, and/or elevated intraocular pressure?  
5 Because I am somewhat confused by those two issues, if  
6 these are the same patients, and what is your definition?

7                   DR. MEMMEN: Well, one, we're going to find out  
8 who these patients are right now because we do have the  
9 backup and we can find that out. I suspect that in this  
10 particular subset of patients, that they are the same  
11 patients. There are four or five there that we will  
12 examine.

13                   The second thing is that the classification for  
14 glaucoma is quite simply a measurement of increased  
15 intraocular pressure exceeding 21 millimeters mercury,  
16 period.

17                   DR. RUIZ: What percentage of the preoperative  
18 patients had glaucoma, by definition? Not a pressure 21,  
19 which doesn't mean glaucoma at all, but had glaucoma. How  
20 many of these patients? And they are all in this group.

21                   DR. MEMMEN: Once again, it depends upon the  
22 definition you use. Patients were not excluded from the  
23 study who did have glaucoma if it was medically controlled,  
24 ~~so depending upon the definition you use is going to be~~

1 determining the number of patients you are going to call  
2 had glaucoma.

3 DR. RUIZ: Those that were under treatment with  
4 a diagnosis of glaucoma.

5 DR. HIGGINBOTHAM: I think it is helpful to  
6 approach this data in three different cohorts because I  
7 think there is a pattern of overreporting that clearly  
8 impacted the posterior capsule opacification rate, that  
9 probably also impacted other observations, such as the  
10 "glaucoma issue."

11 So I'm not sure where this 260 table that has  
12 been talked about came from, but the 190 I think is the  
13 group that we need to talk about because that is the group  
14 that had the 4.7 percent increase, right? And that had  
15 just a transient elevation in intraocular pressure that was  
16 resolved by Form 2, correct? That's also the same group  
17 that had the 50 percent posterior capsule opacification  
18 rate, correct?

19 In my mind, I consider those two somewhat in  
20 the same vein in the sense that there was probably some  
21 overreporting, that these were not actual glaucoma patients  
22 but this was a transient elevation in intraocular pressure,  
23 did not require trabeculectomy, which is important to point  
24 out I think, and probably clinically was not significantly

1 a problem for these patients long term.

2 DR. MEMMEN: I would agree with Dr.  
3 Higginbotham.

4 I wanted to answer Dr. Ruiz' question.  
5 Seventeen patients in the 360 cohort had preoperative  
6 glaucoma under treatment. One patient in the 190 cohort  
7 was a glaucoma suspect.

8 DR. RUIZ: And how many of those contribute to  
9 this statistic?

10 DR. MEMMEN: I am looking for that right now.

11 DR. STULTING: Dr. Ferris?

12 DR. FERRIS: I guess I have a rhetorical  
13 question, as someone who does clinical trials for a long  
14 time. That is, if you are collecting outcome variables and  
15 you had this to do over again, perhaps you would identify  
16 your outcome variables in a way that would identify those  
17 that were just intraocular pressure, for example, as  
18 opposed to glaucoma, which my glaucoma friends tell me are  
19 not the same thing at all -- posterior capsule haze versus  
20 clinically important posterior capsular haze, and so on.

21 It seems very easy to develop forms, but for  
22 people that have some experience doing it, I suspect now  
23 you would agree that it's very important at the beginning  
24 to identify the outcome variables and at least be able to

1 sort out the clinically important events from not  
2 clinically important events.

3 DR. STULTING: Part of the problem is that we  
4 are comparing today's results to technology that existed 20  
5 years ago. That's what the Stark grid represents. It was  
6 published in '83 and it represents implants that were  
7 performed four and five years before that. The definitions  
8 are not what we would necessarily like to use today.

9 There was a day when we reviewed four or five  
10 implant PMAs in a day. Since we don't do those anymore, we  
11 are not quite so practiced at ignoring these definitions  
12 that don't have any clinical significance.

13 But there was a comment made by this panel a  
14 year or so ago, maybe more, requesting the FDA to take data  
15 from recently submitted intraocular lens implant studies  
16 and construct a new grid and create outcome variables that  
17 do exactly what you say. Perhaps we should reiterate that  
18 recommendation today.

19 The Stark grid, for example, has a 6 percent  
20 loss of vision to below 20/40 in a best case analysis.  
21 That means 6 percent loss of vision to below 20/40, either  
22 as a result of the surgery or as a chance happening that  
23 caused it to be lost postoperatively, and I think that's  
24 really higher than virtually every clinical study published

1 in recent memory would give you. In my view of this data,  
2 it is not appropriate to compare it to the Stark grid, but  
3 to contemporary publications, and to ignore as well the  
4 kinds of definitions that are causing us problems right  
5 now.

6 Ms. Lochner, would you like to speak?

7 MS. LOCHNER: Yes. I can't speak to the  
8 definition question, but as far as updating the Stark grid,  
9 we have looked at recent approvals and we basically got  
10 several breakdowns, but what we do is we looked at the last  
11 five approvals. They all happen to be soft material  
12 lenses, and they span approval times from 1991 to 1995.

13 As far as secondary glaucoma itself, we have  
14 data on mean values from these last five approvals, the  
15 mean being 0.2, the median being 0.2, and the maximum rate  
16 being 0.6. The current Stark grid for secondary glaucoma  
17 is 0.5, and that's a persistent rate.

18 So we do have values for several of the other  
19 parameters, but I think it would be too much to go through  
20 all those now. But any others that you might want, we  
21 could give you that information now. We do hope to come  
22 out with an updated grid in the future.

23 DR. STULTING: Can you clarify for the panel  
24 the definitions that were used for glaucoma that you just

1 gave the percentages for?

2 MS. LOCHNER: They would be the definitions  
3 that the companies used in each of their individual PMAs.  
4 As I said, I don't think we ever standardized it back in  
5 the old days to the point of saying it was exactly this  
6 definition. I think it was pretty much on a sponsor by  
7 sponsor basis.

8 DR. STULTING: In order for that to be a useful  
9 number, we're going to need to know those definitions.

10 DR. RUIZ: I would be surprised - I think  
11 that's a remarkably low percentage if you use the criterion  
12 of 21 millimeters mercury. I really do. We're not talking  
13 about glaucoma.

14 MS. LOCHNER: It is a persistent value.

15 DR. GREENIDGE: She's talking about at one  
16 year.

17 DR. STULTING: I think it's pretty clear what  
18 needs to be done to help resolve these questions in the  
19 future. What I would suggest to perhaps address the  
20 panel's questions that have arisen so far today is, if you  
21 can identify those patients, if you have them now, maybe  
22 you could summarize the cases for the few eyes that had  
23 glaucoma, say a little bit about what they had beforehand  
24 and what kind of pressures they were having and how they

1 were treated and the situation, et cetera.

2 Could we do that maybe?

3 DR. MEMMEN: We're working on it right now.

4 DR. STULTING: There is one question I had  
5 before we get to there. It's been said a couple of times  
6 that four people had Orcolon who developed glaucoma. Do  
7 you also have the percentages in the group that did not  
8 develop glaucoma that had Orcolon, so that we can know that  
9 the incidence Orcolon use was higher?

10 The second question that I had was did these  
11 patients who had hyphema and glaucoma cluster as far as  
12 your investigators are concerned? Because the habitual use  
13 of intraoperative or perioperative glaucoma medications and  
14 whatnot can have a significant impact on a number of  
15 transient rises and whatnot as well.

16 DR. MEMMEN: The incidence of Orcolon use, I  
17 don't know the exact numbers, but we'll look at that. As  
18 far as clustering for hyphema, there was some clustering  
19 for hyphema. The investigational aspect of what we found  
20 was that of the 14 patients with hyphema in the 360 cohort,  
21 12 of those patients had scleral tunnels, and two we were  
22 not able to determine what type of incision was used.

23 DR. STULTING: I'm sorry, I didn't understand  
24 what they had.

1 DR. MEMMEN: They had scleral tunnel incisions.  
2 I think that was a very significant issue. There was some  
3 clustering, and then there was also the information you  
4 gave about traumatic surgery, so that is felt to be  
5 contributory to the hyphema rate.

6 When we switched over to more of a clear cornea  
7 or an anterior limbal type of incision for the patients in  
8 the pre-rolled study, the hyphema rate dropped to zero.

9 DR. STULTING: Did you say that they were  
10 mostly in one or two investigators?

11 DR. MEMMEN: Well, there were actually 36, 37  
12 investigators and 36 sites in the first study, so it really  
13 wasn't one or two investigators. It was four or five  
14 investigators, but there were several names that came up  
15 more than once.

16 DR. STULTING: So all the hyphemas were in five  
17 investigators, is that correct?

18 DR. MEMMEN: To the best of my knowledge --

19 DR. RUIZ: All of them used scleral tunnels.

20 DR. MEMMEN: Of the 14 patients who had  
21 hyphemas, in the 12 that we were able to identify the type  
22 of incision that was used, all 12 were scleral tunnels.

23 DR. STULTING: What I really want to know is,  
24 ~~is the incidence of hyphemas unexpectedly high in one or~~

1 two investigators, so that you can reasonably conclude that  
2 it's technique-related, and the majority of investigators  
3 did all right with the lens? Or are they distributed in a  
4 random fashion?

5 DR. MEMMEN: It is clustered among  
6 approximately five or six investigators.

7 DR. STULTING: When you factor in the number of  
8 implants they performed, the percentage that they had was  
9 higher than expected?

10 DR. MEMMEN: Considerably higher. Yes, sir.

11 DR. McCLELLAND: I have several questions for  
12 the sponsors from a consumer perspective. In the study  
13 groups, what consideration was given to informing the  
14 subjects in your various study groups regarding the  
15 expectations of outcomes? What kind of informed consent,  
16 if you will, not just consent to participate, but what  
17 information was given to the participants regarding the  
18 expectations of the outcomes?

19 MR. SCHERFF: This is Clarke Scherff. What I  
20 recall, and we will need to look at it specifically, is  
21 that the patients were given informed consents with an  
22 expectation of the outcomes that I believe at that time  
23 were related to the grid back in 1989, that their outcomes  
24 would be better than what has been noticed with intraocular

1 lenses in the past.

2 DR. McCLELLAND: Did you use information in a  
3 printed booklet form? Again, thinking of older subjects  
4 and perhaps again with obviously some compromised visual  
5 acuity initially, large print patient education booklets,  
6 information booklets kinds of things, were those documents  
7 used so that your subjects had realistic expectations of  
8 the outcomes?

9 MR. SCHERFF: This is Clarke Scherff. The  
10 informed consents were a multi-page 8.5 by 11 format. As I  
11 recall, the print in these booklets was somewhat larger  
12 than normal size 12-point print that we would use for  
13 memos, so that patients could adequately read these forms  
14 and understand what the study was about.

15 DR. McCLELLAND: This is my last question  
16 related to this series. Was the practitioner, the person  
17 who was actually going to be performing the procedure, was  
18 this the person who was responsible for assuring that the  
19 subjects would have this information, or was this delegated  
20 to another member of the health care team? How was that  
21 handled?

22 DR. MEMMEN: James Memmen. The informed  
23 consent is usually given to the patient after verbal  
24 discussion occurs in our practice. We tell the patients

1 that they are a candidate for inclusion in the study, what  
2 the intention of the study is, what the potential risks,  
3 benefits, and options are for the patient, and ask them if  
4 they would be interested in volunteering for the study.

5 We also tell them what the follow-up  
6 responsibilities are going to be and what our feelings are,  
7 what data we have regarding the preliminary studies and so  
8 forth for the patients. We then let them, with a family  
9 member usually, go through the written informed consent.  
10 We have a copy here for you to look at. It's a rather  
11 extensive, large print document, and then they are asked to  
12 sign.

13 DR. McCLELLAND: Thank you.

14 DR. STULTING: Joel?

15 DR. SUGAR: Karen wanted to ask a question  
16 earlier. Go ahead.

17 DR. BANDEEN-ROCHE: Yes. I had first a follow-  
18 up question about the clustering of hyphema, and then a  
19 more general question about the representativeness of the  
20 cohort.

21 About the clustering of hyphema, did the five  
22 or so physicians in which hyphema clustered in the first  
23 study carry over as one of the seven physicians in the  
24 second study?

1 DR. MEMMEN: No.

2 DR. BANDEEN-ROCHE: Secondly, in terms of other  
3 practice variables -- in other words, things that describe  
4 the expertise, or maybe I shouldn't say expertise but  
5 experience and kind of practice describing variables of  
6 physicians -- how representative were the seven in the 190  
7 in the last study relative to the 35?

8 DR. MEMMEN: All of the seven investigators in  
9 the second study were investigators in the first study.  
10 All of the investigators in both studies were board  
11 certified. The average number of implants done by surgeons  
12 in the study is somewhere around 780 or 800 a year. They  
13 are all experienced.

14 DR. BANDEEN-ROCHE: How wide was the  
15 variability? The average was 780.

16 DR. MEMMEN: Right. The lowest surgeons in  
17 both studies would be around 300 to 350 cases a year, and  
18 some of them upward of 4,000 cases a year.

19 DR. BANDEEN-ROCHE: And then finally I would  
20 say, in terms of the overall cohort, this goes to the  
21 question of safety and effectiveness in patients 60 years  
22 of age and over. So I am concerned about the  
23 representativeness of the study cohort relative to patients  
24 who will go on to have these implants in the future.

1           So exclusion criteria aside, can you describe  
2 these patients in terms of things that might impact on  
3 their cataract success, such as their preimplantation  
4 visual acuity or their potential visual acuity? And again,  
5 in terms of provider characteristics.

6           DR. MEMMEN: I think that patient  
7 characteristics for success for these patients are the  
8 exact same as patient characteristics for success for any  
9 patient who is having cataract surgery. Clearly the lens  
10 performs very well, and we have implanted patients in their  
11 30s, and younger patients have been implanted extensively  
12 in Europe. Those patients actually did extremely well.

13           So I think it is a lens that performs well in  
14 all the age groups where there are printed indications  
15 certainly.

16           DR. BANDEEN-ROCHE: But in particular, this  
17 cohort, can you give me a rough idea of what the  
18 preimplantation visual acuity or potential visual acuity  
19 was?

20           DR. MEMMEN: For the 60 to 69 year group in  
21 particular?

22           DR. BANDEEN-ROCHE: No, for the whole cohort,  
23 averaged over age.

24           ~~DR. MEMMEN: I actually didn't derive that~~

1 information as to the exact preoperative visual acuity.  
2 They all had mature cataracts and I really haven't  
3 evaluated that information, although we do have that  
4 information. It's in the PMA.

5 DR. BANDEEN-ROCHE: Thank you.

6 DR. HIGGINBOTHAM: This is Eve Higginbotham.  
7 One very brief question. As I recall, there was one site  
8 that was outside the United States, is that right?

9 DR. MEMMEN: Two.

10 DR. HIGGINBOTHAM: Two.

11 DR. MEMMEN: Yes.

12 DR. HIGGINBOTHAM: But you did not include the  
13 data from those two sites in your 190 cohort?

14 DR. MEMMEN: Those investigators were not  
15 included as investigators in the 190 cohort.

16 DR. HIGGINBOTHAM: They were not investigators,  
17 period.

18 DR. MEMMEN: No. They were only in the 360 --

19 DR. HIGGINBOTHAM: They were in the 360. Did  
20 you include them in the 360?

21 DR. MEMMEN: Yes, ma'am.

22 DR. HIGGINBOTHAM: And were their rates of  
23 complications any different from the rest of the cohort?

24 DR. MEMMEN: Not significantly, no. There was

1 one in Austria and one in Canada and they were both  
2 similar.

3 DR. STULTING: Dr. Sugar?

4 DR. SUGAR: Just a brief question. In your  
5 proposed package insert, you describe a preferred technique  
6 which is different than what you showed on the tape -- that  
7 is, putting the trailing haptic in hand over hand over the  
8 capsule. You rotated in. I presume that you are going to  
9 provide to the surgeons initially purchasing your lens some  
10 kind of a tape. I presume that the package insert will be  
11 changed to include what's in the tape and allow both  
12 techniques.

13 DR. MEMMEN: I can only answer that, in my  
14 experience, dialing the lens in is the usual and preferred  
15 technique, and it certainly was easier, although you  
16 certainly, with the prolene haptics, can very easily --  
17 they are sufficiently flexible that you can use a forceps  
18 to insert them as well.

19 Regarding the packaging information, I am going  
20 to refer that to my colleagues here.

21 MR. SCHERFF: This is Clarke Scherff. At this  
22 time, the proper removal of the lens from the package and  
23 insertion is in the directions for use in the labeling.

24 ~~Tapes have been made but not to be provided specifically as~~

1 part of the labeling but as part of the marketing  
2 information.

3 DR. SUGAR: But the labeling that you have in  
4 our package does not include dialing the lens in. That's  
5 why I commented on it.

6 DR. STULTING: We can make that recommendation  
7 for an addition to the labeling when they approve it if  
8 it's the will of the committee.

9 Dr. McCulley?

10 DR. McCULLEY: A few quick things. How  
11 manipulatable is the lens when it comes pre-folded if there  
12 are some idiosyncrasies with the wound or if one wants to  
13 manipulate putting the lens in? Or does one have to leave  
14 it in its pre-rolled state?

15 DR. MEMMEN: This is James Memmen again. It's  
16 as manipulable as a PMMA lens -- not at all.

17 DR. McCULLEY: And if one tried to manipulate  
18 it, it presumably would damage the lens?

19 DR. MEMMEN: Yes, sir.

20 DR. McCULLEY: Why are you asking for a minimum  
21 age of 60 rather than a lower age?

22 MR. SCHERFF: This is Clarke Scherff. The age  
23 of 60 is the minimum age in all IOL label packages that we  
24 are aware of, and that is the agreed to minimum age.

1 DR. McCULLEY: Agreed to by whom? There is a  
2 consensus agreement in the industry?

3 MR. SCHERFF: It's my understanding it's on  
4 everybody's labeling, this consensus agreement that --

5 DR. McCULLEY: I am aware that there is no lens  
6 label for insertion less than 60. But the question is, if  
7 you have data on patients below 60, why are you asking for  
8 only 60? I guess I'm just wanting to be educated.

9 MR. SCHERFF: In the original supplement, we  
10 actually had a lower age. In an agreement with FDA, we  
11 raised that to 60 to be consistent with the industry.

12 DR. STULTING: So the FDA requested that you  
13 have 60 as the age during the negotiations?

14 MR. SCHERFF: Yes.

15 DR. VAN METER: Do I understand that that means  
16 that they are requesting off-label use?

17 DR. STULTING: Well, it might be a good topic  
18 for conversation. Since there is no lens approved for use  
19 below the age of 60, what are you supposed to do with  
20 people who have cataracts below the age of 60? You either  
21 have to make them aphakic or else you have to use a lens  
22 off-label, and that's a kind of interesting dilemma for the  
23 practitioner.

24 ~~Dr. McCulley's question may have some impact on~~

1 things that we would like to recommend as a group.

2 DR. GORDON: Just a comment. Judy Gordon.

3 DR. STULTING: I'm sorry. He wasn't through,  
4 and he's close enough that he can say that. Go ahead.

5 DR. McCULLEY: Next question, and only two  
6 other quickies, I hope. The wisdom in your study design of  
7 allowing a second investigational device -- most of our  
8 discussions here related to what I would consider to be not  
9 very good study design. Allowing a second investigational  
10 device, the viscoelastic, which has muddied the water  
11 tremendously; and the second, of entering patients that  
12 aren't as clean as they might be -- i.e., those that  
13 entered with preexisting glaucoma -- what are your comments  
14 about those two issues?

15 The two study devices in the same protocol are  
16 being allowed in your protocol, another study device. And  
17 the second of entering patients who have pre-existing  
18 glaucoma, when we have a patient population out there that  
19 we could have studied that would have been cleaner.

20 MR. SCHERFF: This is Clarke Scherff. Back in  
21 the 1989-1990 timeframe when that occurred, it probably  
22 should not have been. We should never have two  
23 investigational devices in a single study.

24 ~~I am not aware of the situation around how that~~

1 occurred, but an IRB should not have allowed that to occur,  
2 as well as the company should not have allowed that to  
3 occur.

4 On the second issue regarding --

5 DR. McCULLEY: Glaucoma.

6 MR. SCHERFF: Glaucoma?

7 DR. MEMMEN: As far as inclusion/exclusion  
8 criteria, in general I think I agree with you. I think it  
9 would be an easier, cleaner study. I did not determine the  
10 inclusion/exclusion criteria for either of these studies.  
11 The overall situation of balancing recruiting with your  
12 inclusion/exclusion criteria, we don't disagree.

13 DR. McCULLEY: I guess my point is, you could  
14 have had an adequate number of patients to be enrolled if  
15 you had had glaucoma as an exclusion criteria in that  
16 patient population.

17 The last question is really for the FDA. When  
18 might we expect a new grid?

19 MS. LOCHNER: We had actually planned to  
20 discuss, perhaps at the October panel meeting, how you  
21 would like the new grid to be determined. We have the data  
22 analyzed several ways on how you would like that to be  
23 determined.

24 DR. SUGAR: The grid should have on its label a

1 shelf life.

2 (Laughter.)

3 DR. MEMMEN: I'd like to answer the two  
4 questions that we deferred, the first for Dr. Stulting. We  
5 do not know the number of patients who received Orcolon.

6 Secondly, regarding the 260 patients and the  
7 523 cohort, of those patients, four of the patients who  
8 came in at Form 5 -- actually, five of the patients who  
9 came in at Form 5 -- four patients at Form 5 were Orcolon  
10 patients. One was a patient who had a secondary glaucoma  
11 after a YAG capsulotomy, which is the fifth patient at Form  
12 5, and that resolved by Form 6. So it drops back down to  
13 four at Form 6.

14 Then at Form 7, where it goes back up to five,  
15 there is an additional patient who had Orcolon who did not  
16 develop significant intraocular pressure until Form 7. So  
17 those account for the patients.

18 DR. STULTING: Do you have any idea what the  
19 overall percent use of Orcolon use was in the study?

20 DR. MEMMEN: I would guess it was rather small,  
21 but I don't know.

22 DR. STULTING: I wasn't aware that it did it  
23 this long-term.

24 DR. RUIZ: Mr. Chairman, I don't think we ought

1 to let go of the 60 age limit, which makes absolutely no  
2 sense at all. We ought to see to get that off of there,  
3 not just for this intraocular lens, but others.

4 DR. STULTING: I suppose that we could make a  
5 labeling recommendation for this lens, and then we can make  
6 an independent generic labeling recommendation. I think  
7 that would be within our purview.

8 Are there any other questions that involve the  
9 sponsor?

10 DR. ROSENTHAL: May I just make a comment?

11 DR. STULTING: Yes, sir.

12 DR. ROSENTHAL: At this point in time the  
13 industry standard is 60, and we would like to keep it at  
14 that level until we can go through the necessary  
15 discussions in-house that would allow further expansion.  
16 I'd appreciate it.

17 We understand and note the panel's comments,  
18 but at this point in time I would think it most judicious  
19 to just use 60 as the lower limit.

20 DR. RUIZ: I bow to your wisdom, Dr. Rosenthal,  
21 but I think you hear us, and there are a lot of patients  
22 under age 60 that go through cataract surgery.

23 DR. ROSENTHAL: Dr. Ruiz, I hear you loud and  
24 clear, and we have heard you loud and clear for apparently

1 many years prior to my arrival.

2 DR. STULTING: I guess what is being expressed  
3 today is that these comments have been made before and we  
4 have heard the same comments from the FDA. I think that we  
5 represent the ophthalmic community who want something else  
6 done. We would like the record to reflect a clearer  
7 indication of our recommendations and frustrations than it  
8 now reflects.

9 With all due respect, I may not be speaking for  
10 the panel but I think I am, and I think that what's being  
11 said is that ophthalmologists want the age limit lowered.  
12 It is current practice to implant lenses in people below  
13 the age of 60. In fact, some people probably consider it  
14 outside of the standard of care if you fail to do it.

15 It seems to me that there is not a whole lot of  
16 manipulation and discussion that ought to occur in the FDA  
17 before that's recognized.

18 Would that be your --

19 DR. RUIZ: Well said, Mr. Chairman.

20 DR. STULTING: Dr. Macsai?

21 DR. MACSAI: Dr. Rosenthal, I would  
22 respectfully request that you also consider setting some  
23 criteria for the evaluation of intraocular lenses in  
24 children. Now you're going to think I'm opening a can of

1 worms, but if you read the ophthalmic literature, it's  
2 becoming more and more and more prevalent above the age of  
3 two in unilateral cataracts in children to either  
4 secondarily implant a PMMA IOL, or primarily implant a PMMA  
5 IOL. It seems that while you're looking at this issue,  
6 this should be also something that's included in your  
7 discussion.

8 DR. ROSENTHAL: It has been one of the issues  
9 that we have been discussing, certainly over the past year.  
10 In fact, both of the issues which you have raised today  
11 have been on our mind over the past year and we do intend  
12 to continue to address them, and we do hear the panel loud  
13 and clear.

14 DR. STULTING: Dr. Greenidge, did you have your  
15 hand up just a minute ago?

16 DR. GREENIDGE: No.

17 DR. STULTING: Any other questions for the  
18 sponsors? I want to make sure that we are finished with  
19 them and then we can ask them to return to their seats and  
20 proceed. Is everybody comfortable we have enough  
21 information to vote?

22 Is there any other discussion we need to have  
23 before proceeding to a vote?

24 DR. MACSAI: Don't we need a motion?

1 DR. STULTING: Yes, but we'll do that in a  
2 minute. I just want to make sure that there is not going  
3 to be prolonged discussion after we start doing this.

4 Ladies and gentlemen, we have been mandated by  
5 the FDA to address specifically questions that they have  
6 formulated for us. So I will now read those into the  
7 record.

8 The first one is, "Based upon the 360 cohort  
9 eyes and/or the 523 extended cohort eyes, has Mentor  
10 provided reasonable assurance of safety and effectiveness  
11 in this device for the visual correction of aphakia in  
12 patients 60 years of age and older, where cataractous lens  
13 has been removed by extracapsular cataract extraction  
14 method?"

15 Second, "The cumulative rates of secondary  
16 glaucoma and hyphema of the MemoryLens exceed the  
17 cumulative rates for secondary glaucoma and hyphema  
18 recorded in the Stark grid. Are the explanations of the  
19 increased cumulative rates of the secondary glaucoma and  
20 hyphema provided by the sponsor acceptable?"

21 Three, "The firm is seeking approval for the  
22 pre-rolled configuration only. Do you believe the clinical  
23 data for the pre-rolled configuration provides adequate  
24 assurance of safety and efficacy?"

1 Four, "Is there any additional information you  
2 would like to see in the labeling?"

3 We didn't used to do this but, best I can tell,  
4 if you vote for approval, these questions are all answered  
5 in the affirmative or that you don't have any problem with  
6 the question that's raised. Does anybody understand these  
7 any different from what I do?

8 Okay. The record will reflect that everybody  
9 agrees that if there is approval, then these questions are  
10 all answered in the affirmative, except for the last one,  
11 but we don't need to have anything more than what we ask  
12 for in the labeling.

13 We need to read into the record the meaning of  
14 the vote, so I will turn the floor over to Ms. Thornton to  
15 do that.

16 MS. THORNTON: The Medical Device Amendments of  
17 the federal Food, Drug and Cosmetic Act require that the  
18 Food and Drug Administration obtain a recommendation from  
19 an outside expert advisory panel on designated medical  
20 device premarket approval applications that are filed with  
21 the agency.

22 The PMA must stand on its own merits, and your  
23 recommendation must be supported by safety and  
24 ~~effectiveness data in the application or by applicable~~

1 publicly available information.

2 "Safety" is defined in the Act as reasonable  
3 assurance based on valid scientific evidence that the  
4 probable benefits to health under conditions of use  
5 outweigh any probable risks. "Effectiveness" is defined as  
6 reasonable assurance that in a significant portion of the  
7 population, the use of the device for its intended uses and  
8 conditions of use, when labeled, will provide clinically  
9 significant results.

10 Your recommendation options for the vote are as  
11 follows:

12 Approval. There are no conditions attached if  
13 you vote for approval.

14 The agency action. If the agency agrees with  
15 the panel, an approvable letter will be sent to the  
16 applicant.

17 Approvable with conditions. You may recommend  
18 that the PMA be found approvable subject to specified  
19 conditions, such as resolution of clearly identified  
20 deficiencies which have been cited by you or by FDA staff.

21 Prior to voting, all of the conditions are  
22 discussed by the panel and listed by the panel chair. You  
23 may specify what type of follow-up to the applicant's

24 ~~response to the conditions of approvable recommendation you~~

1 want -- for example, FDA or panel. Panel follow-up is  
2 usually done through homework assignments to the primary  
3 reviewers of the application or to other specified members  
4 of the panel. A formal discussion of the application at a  
5 future panel meeting is not usually held.

6           If you recommend post-approval requirements to  
7 be imposed as a condition of approval, then your  
8 recommendation should address the following points: the  
9 purpose of the requirement, the number of subjects to be  
10 evaluated, and the reports that should be required to be  
11 submitted. If FDA agrees with panel recommendation, an  
12 approvable with conditions letter will be sent.

13           Not approvable. Of the five reasons that the  
14 Act specifies for denial of approval, the following three  
15 reasons are applicable to panel deliberations: the data do  
16 not provide reasonable assurance that the device is safe  
17 under the conditions of use prescribed, recommended, or  
18 suggested in the proposed labeling; reasonable assurance  
19 has not been given that the device is effective under the  
20 conditions of use prescribed, recommended, or suggested in  
21 the labeling; based on a fair evaluation of all the  
22 material facts and your discussions, you believe the  
23 proposed labeling to be false or misleading.

24 ~~If you recommend that the application is not~~

1     approvable for any of these stated reasons, then we ask  
2     that you identify the measures that you think are necessary  
3     for the application to be placed in an approvable form.

4             If FDA agrees with the panel's not approvable  
5     recommendation, we will send a not approvable letter. This  
6     is not a final agency action on the PMA. The applicant has  
7     the opportunity to amend the PMA to supply the requested  
8     information. The amended application will be reviewed by  
9     the panel at a future meeting unless the panel requests  
10    otherwise.

11            In rare circumstances the panel may decide to  
12    table an application. Tabling an application does not give  
13    specific guidance from the panel to FDA or to the  
14    applicant, thereby creating ambiguity and delay in the  
15    progress of an application. Therefore, we discourage  
16    tabling of an application.

17            But should you consider a not approvable or  
18    approvable with conditions recommendation that gives  
19    clearly described corrective steps -- no. Should, you  
20    should do that. If the panel does vote to table a PMA, the  
21    panel will be asked to describe which information is  
22    missing and what prevents an alternative recommendation.

23            Following the voting, the Chair will ask each  
24    ~~panel member to present a brief statement outlining the~~

1 reasons for their vote.

2 Thank you.

3 Mr. Chairman, you may proceed.

4 DR. STULTING: Do I hear a motion?

5 DR. HIGGINBOTHAM: Mr. Chair?

6 DR. STULTING: Yes.

7 DR. HIGGINBOTHAM: I move for approval of this  
8 PMA.

9 DR. STULTING: Would you like to attach any  
10 conditions, like to the labeling or any other part of it?

11 DR. HIGGINBOTHAM: No conditions.

12 DR. STULTING: Okay. It's been moved that we  
13 recommend approval of this application.

14 Do I hear a second?

15 DR. GREENIDGE: Second.

16 DR. STULTING: Good. The floor is open for  
17 further discussion.

18 Kevin?

19 DR. GREENIDGE: I would just like to make one  
20 comment. In reviewing this application, I saw  
21 documentation that the sponsor had been given an  
22 opportunity to respond to both safety issues, both the  
23 hyphema and the secondary glaucoma.

24 ~~It was my impression that what was provided to~~

1 us satisfactorily addressed concerns regarding the hyphema.  
2 However, it did not satisfactorily address the concerns  
3 regarding the glaucoma. However, after hearing the  
4 response today in the review that we have heard today and  
5 the response to my specific questions, I feel that this  
6 information was supplementary and more comprehensive, and  
7 certainly more convincing than what was previously  
8 provided.

9 So I would just like to state that these  
10 concerns have been addressed to my satisfaction here today.

11 Thank you.

12 DR. STULTING: Dr. Sugar?

13 DR. SUGAR: This is a friendly amendment to the  
14 package insert that we talked about before, that it include  
15 both techniques for insertion.

16 DR. STULTING: And you're talking about  
17 specifically the placement of the haptic, correct?

18 DR. SUGAR: The present package insert as I've  
19 seen it in this document is only for manually inserting the  
20 haptic and dialing it in. It's also an acceptable  
21 technique.

22 DR. HIGGINBOTHAM: I accept that amendment, Mr.  
23 Chair.

24 DR. STULTING: Are there any other

1 recommendations for labeling changes?

2 Just to refresh your memory, there were  
3 questions about sulcus implantation -- or I should say  
4 there were discussions about sulcus implantation, the size  
5 and type of capsulorhexis, age limits, and a video of the  
6 insertion techniques.

7 DR. BANDEEN-ROCHE: The current labeling  
8 indicates insertion either in the capsular bag or the  
9 sulcus. Given the discussion at the beginning of the panel  
10 meeting, I wonder whether it's warranted to state that as  
11 an indication for the sulcus, as well as a small number of  
12 patients in which that sort of implantation was done in  
13 this study.

14 DR. STULTING: Okay. So the issue is raised as  
15 to whether it is appropriate to recommend for either sulcus  
16 or bag implantation.

17 Discussion, please?

18 MS. LOCHNER: I think in the latest amendment  
19 the firm has amended their indication to state the bag  
20 only. I think that was just an oversight that they didn't  
21 correct the insert.

22 DR. STULTING: So the current labeling is bag  
23 only.

24 Any discussion?

1 DR. RUIZ: Also, if you break the anterior or  
2 the posterior capsule, you are going to have to go to a  
3 different lens, when there is really not any particular  
4 reason to do so.

5 DR. STULTING: So your recommendation would be  
6 to label it to permit either type of implantation  
7 technique?

8 DR. RUIZ: Or not say either place.

9 DR. STULTING: Further discussion? Dr. Macsai?

10 DR. MACSAI: Even if it is labeled for capsule,  
11 studies have shown it may end up in the sulcus in the best  
12 and most experienced of hands.

13 Second of all, when you say that it's approved  
14 for sulcus fixation, that may be misinterpreted to mean  
15 that it is okay for sutured sulcus fixation, and this style  
16 of lens would not be optimal for that procedure because of  
17 the fact there are no islets on the haptics.

18 DR. STULTING: Dr. Van Meter?

19 DR. VAN METER: I think sulcus fixation would  
20 be reasonable because there are times when the lens may  
21 unfold and then you note that one loop is not in the  
22 capsular bag. Explantation is obviously a problem. I  
23 think it is far more reasonable to leave a lens in the  
24 sulcus than to try to explant it.

1 DR. STULTING: Donna?

2 MS. LOCHNER: I just wanted to give a little  
3 background into the office policy regarding indication  
4 statement. In the last few years we have become much  
5 stricter in the sense of not allowing indication statements  
6 to include uses that weren't specifically clinically  
7 studied. That is why in the last few years you have seen  
8 the labeling shift to state "bag only."

9 We do allow a sort of hedging statement to be  
10 made to the effect that if the situation is compromised, it  
11 must be placed in the sulcus. That is up to the surgeon's  
12 discretion to do that, but we specifically require that the  
13 indication statement itself state what was studied.

14 So I think with the indication stating  
15 explicitly what was studied, which was the bag, and another  
16 statement in the labeling that says if there are problems  
17 it is up to the surgeon, the surgeon may use sulcus  
18 placement, I think takes care of the dilemma.

19 DR. STULTING: Dr. McCulley?

20 DR. MCCULLEY: As a practicing ophthalmologist,  
21 occasionally a lens will end up not where it was intended  
22 to be. If the product labeling is very restrictive and,  
23 looking at it from a medical/legal standpoint, if it's in  
24 the sulcus and we specifically said "bag only" and it ends

1 up in the sulcus, then if the lens is a lens that did have  
2 a configuration that would have allowed reasonable sulcus  
3 fixation, then we are tremendously disadvantaged in the  
4 courtroom.

5 DR. STULTING: I believe, if I am not mistaken,  
6 they did have implantations in the sulcus. They didn't  
7 have 300 of them, but they did have them. So it would be  
8 incorrect to say that it was not studied. It just was not  
9 studied in a large group.

10 MS. LOCHNER: I can't speak to the legal issue,  
11 and I think we can raise your concerns, but I think you  
12 have to understand that the Division itself is somewhat  
13 restricted in terms of what we can allow, for basically  
14 regulatory legal reasons.

15 But I think it is duly noted and we should  
16 bring that fact, that the intended placement isn't always  
17 the exact placement.

18 DR. STULTING: I think one of the jobs of this  
19 panel is to provide you with expert opinion about what  
20 devices ought to be approved and how they ought to be  
21 approved. So as I understand our role and the law, we are  
22 not required to follow "FDA policy," if we believe that  
23 that policy is not appropriate in the clinical practice  
24 setting.

1           So if the panel believes that it is appropriate  
2           for this lens to be approved for the sulcus, or if they  
3           believe that it is appropriate to be implanted in 50-year-  
4           olds, then we should make that recommendation. If the FDA  
5           wants to override it, that's fine. But I don't think the  
6           FDA should be dictating to the panel what the  
7           recommendation should be based on FDA policy.

8           MS. LOCHNER: No. I apologize. I didn't  
9           intend for it to be understood that way. We want your  
10          recommendations. I think given your recommendations and  
11          the weight that they have is the only way that we may be  
12          able to influence policy that we are forced to work with.

13          So I think we definitely want your  
14          recommendations, but by way of understanding why it is that  
15          those recommendations in the recent past haven't been  
16          taken, I offer this background, and I do wholeheartedly ask  
17          that you give your recommendations so that we can  
18          potentially make changes. But we are bound by what we can  
19          legally do as well.

20          DR. STULTING: We understand that. But if  
21          somebody from the outside reads the approval process  
22          transcripts over the past ten years, they have all said 60  
23          years of age or older. If that is really not the will of  
24          the committee, then there should be some recommendations

1 for approval below 60 years of age. Then when you  
2 investigate that point at a later time, you will have some  
3 data to work with, the opinions of the advisory committee.

4 Dr. McCulley?

5 DR. McCULLEY: Two things. One, on the age  
6 thing that I brought up, I personally would like to defer  
7 to the request made by the FDA. I think it sounds as  
8 though it's being addressed, and I don't think that it is  
9 wise on our part to interfere any more than offer the  
10 opinion we have offered at this time.

11 I would like to make a plea on the product  
12 labeling, though, that you don't create a situation where  
13 you put us in a medical/legal malpractice box if a lens  
14 ends up in the sulcus.

15 DR. STULTING: I think that point is pretty  
16 well made.

17 I think the issue of sulcus versus bag  
18 implantation is still on the table. Is there any other  
19 discussion on that?

20 Could we have that as a motion for amendment,  
21 and then we can deal with it. The current labeling says  
22 "bag only," correct? If someone would like to amend that  
23 to include sulcus implantation under specified conditions,  
24 then we can make that amendment.

1 DR. HIGGINBOTHAM: So moved.

2 DR. STULTING: Second?

3 PARTICIPANT: Second.

4 DR. STULTING: It has been moved and seconded  
5 that we amend the motion so that we recommend a change in  
6 the labeling to permit sulcus implantation based on the  
7 data presented, which includes some cases of sulcus  
8 implantation, and that the labeling should be created in  
9 such a way as to indicate that that is not primarily what  
10 the lens was intended for, and that it is not being labeled  
11 to permit a sutured implantation in the sulcus without  
12 capsular support.

13 Further discussion?

14 DR. BANDEEN-ROCHE: Should it be clear in the  
15 labeling that the actual number of sulcus implantations was  
16 quite low?

17 DR. STULTING: Okay, I think that's acceptable.  
18 And that the labeling also indicate the number of sulcus  
19 implants on which this recommendation was based.

20 So there's no further discussion.

21 Those in favor of that amendment? Raise your  
22 hands high, those who are voting members. If you are not a  
23 voting member, don't raise your hands.

24 (Show of hands.)

1 DR. STULTING: There are 11 yes votes and 11  
2 voting members, so that amendment passes.

3 Is there any other discussion of any amendments  
4 or any other discussion of the motion on the floor, which  
5 is to recommend approval with the conditions that we have  
6 stated so far? Those relate to dialing implantation of the  
7 lens and to the labeling for sulcus implantation with the  
8 modifications that we discussed. Is everybody clear about  
9 what we are voting on?

10 Is there any further discussion?

11 DR. MACSAI: Mr. Chairman, I call for the  
12 question.

13 DR. STULTING: Excellent. I have stated the  
14 motion with the amendments, and so we need to move to a  
15 vote.

16 Those in favor, please raise your hands.

17 (Show of hands.)

18 DR. STULTING: That's 11 yes votes and zero no  
19 votes.

20 We also have this other little thing that we  
21 have to do according to the new way of doing things, and  
22 that is that we must poll the panel. Those of you who have  
23 voted need to state your reasons for voting the way you  
24 voted.

1 Did I correctly represent that?

2 MS. THORNTON: That's right.

3 DR. STULTING: That can be as brief as you wish  
4 it to be, but the record needs to reflect that we did that.  
5 So we will start over there with Dr. Sugar and you can say  
6 why you voted the way you voted.

7 DR. SUGAR: Yes. It's fine.

8 (Laughter.)

9 DR. STULTING: Excellent.

10 DR. BANDEEN-ROCHE: Yes. I believe its safety  
11 and effectiveness was reasonably demonstrated.

12 DR. SONI: I voted for approval based on the  
13 sponsor's data and information on safety and efficacy.

14 DR. RUBIN: I voted for approval because I  
15 think that safety and effectiveness have been demonstrated.

16 DR. HIGGINBOTHAM: The data clearly illustrated  
17 in the last cohort -- that is, the 190 -- supports this  
18 approval, so that is why I voted yes.

19 DR. McCULLEY: Ditto.

20 DR. BRADLEY: I voted yes because I think  
21 safety and efficacy have been demonstrated.

22 DR. BULLIMORE: Demonstrated safety and  
23 efficacy.

24 ~~DR. GREENIDGE: Demonstrated safety and~~

1 efficacy.

2 DR. MACSAI: The same.

3 DR. VAN METER: Demonstrated safety and  
4 efficacy.

5 DR. STULTING: Did we accomplish that goal?  
6 Okay.

7 Yes, Dr. Rosenthal.

8 DR. ROSENTHAL: Mr. Chairman, since the panel  
9 is in a mood for giving advice this morning, I would  
10 appreciate hearing from you about the issue of how we  
11 should approach the problem of elevated intraocular  
12 pressure, sustained glaucoma, a single temporary rise in  
13 intraocular pressure, because I think in developing a new  
14 grid, and certainly in developing the PDP issue, it is  
15 going to have to be done well up front, and I don't think  
16 it's in the best interest of the companies to make their  
17 own definitions, since they may get into trouble.

18 DR. HIGGINBOTHAM: I think that's an excellent  
19 suggestion because it's all in the definition, as we know.  
20 I would suggest that we not discuss this at this time  
21 because it's a more complex discussion, and perhaps a  
22 homework assignment might be the way to handle that. So  
23 that would be my suggestion.

24 DR. ROSENTHAL: So, ditto. I will send it to

1 the two glaucoma experts as a homework assignment.

2 DR. STULTING: That's what I was about to  
3 suggest. I think that's an excellent way to do it. In  
4 fact, as a more generic issue, as you develop the new grid,  
5 it might be a good idea to send working documents around as  
6 they are developed. As we all came here, we'd never seen  
7 or heard any information or anything that had been derived  
8 so far, and you have obviously done some work on it.

9 You might want to send it around so that we can  
10 look at it and find other things that might stick out in  
11 one person's mind and see if we can get this done fairly  
12 quickly.

13 DR. FERRIS: Rick Ferris. I agree with that  
14 point because I think there are a number of these items  
15 that are not differentiating clinically important events  
16 from clinically trivial events and that there are ways of  
17 doing that. I would be happy to help.

18 DR. STULTING: Yes. In fact, Dr. Ferris is  
19 probably a good person to review these as well because  
20 these are subjects of NEI-supported research and they have  
21 the same problems of figuring out what definitions are and  
22 how to follow and what is clinical significance and what  
23 isn't.

24 DR. ROSENTIAL: I appreciate the panel members'

1 offer for assistance.

2 DR. STULTING: Judy?

3 DR. GORDON: Judy Gordon. Just one last  
4 comment that I started to make before. I interrupted Dr.  
5 McCulley. But again, it is just an easier approach for a  
6 manufacturer to take to perpetuate what has been done  
7 traditionally. So I think there needs to be a careful and  
8 thoughtful review of all of these issues reviewed by panel,  
9 clear definitions and then a starting point to move forward  
10 for everyone so that data across lenses and across studies  
11 are comparable, and that all manufacturers have a clear  
12 understanding of what is required. The same would apply  
13 for age change or requirements for labeling for scleral  
14 bag, et cetera.

15 My only concern is that there not be as a  
16 result of this increased burdens to manufacturers because  
17 these products generally are very well established in good  
18 history and one would be reluctant to see a manufacturer  
19 get into a situation of having to establish that to implant  
20 patients from 50 to 60 requires a whole new study or  
21 something along those lines. It needs to intuitively make  
22 sense and to fit in with what is current standard practice  
23 today.

24 DR. STULTING: I think I just heard Judy

1 volunteer to review these from a perspective of industry.

2 DR. GORDON: Thank you.

3 DR. STULTING: Any other business? Did you  
4 have something to say before lunch?

5 MS. THORNTON: Yes. I would just like to ask  
6 the panel members to do something I know you have been  
7 dying to do, and that is leave your documents here with us.  
8 We would like to have them back, the ones that pertain to  
9 the discussion this morning. Just leave them at your  
10 places or bring them down during lunchtime so they can be  
11 turned over to the contractor. We would appreciate it.

12 DR. MACSAI: Sally, can we leave these?

13 MS. THORNTON: Your folders you may leave on  
14 the table, yes.

15 DR. MACSAI: What about folders for this  
16 afternoon?

17 MS. THORNTON: For this afternoon, leave your  
18 folders on the table.

19 DR. STULTING: You're not going to come and get  
20 them while we're gone, right?

21 MS. THORNTON: Yes.

22 DR. STULTING: They will come and get them  
23 after we finish this afternoon, so you can leave stuff here  
24 now.

1 I have a note that says we have to take at  
2 least one hour, so let's come back at 1:15.

3 (Whereupon, at 12:10 p.m., the meeting was  
4 recessed for lunch, to reconvene at 1:15 p.m.)  
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18 AFTERNOON SESSION

(1:32 p.m.)

19 DR. STULTING: I'd like to reconvene the  
20 meeting and call it to order once again. The subject of  
21 discussion this afternoon is P960028. Ms. Lochner will  
22 begin the presentation.

23 MS. LOCHNER: Thank you.

24 ~~Again, I'd like to acknowledge the hard work of~~

1 the PMS review team for this PMA, the team leader and  
2 engineering reviewer, Ashley Boulware; the clinical  
3 reviewer, Malvina Eydelman; the vision science reviewers,  
4 Don Calogero and Bruce Drum; toxicology, Susanna Jones;  
5 microbiology, Lawrence Romanell; statistical, Melvin  
6 Seidman; and labeling, Carol Clayton. Thank you.

7 Now I'd like to turn the meeting over to Ashley  
8 Boulware who will provide an introduction to the PMA.

9 MS. BOULWARE: Thank you, Donna.

10 Good afternoon members of the panel, Ms.  
11 Thornton, Dr. Rosenthal, ladies and gentlemen. PMA P960028  
12 requests approval for the AMO Array Model SA40N Multifocal  
13 Intraocular Lens. The sponsor has proposed that the lens  
14 be indicated for the visual correction of aphakia in  
15 persons 60 years of age or older in whom a cataractous lens  
16 has been removed by extracapsular cataract extraction or  
17 phacoemulsification and who desire multifocal vision.

18 The array multifocal lens would also be  
19 indicated for those patients who desire increased depth of  
20 focus and associated near vision without reading add versus  
21 a comparable monofocal IOL, and reduced spectacle  
22 dependence and usage when compared to a monofocal IOL,  
23 particularly with bilateral implantation; and for whom the  
24 ~~potential visual side effects associated with multifocality~~

1 are acceptable.

2 The lens is intended for placement in the  
3 capsular bag.

4 The clinical study and this PMA was conducted  
5 on Model SSM26NB. However, the sponsor is requesting  
6 approval for Model SA40N, a Tier A modification of the  
7 clinically studied model. The differences between Models  
8 SA40N and SSM26NB include a change in the type of  
9 ultraviolet-absorbing silicon optic material from SLM-1 to  
10 SLM-2, both of which have been clinically studied; a change  
11 from polypropylene haptics to extruded PMMA haptics; and a  
12 change to a nearly constant center thickness design to  
13 provide more consistent folding characteristics.

14 The multifocal optic itself is unchanged, and  
15 the identical monofocal version of the proposed lens has  
16 been PMA-approved. The lens has a 6-millimeter optic  
17 diameter and modified C haptics, which result in an overall  
18 diameter of 13 millimeters. The biomedical engineer has  
19 determined that the differences between the clinically  
20 studied and proposed models should not have a significant  
21 effect on either the optical or mechanical properties of  
22 the lens.

23 The primary panel reviewers for P960028 are  
24 ~~Drs. Bradley, Bullimore, McCulley, and Rubin.~~ The sponsor

1 has been advised of the questions and concerns raised by  
2 the primary panel reviewers and FDA's clinician, Dr.  
3 Malvina Eydelman. Representatives from Allergan will now  
4 present data from the PMA. Following the sponsor's  
5 presentation, Dr. Eydelman will summarize issues from her  
6 clinical review, and I will discuss issues raised in the  
7 vision science reviews.

8 Thank you for your attention.

9 DR. YAROSS: Good afternoon. My name is Marcia  
10 Yaross, and I'm an employee of Allergan. Today I'll be  
11 presenting data and information from PMA P960028, which is  
12 for the AMO Array Multifocal Intraocular Lens, Model SA40N.  
13 As Ms. Boulware has indicated, it is a silicone, UV-  
14 absorbing, multifocal posterior chamber IOL.

15 The Model SA40N is a three-piece, foldable  
16 design. It is a 13-millimeter overall diameter lens, and  
17 has a 6-millimeter optic. The optic and haptic materials  
18 have been previously established as safe and effective, and  
19 the lens is otherwise identical to currently marketed  
20 monofocal model SI40NB, except for the optical design.

21 The optical design is what is unique to the AMO  
22 Array Multifocal IOL. The lens has a zonal progressive  
23 multifocal optic. The design is distant-dominant for  
24 safety, and the add power is 3.5 diopters.

1           Next, this slide presents a schematic diagram  
2 of the changes from base power, which is indicated with the  
3 X axis, in each of the concentric zones of the optic. The  
4 concentric zones provide a power range that corresponds to  
5 either distance, intermediate, or near powers. Important  
6 considerations of this design is its smooth, continuous  
7 surface. The lens design is weighted to provide  
8 approximately half of the light to distance, and smaller  
9 percentages to near and to intermediate at typical pupil  
10 sizes.

11           Again, as Ms. Boulware has indicated, the  
12 relationship between the SA40 and multifocal, for which we  
13 are seeking approval, and the clinically investigated  
14 SSM26NB has been deemed to be a tier A variation of the  
15 clinically investigated model. Tier A status was approved  
16 under our IDE in accordance with the January 1995 FDA draft  
17 guidance document.

18           The optical design of the SA40N is identical to  
19 that of clinically investigated SSM26NB, and the  
20 differences are again the higher refractive index of the  
21 SLM-2 material resulting in a thinner lens, and the  
22 constant center thickness and PMMA haptics of established  
23 monofocal model SI40NB. The SI40NB lens has been  
24 commercially available for over two years.

1 Dr. Tarantino will now discuss the clinical  
2 study design.

3 DR. TARANTINO: Good afternoon. My name is  
4 Nick Tarantino, and I'm an employee of Allergan. What I  
5 would like to present this afternoon are the basic aspects  
6 of the clinical study that was conducted to support this  
7 PMA.

8 A total of 456 subjects were enrolled into this  
9 study. Over the one-year period, only about eight  
10 subjects, or less than 2 percent, were lost to follow-up.  
11 Of the 456 subjects, 400 achieved cohort status, and of  
12 those, 392 achieved best case. One hundred and forty-seven  
13 subjects were implanted bilaterally. Their second eyes  
14 were treated as non-core. Second eyes continue to be  
15 enrolled in the study as the subjects request.

16 Several substudies were conducted in order to  
17 help better understand the clinical performance and risks  
18 and benefits associated with this particular multifocal  
19 IOL. What I'd like to do now is briefly discuss the  
20 objectives, design, and some of the demographics relative  
21 to these eight substudies listed here.

22 The monofocal fellow eye control consisted of  
23 123 core subjects, and of those, 102 cohort subjects. In  
24 ~~this particular study, one eye was implanted with the~~

1 multifocal IOL, and the fellow eye was implanted with a  
2 similarly designed SI26 as a control. This was  
3 particularly done in order to make paired-eye comparisons  
4 between the multifocal IOL and the monofocal IOL.

5 In the contrast sensitivity study, there were  
6 239 multifocal eyes and 67 monofocal eyes from the study  
7 listed above. This study was actually done in two  
8 different ways. For distance, the Regan contrast charts  
9 were used, with 96 percent, 50 percent, 25 percent, and 11  
10 percent contrast. This was performed with BAT off, BAT  
11 low, and BAT medium to simulate different variations of  
12 glare. For near, the CAT charts were used at 100 percent,  
13 50 percent, 25 percent, and 12.5 percent, using the same  
14 BAT illuminations to simulate the glare as well for those.

15 The contrast sensitivity data were validated by  
16 way of a contrast sensitivity reproducibility study with 14  
17 multifocal eyes. The vision field substudy was a paired-  
18 eye comparison whereby, in a masked and randomized fashion,  
19 the investigator and medical monitor reviewed the different  
20 visual fields taken from a multifocal eye versus a  
21 monofocal eye to see if any difference could be detected.

22 In the fundus photography study, again paired-eye  
23 photographs were evaluated in a randomized and evaluator-  
24 ~~masked comparison with five evaluators who were asked to~~

1 judge the clarity of the photographs. The objective was to  
2 determine if any clinically significant loss of image  
3 resolution in the fundus photographs could be detected.

4 In the depth of focus study, 10 subjects, again  
5 in a paired-eye comparison, were evaluated, and defocus  
6 curves were run on these 10 subjects with three different  
7 pupil sizes per eye. This was done in order to be able to  
8 determine if an increased depth of focus could be realized  
9 through the multifocal IOL. An additional supplemental  
10 depth of focus study was conducted when we were asked to  
11 take a look specifically at those patients that were able  
12 to achieve 20/20 distance and J1 plus near through distance  
13 corrected lenses, to see if the depth of focus matched the  
14 theoretical depth of focus that could be performed through  
15 this particular lens.

16 A quality of life study was conducted with a  
17 multifocal-specific quality of life instrument that was  
18 developed and validated in conjunction with Dr. Jonathan  
19 Javit from Georgetown University. In this study, a  
20 modified version of the cataract-type spec was used as the  
21 instrument -- however, with multifocal-specific questions.  
22 This particular study was a parallel group comparison  
23 between 100 bilateral multifocal subjects and 103 bilateral  
24 monofocal subjects, again to see if a measurable difference

1 in quality of life could be determined.

2 A driving simulation study was conducted with  
3 33 bilateral multifocal subjects and 33 bilateral monofocal  
4 subjects in order to evaluate any impact of low contrast  
5 driving performance and safety that this multifocal IOL may  
6 have. Again, this was a parallel group comparison study.  
7 We'll go into this particular study in much greater detail  
8 a little bit later on.

9 DR. BRADLEY: Excuse me. Could you speak up a  
10 little bit?

11 DR. TARANTINO: I will, yes.

12 We believe the studies have determined the  
13 safety and effectiveness of the AMO Array Multifocal Lens  
14 relative to the following indications: for the visual  
15 correction of aphakia in persons 60 years of age or older  
16 and who desire multifocal vision; for those patients who  
17 desire increased depth of focus and associated increased  
18 near vision without reading add and reduced spectacle  
19 dependence and usage, particularly with bilateral  
20 implantation for subjects in which the potential visual  
21 effects associated with multifocality are acceptable.

22 The results demonstrating the safety and  
23 effectiveness relative to these indications will now be  
24 ~~presented by the study's medical monitor, Dr. Roger~~

1 Steinert.

2 DR. STEINERT: Thank you, Nick.

3 My name is Roger Steinert. I'm an assistant  
4 clinical professor of ophthalmology at Harvard Medical  
5 School, and in practice at Ophthalmic Consultants of  
6 Boston. I am the medical monitor on this study and have  
7 been a paid consultant to Allergan in that capacity. I  
8 have no financial interest in this lens, nor do I have any  
9 financial interest in Allergan itself.

10 I thank you for the opportunity to speak and  
11 present the clinical efficacy and safety data in summary  
12 fashion. These, of course, are only the highlights of the  
13 many volumes of data that you have. The first set of  
14 slides that I'd like to present relate to our intention of  
15 having an intraocular lens that preserves the primary  
16 benefit of conventional multifocal lenses -- namely,  
17 correction of aphakia.

18 In this slide, you see the cohort patients  
19 represented here, and the best-case patients represented  
20 here, the rate of 20/40 or better being 98 percent for all  
21 cohort patients, compared to 88 percent in the historical  
22 FDA grid; 99 percent 20/40 or better in the best-case  
23 patients, compared to 94 percent for best-case in the  
24 ~~historical FDA grid; the rate of 20/20 or better of being a~~

1 little over 70 percent for each of these groups.

2 In addition, we looked at the ability to see at  
3 the level of J3, shown here, or J1, shown here, again for  
4 the cohort patients or the best-case patients with  
5 additional add, if required, again simulating the  
6 circumstance that occurs with current monofocal lenses.  
7 You can see how high a rate we have, in the high 90s, of  
8 achieving that; and fully 100 percent of the patients do  
9 achieve J3 or better in the non-macular-limited cases.

10 Now, beyond that, of course, we want to see  
11 what the specific benefit of this lens is with regard to  
12 its multifocal properties. This first slide here shows the  
13 increase in uncorrected near acuity, or near acuity when  
14 distance corrected, with multifocal eyes, in each case  
15 achieving a mean acuity of 20/33, compared to the mid 20/50  
16 level for monofocal eyes; in other words, an approximately  
17 two-line improvement in near visual acuity -- highly  
18 statistically significant in both cases.

19 In another way of looking at this, to go  
20 forward then, is that the patients really want to see, of  
21 course, well in the distance and well at near  
22 simultaneously. So now what we're looking at are the rates  
23 of being 20/40 or better, and simultaneously J3 or better  
24 uncorrected visual acuity in the multifocal eyes compared

1 to monofocal eyes.

2 Now, this data comes from the substudy of  
3 patients who had a unilateral implant of the multifocal  
4 lens, and then monofocal in the other eye. You see 77  
5 percent for the multifocal, having simultaneously 20/40 in  
6 J3, compared to 46 percent for monofocal. Indeed, we were  
7 surprised at that high level. I think most people feel  
8 that that's higher than actually is the usual clinical  
9 experience for monofocal lenses. It's remarkable that,  
10 despite this high level, again there is this big  
11 difference, and it achieves a high level of statistical  
12 significance.

13 Moreover, when you now look at patients who had  
14 bilateral implantation of the multifocal lens, and again  
15 look at the same criteria of 20/40 and better, and J3 or  
16 better uncorrected or distance corrected, or additional add  
17 if needed, 98 percent of subjects bilaterally implanted,  
18 without any correction whatsoever, are simultaneously at  
19 least 20/40 and J3. This incremental improvement shows the  
20 added benefit of bilateral implantation.

21 Now, a particular analysis was performed on the  
22 small number of patients who were 20/40 or better at  
23 distance, and yet at near were not J3. We looked at a  
24 ~~number of variables to try to explain this phenomenon, and~~

1 none of those variables in fact could explain this finding.  
2 However, we wanted to present one particular one, more out  
3 of interest than having an answer, which is that we looked  
4 at dominance. It is remarkable that there is a greater  
5 proportion of non-dominant eyes seeing better than 20/40 in  
6 the distance, and yet worse than J3 at near.

7 This is without any distance correction; this  
8 is with distance correction. You can see that there are  
9 many more falling into the non-dominant eye than the  
10 dominant eye group.

11 Nevertheless, it's important to note a couple  
12 of things. One is that more than half of these people who  
13 are not J3 are just one line worse. Almost 90 percent of  
14 them are within two lines of J3, meaning at about the 20/60  
15 or better level at near. So it's not that they're falling  
16 way off the map.

17 Beyond that, though, we don't really know what  
18 to make of this, because dominance, first of all, is a  
19 binocular test, not a monocular test. Finally, you have to  
20 understand that the determination of dominance, although it  
21 was part of the protocol, was done on patients with  
22 bilateral cataracts. It was not at all clear that in fact  
23 we effectively did determine which eye was dominant, since  
24 ~~there were cataracts in those eyes. But we present that,~~

1 at least just for your interest.

2 Now, clearly we want to be able to demonstrate  
3 an increased depth of focus in a multifocal lens. Indeed,  
4 that was achieved. This analysis looks at the depth of  
5 focus when the patients are deliberately defocused from the  
6 refractively determined point of emmetropia. You see here  
7 the depth of focus where vision is 20/40 or better for  
8 multifocal eyes, or for monofocal eyes. This is where we  
9 cut it off from plano and only de-focus in the minus  
10 direction; in other words, to work into the plus side.  
11 This is the full range of testing, which actually went from  
12 +5.0 to -5.0. You see that, no matter which way this  
13 analysis is done, there is approximately one diopter  
14 greater depth of focus where the patients see 20/40 or  
15 better -- again, highly statistically significant.

16 This is a curve that is not used clinically,  
17 and therefore may look a little unfamiliar. But what this  
18 represents is that de-focusing process, starting at +5.0  
19 and working through -5.0, and measuring visual acuity.  
20 Now, we did the visual acuities with the high-contrast  
21 Regan chart, which is why this says "Regan line." But  
22 functionally, you can think of this in terms of visual  
23 acuity. The green line here represents the mean of the  
24 difference between a multifocal eye in one eye, and the

1 monofocal eye in the other eye, of the subset of patients  
2 who have one lens in each eye and who are specifically  
3 recruited for this specific test as a later substudy.

4 This clearly shows the impact of the multifocal  
5 optic, as the minus forces the patient's distance vision  
6 into the area of the multifocality instead of the normal  
7 distance area, and the lower curve here representing the  
8 lower confidence interval. So the area in which there is a  
9 statistically significant impact of the add power that is  
10 in the Array lens is indeed from -2.0 to -4.0.

11 An additional supplemental substudy was  
12 performed on a very small number of patients at one site  
13 who were true best-case patients. The point of this was to  
14 identify patients who would not have a retinal limit to  
15 their acuity, because if there's a retinal limit, then you  
16 will not see the true performance of the implant. The idea  
17 was to see what the performance of the implant would be  
18 where there was no retinal limit or other limit to the  
19 acuity. So these are patients who are at least 20/20 at  
20 distance, and at least J1 plus at near. When you do this  
21 same de-focusing kind of test, you see that in fact their  
22 mean vision at distance goes above 20/20, and they retain  
23 the 20/40 vision out to -4.0.

24 ~~The fact that this peak, which is the reading~~

1 area, is not as high as the distance area is a reflection  
2 of the design of the lens, which is distance dominant, as  
3 Dr. Yaross discussed at the beginning.

4 Now, another way of looking at increased depth  
5 of focus is also to look at the through focus in the  
6 clinical version of that, to see the patients who are 20/40  
7 or better at distance, J3 or better at near, and also 20/60  
8 or better at intermediate, which is the generally accepted  
9 useful level for intermediate distance. You see that  
10 multifocal bilateral implant patients have that occur --  
11 I'm sorry. This is not bilateral, this is unilateral.  
12 Sixty-one percent of the multifocal eyes achieve that,  
13 compared to only 39 percent of the monofocal eyes. Again,  
14 this was highly statistically significant.

15 This, in turn, if we've achieved what we're  
16 setting out to do, should translate into decreased  
17 spectacle dependence. In fact, we can demonstrate this  
18 quite dramatically. In this case, we are showing you data  
19 from the bilateral implanted patients, bilateral multifocal  
20 subjects, or bilateral monofocal subjects when they were  
21 asked to rate how much they wear spectacles, whether they  
22 either said, "Always," "Never," or something in between.

23 In fact, you see that 12 percent of the  
24 ~~monofocal patients but 41 percent of the multifocal~~

1 patients said they never wear glasses -- highly  
2 statistically significant. On the flip side, 34 percent of  
3 the monofocal patients are always wearing glasses, whereas  
4 only eight percent of the multifocal bilateral implants  
5 always wear glasses.

6 Another way of looking at decreased spectacle  
7 dependence is to ask the patients -- and there was a survey  
8 done at several of the postoperative intervals that asked  
9 them to report their overall score on a scale of 1 to 5  
10 here of their perception of their overall vision, their  
11 overall global quality of vision, whatever that would mean  
12 to them.

13 These, then, are again bilateral multifocal  
14 versus bilateral monofocal patients from the quality of  
15 life study. You see that without glasses -- highly  
16 statistically significant -- a higher quality rating for  
17 the multifocal patients compared to monofocal. But even  
18 when they were then asked to rate the quality of their  
19 vision with glasses, the multifocal patients rated their  
20 quality as higher than the monofocal. In this survey, that  
21 maintained statistical significance.

22 This now looks at the patients who were  
23 bilateral multifocal implants and asks if they can function  
24 comfortably without glasses. You see again the impact as

1 these numbers get higher and higher. Eighty-one percent at  
2 near, jumping to 93 percent for intermediate, and no  
3 difference at distance. So with the bilateral multifocal  
4 implant, they feel just as comfortable without glasses at  
5 intermediate as they do in distance.

6 So in summary, regarding efficacy, we believe  
7 that this study has shown that the multifocal implant can  
8 achieve a fundamental correction of aphakia that is  
9 equivalent to the monofocal implant. In addition, there is  
10 an increased near level of acuity without the reading add  
11 that is typically needed for monofocal implants. We've  
12 demonstrated an increased depth of focus. It's as defined  
13 at the level of 20/40 or better vision, compared to  
14 monofocal; and we have demonstrated decreased spectacle  
15 dependence and usage and an overall perception of an  
16 improved quality of vision compared to monofocal implants.

17 I'd like to shift to consideration of the  
18 safety data. In turn, we'll consider complications,  
19 contrast acuity, driving simulation testing, optical  
20 symptoms, and adverse events.

21 First of all, looking at persistent sight-  
22 threatening complications, we see that the study data at  
23 one year is all within the historical FDA grid for these  
24 complications, as expected, because the platform of this

1 lens is PMA-approved implant.

2 Now, shifting to contrast acuity at distance,  
3 we looked at contrast acuities, you've heard, with the  
4 Regan contrast acuity tests. What we're presenting here is  
5 the best corrected monocular distance contrast acuity  
6 without any induction of glare, and a medium-sized pupil,  
7 so that the multifocal element is at play. What you see  
8 here is that, for high contrast and medium contrast, there  
9 is no difference between the multifocal and monofocal  
10 patients at distance.

11 When you get down to 25 percent contrast, a  
12 statistically significant small difference occurs. Then at  
13 11 percent contrast, that difference becomes slightly more  
14 accentuated.

15 Not all of you may be familiar with these  
16 charts or exactly what this means, so we brought along two  
17 of them. This is the 25 percent contrast acuity chart. In  
18 this illumination, you may have some trouble seeing that  
19 I'm holding anything other than a white piece of paper.  
20 Just to give you relevance on this, the difference is that  
21 this is the mean acuity level for the monofocal patients;  
22 this is the mean acuity for the multifocal patients. That  
23 is the difference at the 25 percent level.

24 Now, if you enjoyed that exercise

1 DR. BULLIMORE: What test distance is that  
2 referred to? Is that for the 10 feet, 20 feet?

3 DR. STEINERT: This is 10 feet.

4 This is the 11 percent contrast chart -- even  
5 foggier. As you can see, everyone is moving up because all  
6 patients, all normals have reduced acuity as the contrast  
7 goes down, this now being the mean level for the monofocal,  
8 this being the mean level for the multifocal -- again,  
9 approximately a one line difference.

10 We also looked at contrast acuity at near,  
11 where there has recently in the past few years been the  
12 development of contrast acuity charts. This is somewhat  
13 equivalent to the Regan charts designed for near, designed  
14 by Jack Holiday, I believe. In near acuity, it's  
15 interesting. Actually, the multifocal slightly out-  
16 performed the monofocal at the 25 percent level. The  
17 difference only shows up at the lowest level, which in the  
18 near charts happens to be 12.5 instead of 11 percent  
19 contrast. Then there is a statistically significant  
20 difference at near.

21 We then specifically looked at patients where  
22 the multifocal eye -- these are patients again from this  
23 multi in one eye, mono in the other subset, where the  
24 multifocal eyes were more than two lines worse than the

1 monofocal eye with the contrast chart. You see that, as  
2 just shown, there is an increase in the percentage of  
3 subjects with a more than two line disparity as you go to  
4 lower levels of contrast, and that also goes up slightly  
5 with induction of glare with the BAT tests of either low or  
6 medium.

7           Looking at the same type of analysis with the  
8 near chart again, there is an increase as you go to lower  
9 contrast, and a little bit with higher glare as well, for  
10 the near charts; again, particularly notable only for the  
11 very low contrast near chart.

12           I'd now like to ask Dr. John Bloomfield to  
13 present the driving simulation study.

14           DR. BLOOMFIELD: Thank you, Roger.

15           My name is John Bloomfield. I'm the principal  
16 research scientist and manager of the Human Factors Group,  
17 the Iowa Driving Simulator. I'm here as a consultant for  
18 Allergan. I have no financial interest in the lens or in  
19 the company.

20           We're going to begin by showing you some video,  
21 and I'm going to talk over that. Currently there are two  
22 operating advanced driving simulators in the world. One of  
23 these is the Diamler Benz Simulator, which is located in  
24 Berlin and which is used primarily by Diamler for in house

1 research. The other is the Iowa Driving Simulator. There  
2 is a third device, which is the National Advanced Driving  
3 Simulator that is under development. That, like the Iowa  
4 Driving Simulator, will be located in the University of  
5 Iowa in Iowa City.

6 The Iowa Driving Simulator is operated out of  
7 the University Center for Computer-Aided Design. It is  
8 used to investigate future highways to study collision  
9 avoidance warning systems, and for medical investigations,  
10 including studies of the effects of Alzheimer's disease and  
11 the effects of antihistamines.

12 There are two versions of this real-time,  
13 interactive, state-of-the-art simulator. One of them is a  
14 moving base version. It utilizes a hydraulically actuated,  
15 60-degrees-of-freedom Stuart platform. The second, which  
16 is a fixed-base version, was chosen for this substudy,  
17 where we look at the Allergan AMO Array Multifocal  
18 Intraocular Lens. This second version was chosen for the  
19 study because of its enhanced graphic resolution  
20 capabilities, which were essential to the investigation and  
21 the visual components substudy.

22 The objective of the substudy was to determine  
23 the impact of the multifocal intraocular lenses on driving  
24 performance and driving safety while driving at night and

1 in low contrast conditions.

2 We just froze this for a moment so I could  
3 explain. The person who is very blurry to the right is  
4 actually an actor. He is not one of the subjects. The  
5 subjects were not shown because of privacy reasons. The  
6 person to the left is our experimenter, who was with the  
7 drivers throughout all of the simulated runs.

8 Each test subject who participated in the  
9 substudy sat behind the wheel of a modified Ford Taurus.  
10 This vehicle responded realistically when the subject used  
11 the steering wheel, the brake, and the accelerator pedal.  
12 The subject got to view a virtual world that was projected  
13 onto a screen that was nine feet in front of his or her eye  
14 point. From this point, the continuous visual field  
15 projected onto the screen from three color projectors was  
16 60 degrees wide and 20 degrees high.

17 While driving, each subject heard the sounds of  
18 the vehicle's engine and tires in appropriate pitch and  
19 volume, further enhancing the realism of the driving  
20 experience.

21 Although it's difficult to read the signs here  
22 on this screen, the resolution seen by each subject was  
23 substantially better than you see here.

24 ~~We took steps to validate the realistic nature~~

1 of the simulation. Pre-test measurement and post-test  
2 analysis of the sign recognition data demonstrated that the  
3 simulator's projected letter resolution didn't limit the  
4 sign recognition distances. The signs were presented so  
5 that the angular signs in color conformed to U.S. federal  
6 highway standards.

7 Now, to simulate driving at night when there  
8 was a glare from an oncoming source, the subject's face was  
9 illuminated with five luchs, which approximates two  
10 headlights at about 50 feet. This is based on field  
11 measurements. The lowest contrast environment involved  
12 driving in fog, which you see here. We simulated the fog  
13 using a custom feature of the simulator's imaging system  
14 which effectively increases the optical density as the  
15 object moves further away.

16 Now, could you freeze this one for a moment,  
17 please? When this comes back again, you're going to see  
18 four different shots. The shot that's to the top right is  
19 the frontal view of the subject that's taken from a camera  
20 that's mounted inside the vehicle on the dash. Below that,  
21 there's another shot of the subject which is taken from the  
22 side view. To the lower side on the right there is a shot  
23 of the subject's feet, so you can see the accelerator and  
24 the pedal. The upper right is the central panel of the

1 three that is shown to the subject when they're driving  
2 along.

3 The fog level that we chose for this experiment  
4 was based on a published, observational, on-the-road study  
5 of driving in fog. We chose a level that elicits about a  
6 25 percent reduction in vehicle speed. Each subject  
7 carried out, in sign recognition, hazard avoidance tasks in  
8 all three environmental conditions.

9 We evaluated the performance of 33 bilaterally  
10 implanted AMO Array subjects, and a control group of 33  
11 bilaterally implanted monofocal subjects.

12 I should mention that, in addition to these 66  
13 people, there were eight other subjects who were eliminated  
14 from the study. Five of them were eliminated because they  
15 suffered from simulator sickness. Three of those five were  
16 monofocal subjects, two were multifocal, and the other  
17 three who were eliminated were eliminated because they were  
18 unable to comply with the instructions. Of those three,  
19 two were monofocals and one was multifocal.

20 Pre-test evaluations confirmed that the tests  
21 and the control subjects were without pathology and had no  
22 clinically significant posterior capsular opacification.  
23 In addition, they had uncorrected or best corrected  
24 distance acuities of at least 20/30. The subjects were

1 this correction while they were in the simulator if they  
2 typically used it when they were driving. In addition,  
3 they drove at least 1,500 miles a year.

4 Each subject drove on a two-lane rural road and  
5 a six-lane expressway. They drove these roads under the  
6 three environmental conditions, at night in clear weather,  
7 at night with glare, and in fog. All three conditions were  
8 presented in random to each subject.

9 The driving performance measures that were  
10 collected electronically included traffic sign recognition  
11 distances, and hazard detection and hazard avoidance data.  
12 Other performance data, such as the ones described here,  
13 speed and steering, were also collected. In addition, we  
14 used video recordings to analyze the subjects' responses to  
15 the roadway hazards.

16 The sign recognition task was conducted first.  
17 For this, a series of 15 signs appeared at the side of the  
18 road. There were five guidance signs, five regulatory  
19 signs, and five warning signs. As soon as the subject knew  
20 what each of the signs said, he or she would press a button  
21 that was on the steering wheel. When this button was  
22 pressed, three things would occur. First, the writing on  
23 the sign would disappear. Second, the distance between the  
24 sign and the driver was recorded. Third, the driver told

1 the experimenter what the sign said.

2 Two measures of performance were recorded for  
3 this sign recognition task. They were the percentage of  
4 signs that were currently recognized and the sign  
5 recognition distance.

6 In the data analysis that we did after we'd  
7 collected this information, when the sign recognition  
8 distance data were calculated, they were corrected to take  
9 account of the button-press reaction time of each subject.

10 The second driving task involved hazard  
11 detection and avoidance. One hazard situation involved a  
12 car which came onto the road from the shoulder and then  
13 signalled it was turning left. The others were stationary  
14 objects on the road. They included a gray ball, a medium-  
15 contrast blue suitcase, and a bright orange traffic cone.  
16 You just saw the suitcase.

17 Three measures of performance were recorded for  
18 these hazard situations. They were the percentage of  
19 hazards being recognized as present, the initial hazard  
20 recognition distance, and the subject's ability to avoid  
21 the hazard.

22 The subjects' physical reactions recorded on  
23 video were used to establish the initial hazard recognition  
24 distance. Electronically recorded data we used to evaluate

1 the subjects' success at avoiding these hazards.

2 Now, in summary, this was a technologically  
3 sophisticated, state-of-the-art driving simulation  
4 experiment. We measured the distance in which each subject  
5 could recognize 15 different road signs. We also collected  
6 hazard detection and hazard avoidance data for four  
7 potential hazard situations. These data were collected  
8 from each of 33 test subjects and 33 controls in three  
9 randomly presented environmental conditions.

10 Now I'll move over and talk about some of the  
11 results from this study. We had essentially 30 measures of  
12 performance that involved sign recognition, hazard  
13 detection, and hazard avoidance. There were no  
14 statistically significant differences between the  
15 multifocal test subjects and the monofocal controls for 26  
16 of these 30 measures. For four of the 30 measures -- that  
17 is, for 13.3 percent -- statistically significant  
18 differences were obtained.

19 The experiment provided sufficient resolution  
20 to detect the theoretically expected differences between  
21 the test and control subjects -- they were based on  
22 contrast acuity results -- as well as those based on age  
23 and driving conditions.

24 ~~What we're going to do now is look at some of~~

1 the results. The first set that we see here, these show  
2 the percentages of signs that were correctly identified by  
3 the multifocal test subjects and the monofocal controls for  
4 each of nine combinations of three sign types and three  
5 environmental conditions. You'll see from this chart that  
6 we have a number of NSs on here. Eight of the nine  
7 comparisons, in fact, were where we found no significant  
8 differences.

9           You'll see that, therefore, the guide signs in  
10 all three of the environmental conditions -- night, night  
11 and glare, and fog -- and for the regulatory signs for all  
12 three conditions -- also, you'll see there were no  
13 significant differences between the groups for the warning  
14 signs in night with glare and in fog.

15           Now, there is one significant difference on  
16 there. We have to take a look at that. This is for the  
17 warning signs in clear weather at night. Here there was a  
18 statistically significant difference. This is the first of  
19 those four main measures where we found a difference. What  
20 you'll see here is that the monofocal subjects did identify  
21 a higher percentage of warning signs under these conditions  
22 than the monofocals. This is true for the younger of the  
23 drivers and the older drivers as well.

24           It should be noted, however, that for the

1 subjects who currently identified the warning signs under  
2 these conditions, there was no corresponding statistically  
3 significant difference in the sign recognition distances  
4 when we compared the test and the control subjects.

5 This next slide shows another set of  
6 comparisons. This time it's for sign recognition  
7 distances. Again, we're comparing the multifocal test  
8 subjects with the monofocal controls. In this case, you'll  
9 see that for night time, when it was clear, which is this  
10 up here, there are no significant differences for any of  
11 the three signs. Similarly, for night when there's glare,  
12 there are no differences between the signs. Also, if we  
13 look at the regulatory signs in fog, there are no  
14 differences here.

15 So again, there are seven places out of the  
16 nine where there are no differences between the two sets of  
17 subjects. We do have differences for the fog for these two  
18 situations, and we're going to take another look at those  
19 now.

20 So, first of all, we're looking at the  
21 recognition distance for guide signs in fog. What you'll  
22 see is that the recognition distances are longer for the  
23 monofocal controls. The monofocals are gray; the test  
24 subjects are yellow. This is the younger group over here.

1 We have the older group, and we have essentially the same  
2 difference between the groups for both of these.

3 Now, it should be noted, however, that the  
4 federal guidelines are that the drivers should have  
5 recognition times of about 1.5 to 3 seconds. Here, when  
6 they were driving in fog, the drivers were going at 35  
7 miles an hour, which is about 51 feet per second, which  
8 means that even in the worst cases here for this group and  
9 this group, the drivers had over 3 seconds in which to  
10 respond to the signs. So, essentially, even though there's  
11 a difference in the recognition distance, the subjects  
12 would have had plenty of time to respond to these signs  
13 anyway.

14 If we look at the other difference -- this is  
15 for warning signs in fog. This time we don't have them  
16 split by ages, we just have the comparison of all drivers.  
17 This time we have 95 feet recognition distance for the  
18 multifocal test subjects, and 112 for the monofocals. In  
19 this case, they would have had approximately 1.9 seconds in  
20 which to respond. So this is again within federal  
21 guidelines. This is a statistically significant difference  
22 that has no particular operational significance.

23 Now, in addition to the main 30 measures of  
24 performance, 18 of which I've showed you, we also ran some

1 post hoc tests that focused on individual signs. The sign  
2 that's illustrated here, which is a loose gravel sign in  
3 fog, proved to be the worst case. For the older subjects,  
4 the sign recognition was 26 percent shorter for the  
5 multifocal subjects -- that's this block here -- when we  
6 compare that with the monofocals.

7 In terms of the federal guidelines, there's no  
8 problem for the group of data over here, for the younger  
9 drivers, or for the monofocals. For the multifocal drivers  
10 here, they would have had about 1.3 seconds to respond if  
11 they'd been traveling at the average speed of 35 miles an  
12 hour. This is slightly less time than is recommended by  
13 the guidelines. However, it is reasonable to assume that  
14 these subjects may have been driving slower than average  
15 and should have had sufficient time to respond to this  
16 sign.

17 Now we're going to look at another post hoc  
18 comparison. This time it shows you a case where the  
19 multifocal test subjects, who are in yellow, had better  
20 scores than the monofocal subjects. There were some cases  
21 where this occurred. Here, the recognition distances are  
22 extremely long, so that there's no problem about  
23 recognizing the signs, although we do show this difference.

24 ~~Now we're going to move back from the post hoc~~

1 tests on individual signs to the last set of main measures  
2 of performance. Now, these are the measures that were  
3 obtained in response to potentially hazardous situations.  
4 One thing I should mention is these situations were  
5 selected deliberately so that some of the potential hazards  
6 would be difficult to detect. As we go from the ball,  
7 through the traffic cone and the suitcase, to the  
8 automobile, they get easier to detect.

9 In spite of this range, what we find is that  
10 there's very little difference between the multifocal and  
11 monofocal. We found no statistically significant  
12 differences for the hazard rate -- that is, the percentage  
13 of times at which they detected the hazard -- and no  
14 difference -- and this one's actually more important.  
15 There's no difference in their ability to avoid hazards.

16 We do find that when we look at hazard  
17 detection distance for one of the cases -- this one's the  
18 suitcase -- that there is a difference between mono and  
19 multifocal, and we're going to take a look at that.  
20 Actually, when we do, we'll look at the ball and the cone  
21 at the same time. Here's the statistically significant  
22 difference for the suitcase. These differences are in the  
23 same direction. They are non-significant.

24 So, what we have are the three cases where the

1 monofocals in fact are performing better than the  
2 multifocals. As I said, although the detection distance is  
3 different here, the important point about this data is that  
4 when it came to avoiding these hazards, there were no  
5 differences between the two groups, even though it was  
6 possible for the monofocals to see them a little sooner.

7 Now, in summary, we can say what we had here  
8 was a high-resolution driving simulation experiment. There  
9 were 26 of 30 cases where there were no statistically  
10 significant differences found between the multifocal test  
11 subjects and the monofocal controls.

12 We did find some differences between these two  
13 groups. However, it's important to point out that, from a  
14 driving safety perspective, these four statistically  
15 significant differences did not translate into operational  
16 significance. There was nothing to indicate that the  
17 multifocal test subjects would drive any less safely than  
18 the monofocal controls.

19 Nonetheless, draft labeling describes the  
20 results and recommends that multifocal patients may need to  
21 exercise caution when driving at night or in poor  
22 visibility conditions. Historically, such caution has been  
23 deemed adequate to address the potential risks of other  
24 ~~medical products, such as antihistamines, which may affect~~

1 driving safety.

2 Dr. Steinert will now continue.

3 DR. STEINERT: Thank you, Dr. Bloomfield.

4 The driving simulation study was an attempt to  
5 bring into the real world these issues of contrast  
6 sensitivity and glare that we are all interested in, and  
7 yet in the clinical lane, when we measure it, we're not  
8 quite sure what it all means.

9 Another way of looking at these issues is in  
10 fact to look at the patients' reporting of optical symptoms  
11 that might be related to night driving and halos, et  
12 cetera. So this slide represents the cohort subjects who  
13 spontaneously reported the observance of night flare and  
14 halo of any severity. At any point in time, the cumulative  
15 rate is 44 percent; the persistent rate of the cohort  
16 patients of one year is 27 percent.

17 There is no control on this. There is no  
18 historical control at all that we're aware of that we could  
19 really use for comparison on this. So we then went to the  
20 subjective questionnaire and asked patients to  
21 differentiate between the multifocal and monofocal eye, and  
22 we looked at the percentage complaints of moderate to  
23 severe halo, glare, and flare, or night vision, comparing  
24 multi to mono.

1           You can see in each of those cases, indeed  
2           there is an increase in each of these complaints, although  
3           it is notable how many of the monofocal patients also will  
4           say that they're having moderate to severe difficulty with  
5           these problems with conventional, currently accepted  
6           monofocal implants.

7           To try to ground us even more in reality, we  
8           then looked at the multifocal cohort subjects who reported  
9           having severe halos at one year. That amounted to 59  
10          patients. Interestingly, of those 59 patients, 33 said  
11          they'd like the implant again, and 46 said they were happy.  
12          So again, how do you ground this in reality? This is just  
13          one of the attempts to do that.

14          Looking at adverse events -- again, these are  
15          the major adverse events from the FDA historical grid. You  
16          see we have none of them in the study, either within the  
17          first year or after one year, up to the date of the PMA  
18          closure in May of 1996, with the exception of secondary  
19          surgical intervention, which runs at about the level of the  
20          grid, with 10 secondary interventions in the first year and  
21          then four more reported up to the point of the PMA closure.

22          Surgical explants are obviously one of the key  
23          measures that you want to look at in this type of a study.

24          ~~Six of the lenses in the core study in fact were implanted,~~

1 for a rate of 1.3 percent. We believe in looking at the  
2 case histories, that four of those, or 0.9 percent, were  
3 related to the multifocal lens itself.

4 Three of the four were for optical symptoms,  
5 such as the night flare, halo, starburst, or a perception  
6 of haze, and one was due to a secondary surgical procedure.  
7 Two, at a rate of 0.4 percent, were unrelated to the  
8 multifocal lens optic itself, but rather appeared to be due  
9 to biometry errors in the A scan and the patient being  
10 unhappy with the endpoint as far as spherical equivalent.  
11 These explant data will be provided in the suggested draft  
12 labeling.

13 In particular, we're interested in the issue on  
14 these secondary interventions of those performing the  
15 posterior pole to see whether there is any impact of the  
16 multifocal optics. There were, in fact, seven  
17 vitreoretinal procedures reported for patients in the core  
18 study who had a multifocal lens, consisting of one repair  
19 with vitrectomy and repair of macular hole, one argon laser  
20 retinopexy, one scleral buckling procedure, one peripheral  
21 cryopexy, one subject having three laser vitreolysis  
22 procedures, one patient having combined vitrectomy and some  
23 form of laser vitreolysis, and one patient having a  
24 ~~vitrectomy with a macular membrane peel.~~

1           Since that time, and since the submission of  
2           the PMA -- as a matter of fact, just several weeks ago --  
3           Allergan first was informed of one additional removal of an  
4           epiretinal membrane in a patient with a multifocal implant.  
5           I'd like to discuss these cases next.

6           There was no difficulty with stereopsis or  
7           visualization of either the posterior pole or the  
8           peripheral retina reported in six of the seven posterior  
9           procedures that I just reviewed. So lasers, peripheral  
10          cryopexies, scleral buckling -- no difficulty reported.

11          However, there was one case of an epiretinal  
12          membrane peeling, the first of the two of these cases,  
13          where the surgeon said that he had difficulty maintaining  
14          stereopsis and experienced occasional diplopia. It was the  
15          opinion of that vitreoretinal surgeon that this was due to  
16          the multifocal optic, and he requested that the multifocal  
17          lens be exchanged, which it was, for a monofocal lens.  
18          That surgery was done uneventfully. The patient then had  
19          completion of the epiretinal membrane peeling.

20          Subsequently, we had this recent case that  
21          actually was done in January, although not reported until  
22          June 23rd. I have been in communication with that surgeon,  
23          and he has subsequently written a report on that. That has  
24          been submitted to FDA. It was his opinion that he could

1 successfully perform the epiretinal membrane peeling  
2 without difficulty. He did feel that he perhaps was  
3 working a little harder to maintain a good focus but that  
4 he could in fact do that. He did not experience diplopia,  
5 and he did not have any difficulty in getting down to the  
6 retina and peeling the membrane attributable to the  
7 implant.

8           Nevertheless, we pursued this further and  
9 created a rabbit model for retinal visualization. Three  
10 vitreoretinal surgeons were asked to perform vitrectomies  
11 and simulated epiretinal membrane peelings on rabbits who  
12 had a multifocal implant in one eye and a monofocal in the  
13 other. The surgeons did not know which eye had which  
14 implant.

15           In all cases, the surgeons were able to perform  
16 the vitrectomies and the simulated maneuvers, which  
17 consisted of things such as putting small fragments of  
18 suture material directly against the retina and then going  
19 in and picking it up without damaging the retina, et  
20 cetera. They were able to perform those through the  
21 multifocal lens without difficulty.

22           But again, they did feel that perhaps there was  
23 a mild difference in visibility between the multifocal and  
24 monofocal lenses. But they did not feel that it affected

1 their adequate view of the retinal structures.

2 I was present at one of these as well, and  
3 looked myself. Although I'm not a vitreoretinal surgeon, I  
4 could not see the difference, nor did I feel it would have  
5 been an issue for me, foraging around in the posterior pole  
6 as an anterior segment surgeon.

7 What does this all mean? Because that's really  
8 what this is all about. What does this mean to the  
9 patients to have a multifocal implant? I'd like to just  
10 show you three summary versions of that. One is from the  
11 subjective patient questionnaires, asking, "Are you  
12 satisfied with your surgery?" The percentage of cohort and  
13 bilateral multifocal patients said that they were  
14 moderately to very satisfied with this surgery. It goes  
15 from 95 percent for the entire cohort to 100 percent of  
16 those having bilateral implantation.

17 If asked, "Would you have the multifocal  
18 implant again?" the number saying yes was 85 percent for  
19 the cohort and 98 percent for those receiving the bilateral  
20 multifocal lens.

21 Finally, from the quality of life substudy done  
22 by Dr. Javit, et al., this is an analysis of patients with  
23 bilateral multifocal compared to bilateral monofocal.

24 ~~First, with no glasses present at all, they were asked to~~

1 rate. Now it's a score of zero to 4, instead of the  
2 earlier zero to 5 I showed you, but zero being not  
3 satisfied and 4 being extremely satisfied. Mean score for  
4 the multifocal patients, overall satisfaction with vision,  
5 was 3.6, compared to 2.9 for the monofocal -- highly  
6 statistically significant.

7           Interestingly, though, when these patients were  
8 then asked, "For those of you who wear glasses, what is it  
9 now like with your glasses?" -- so that the monofocal  
10 patients had both distance and add, if that was what they  
11 had, and the subgroup of the multifocal patients who said  
12 they occasionally use glasses -- these numbers come up.  
13 The monofocal comes up to the multifocal level but does not  
14 pass it. In my opinion, on a clinical basis, that means  
15 that the patients with the multifocal lens do not perceive  
16 that the benefit that they get from the multifocal lens has  
17 cost them, in terms of their overall quality of vision.

18           Now I'd like Dr. Yaross to conclude the  
19 presentation.

20           DR. YAROSS: Thank you, Dr. Steinert.

21           In order to provide physicians with a summary  
22 of the pertinent clinical data, which we've just touched on  
23 in this presentation, we have prepared draft physician  
24 labeling that has a detailed presentation of the potential

1 risks and the potential benefits of this multifocal IOL.  
2 This draft labeling has been provided to the panel in their  
3 reviewer packages.

4 In addition, we have also drafted a patient  
5 brochure. This brochure has been created in order to  
6 provide a basic discussion of cataract surgery, a  
7 comparison of the risks and the benefits of the monofocal  
8 versus the multifocal IOL, and also provides computer  
9 representations of some scenes at near and distance to  
10 permit visualization of the tradeoffs of each of these  
11 modalities for the correction of aphakia.

12 In summary, we believe this clinical study has  
13 presented valid scientific data demonstrating the  
14 effectiveness of the AMO Array Multifocal IOL for the  
15 proposed indications for use. Potential risks have been  
16 identified and are outweighed by the potential benefits in  
17 the vast majority of the indicated population. In  
18 addition, labeling has been drafted to allow patients and  
19 physicians to make informed choices as to which type of IOL  
20 is in the best interests of an individual patient.

21 The AMO Array may represent the most thoroughly  
22 studied intraocular lens to date. We believe it provides a  
23 new option for patients who understand the risks and the  
24 benefits, and for whom it is the lens of choice.

1 Allergan believes this PMA has met the  
2 statutory threshold for a reasonable assurance of safety  
3 and effectiveness, and consequently for PMA approval.

4 We would be happy to answer any questions that  
5 the panel may have at the appropriate time. Thank you very  
6 much.

7 DR. STULTING: We need to have you vacate that  
8 table. We'll have you come back in just a minute. These  
9 are the new rules.

10 DR. EYDELMAN: I would like to thank the  
11 sponsor for providing me with a copy of their presentation  
12 prior to this meeting, allowing me to avoid redundancy in  
13 my presentation. Today I will therefore only highlight  
14 some points for panel consideration and will not present a  
15 comprehensive review of the clinical studies in this PMA.

16 No statistically significant difference was  
17 found between multifocal and monofocal eyes in either  
18 uncorrected or distance-corrected intermediate visual  
19 acuity results. It is important for the surgeons and  
20 patients to be aware that this multifocal IOL does not  
21 improve visual outcomes at intermediate distances.

22 The sponsor proposes that AMO Array Multifocal  
23 Lens be indicated for those patients who desire near vision  
24 ~~without reading add. As you saw in the sponsor's~~

1 presentation, indeed, a significantly larger percentage of  
2 multifocal eyes achieved a visual acuity of J3 or better  
3 than did the monofocal eyes both with and without distance  
4 correction. However, 11.6 percent of subjects who were  
5 able to achieve 20/40 or better with distance correction  
6 did not achieve J3 or better with distance correction at  
7 the one-year visit.

8           Even though the sponsor states that 43 of these  
9 subjects were able to achieve J3 or better at some visit  
10 throughout the study, appreciation of the near focal image  
11 was not a lasting benefit for these subjects. There was no  
12 good explanation provided for these subjects' inability to  
13 appreciate the near focal image.

14           Chronic drop miosis was an exclusion criterion  
15 in this study. Thus, the minimum pupillary size needed to  
16 appreciate any benefit from multifocal was not studied  
17 directly. Considering the multizone design, one can see  
18 that as pupil size decreases, the lens will perform more  
19 like a monofocal. Some subjects with centered lenses and  
20 pupils smaller than 2.5 millimeters may not have enough  
21 near vision areas of their lens exposed to be useful.  
22 Thus, subjects' pupillary size under the usual lighting  
23 conditions must be an integral part of all preoperative  
24 evaluations when considering this lens.

1           Optical visual symptoms most frequently  
2           resulting in moderate and severe difficulty were halos.  
3           Cumulative incidence of halos was 44.3 percent; and  
4           persistent incidence, 26.8.

5           Even though 49 percent of subjects who reported  
6           severe halos were very satisfied, and 32 were moderately  
7           satisfied with their results of this surgery, mean halo  
8           scores were significantly lower for subjects who indicated  
9           that they would elect the multifocal IOL again, compared to  
10          subjects who would not.

11          Based on the subjective assessment, the visual  
12          effect appears to be most noticed by subjects under low  
13          illumination conditions, with driving at night being the  
14          primary activity affected. The most common reason subjects  
15          indicated that they would not receive the multifocal IOL  
16          again was problems with halos at night.

17          Additional risk associated with this IOL is the  
18          reduction of visual acuity under low contrast conditions.  
19          Even though the real-world impact of differences found  
20          between monofocal and multifocal eyes at the low contrast  
21          level may be minimal for some patients, performance of  
22          visual tasks at low contrast levels might be imperative to  
23          others.

24          An adverse event associated with the surgeon's

1 perceived difficulty with performing a macular peel in one  
2 multifocal subject was reported in this PMA and described  
3 in the sponsor's presentation. Animal study consisting of  
4 vitreoretinal surgery performed in rat eyes which had been  
5 implanted with the AMO Array and otherwise comparable  
6 monofocal lenses was performed to evaluate this potential  
7 problem.

8 One of the two surgeons in a substudy reported  
9 that while the views during surgery were equally good for  
10 multifocal and monofocal IOLs, the image quality and depth  
11 of field did not appear as good through their Array IOL as  
12 through the standard silicone IOL.

13 On July 1, FDA became aware of another report  
14 associated with epiretinal membrane peeling procedure. The  
15 surgeon reported that during the surgery, the focus on the  
16 retina shifted and the eye had to be repositioned more  
17 frequently than is usually done.

18 The effect of decentration of multifocal IOL  
19 has more potential visual complications than its monofocal  
20 counterpart. The sponsor reports a total number of  
21 decentration in U.S. study being 10. Two of these  
22 incidences caused adverse events requiring eventual lens  
23 repositioning and IOL exchange due to optical visual  
24 symptoms. Unfortunately, the lower number of total cases

1 of decentration in U.S. clinical study provide us with  
2 little information on effects of decentration of multifocal  
3 IOL. Following wide distribution of this lens, however,  
4 one can predict this to become more of an important issue.

5           Due to the unique design of AMO Array  
6 Multifocal IOL, it is important for the future users of  
7 this lens to be aware that this study did not provide any  
8 data about effects on eyes with vision-limiting pathology.  
9 Inclusion criteria specified that visual potential in  
10 operative eye had to be 20/30 or better. Therefore,  
11 whether there would be any benefit of multifocal optic  
12 appreciated in eyes with vision-limiting pathology is  
13 unknown.

14           Patient selection for this study ensured that  
15 the total postoperative corneal astigmatism did not exceed  
16 1.5 diopters. Unlike its monofocal counterpart, multifocal  
17 IOL could potentially create incapacitating visual  
18 aberrations for the subjects with large astigmatic errors.  
19 This study did not address the efficacy and/or  
20 complications of multifocal IOL in subjects with  
21 significant astigmatism.

22           It is a common clinical practice to aim for  
23 slight myopia when implanting IOL in previously myopic  
24 subjects. It is important for surgeons to be aware that

1 this lens needs to be targeted for emmetropia at distance.

2 In the clinical trial, the majority of both  
3 multifocal and monofocal eyes required +1.75 to +2.5 of add  
4 to achieve the best possible visual acuity. The fact that  
5 the appropriate add power, when required, is expected to be  
6 the same as for monofocal is not intuitive and should be  
7 communicated.

8 Ashley will now discuss the depth of focus and  
9 the driving simulation substudies.

10 MS. BOULWARE: I would like to continue by  
11 discussing the depth of focus and driving simulation  
12 substudies performed by the sponsor. I would also like to  
13 add that my presentation is based on the vision science  
14 reviews performed by Mr. Don Calogero and Dr. Bruce Drum.

15 The initial depth of focus study involved  
16 testing 10 subjects with one multifocal and one monofocal  
17 eye at three different pharmacologically-induced pupil  
18 sizes. Data generated from multifocal eyes with pupil  
19 sizes smaller than 2.5 millimeters resulted in small or no  
20 near peaks, as predicted by an analysis of the lens design.

21 However, the individual curves were both  
22 broader and lower than theoretically predicted. FDA staff  
23 hypothesized that the results may reflect fatigue, chart  
24 memorization, or other factors.

1           At the agency's request, the sponsor tested an  
2 additional 15 multifocal eyes at the naturally-occurring  
3 pupil sizes in an attempt to minimize these artifacts.  
4 While the individual peaks were still broader than  
5 expected, the multifocal eyes with pupil sizes greater than  
6 or equal to 2.5 millimeters achieved an average near peak  
7 of 20/34, closer to theoretical prediction.

8           Looking at both studies, 8 percent of the  
9 multifocal eyes with pupil sizes between 2.5 and 4  
10 millimeters appeared to receive no near benefit from the  
11 lens, confirming the clinical near acuity testing.  
12 Interestingly, of the 25 multifocal eyes tested, 18  
13 achieved J1 or better in the clinical near acuity testing,  
14 but only three demonstrated near peaks of 20/25 or greater  
15 in the depth of focus testing.

16           Turning now to the driving simulation substudy,  
17 it is important to note that the study was designed to  
18 detect a 25 percent difference between the multifocal and  
19 monofocal groups under best-case or clear nighttime  
20 conditions. The sponsor has stated that, for a number of  
21 conditions, no statistically significant differences were  
22 found. However, this may be due to the small sample sizes,  
23 not because large differences were not present.

24           ~~The sponsor has presented separate analyses for~~

1 the numbers of signs correctly identified and for the  
2 recognition distances. However, these analyses may be  
3 misleading. FDA has performed an analysis which eliminates  
4 the situation where more signs were correctly identified by  
5 one group, but at shorter distances.

6 FDA's analysis looks at the situation where one  
7 group correctly identified more signs, and identified them  
8 at greater distances. You can see in this graph that for  
9 all targets, the monofocal group performed significantly  
10 better than the multifocal group. While the sponsor has  
11 reported mean object detection distances that were within  
12 safety guidelines, mean values may also be misleading. In  
13 six of nine hazard trials, on average, 13 percent more  
14 multifocal subjects failed to detect the hazard before they  
15 were closer than 100 feet. At speeds of 30 miles an hour  
16 or greater, a driver would not usually be able to stop  
17 safely within 100 feet.

18 The two previous slides primarily addressed  
19 which group displayed superior overall performance, but not  
20 the magnitude of the differences between the groups. The  
21 sponsor has stated that the differences were statistically  
22 significant under four of the test conditions. The next  
23 two slides illustrate the magnitude of the differences in  
24 two instances where they are statistically significant.

1           For the truck crossing sign, under clear  
2 nighttime conditions, the multifocal drivers failed to  
3 identify the sign in 51 percent of the trials, a 30 percent  
4 higher rate than the monofocal drivers. You can also see  
5 that this higher failure rate occurred at a closer average  
6 recognition distance.

7           This slide depicts the detection rates for the  
8 ball hazard, averaged over all conditions, and for drivers  
9 under 75 years of age. The multifocal drivers failed to  
10 detect the hazard in 57 percent of the trials, an 18  
11 percent higher rate than the monofocal drivers. Again, the  
12 higher failure rate occurred at a closer average detection  
13 distance. It should be noted that these differences  
14 disappear in drivers older than 75.

15           Based on the results of the driving substudy,  
16 the sponsor has included a summary of the findings in the  
17 physician and patient labeling to make multifocal drivers  
18 aware of the differences so that they may attempt to  
19 compensate, for example, by slowing down. Another outcome  
20 of this substudy has been the addition of language to the  
21 labeling which advises patients to exercise caution when  
22 driving at night or in poor visibility conditions.

23           The following are questions the agency would  
24 ask that the panel address in your discussion.

1           First, do you believe the sponsor has  
2 adequately defined and demonstrated an increased depth of  
3 focus as stated in the labeling?

4           Both depth of focus testing and Jaeger near  
5 acuity testing were performed on 25 cohort subjects. While  
6 18 subjects achieved J1 or better in the uncorrected near  
7 acuity testing, only three of these subjects had a near  
8 peak on the depth of focus curve which was greater than or  
9 equal to 20/25. Do you think the sponsor's explanation for  
10 this discrepancy is adequate, and should it be included in  
11 labeling?

12           Do the results of the contrast sensitivity and  
13 glare testing and the reports of optical/visual phenomena  
14 provide reasonable assurance of safety and effectiveness?

15           Do the safety and effectiveness outcomes  
16 support approval for the proposed indications?

17           Do the indications, warnings, and precautions  
18 in the current draft physician and patient labeling  
19 adequately reflect the data and experience from the driving  
20 simulation substudy?

21           Do you feel that the following information  
22 should be communicated to the physician and patient? If  
23 so, in what manner? First, the same degree of near benefit  
24 was not achieved by all patients. The imaging quality and

1 depth of field through the multifocal IOL may potentially  
2 impact vitreoretinal surgery. The clinical study involved  
3 patients with potential visual acuities of 20/30 or better.  
4 No data are available on the performance of the multifocal  
5 lens in patients with lower potential visual acuities  
6 and/or ocular pathologies.

7 An analysis of the lens design predicts that  
8 patients with pupil diameters less than 2.5 millimeters may  
9 have a lesser degree of near benefit. There are no data  
10 available on the performance of the multifocal lens in  
11 patients with final postoperative astigmatism exceeding 1.5  
12 diopters.

13 Finally, limited data are available on subjects  
14 with poor preoperative best spectacle corrected visual  
15 acuity.

16 Is there any additional information you believe  
17 should be included in the physician or patient labeling?

18 Thank you for your attention.

19 DR. STULTING: Can we have the lights up,  
20 please?

21 We have a choice of taking a break now or  
22 taking a break in the middle of discussion. How many of  
23 you folks would like to have it now?

24 (Show of hands.)

1 DR. STULTING: How many would like to have it  
2 later?

3 (Show of hands.)

4 DR. STULTING: Come on, let's have some  
5 consensus.

6 All right. Let's go ahead and have it now.  
7 We'll have you back here in 15 minutes, please.

8 PARTICIPANT: That's too long.

9 PARTICIPANT: Make it shorter.

10 DR. STULTING: Ten minutes, please.

11 (Recess.)

12 DR. STULTING: I'd like to reconvene the  
13 meeting. We'll move into the panel review and discussion  
14 phase.

15 The first presenter will be Dr. McCulley.

16 DR. McCULLEY: I think I'm going to paraphrase  
17 my comments a good deal. I do want to compliment the  
18 company on a job very well done. Your accountability  
19 approaching 90 percent, the manner in which you presented  
20 your data -- it was something that deserves separate  
21 compliment.

22 I'd also like to compliment the FDA reviewers,  
23 Drs. Eydelman, Drum, and Calogero, who provided excellent  
24 reviews that made it much easier for me to review.

1 I'm in pretty much agreement with the things  
2 that have been presented. Most of my comments are going to  
3 relate to issues related to product labeling.

4 I would like to make one comment before I get  
5 into that, and that is that the patient population  
6 presented here, at least as I read it, probably would not  
7 represent the typical HCFA patient population in that 68  
8 percent of the patients preoperatively saw 20/40 or better  
9 at distance and 84 percent J3 or better at near. So that's  
10 a little bit different than what we would normally  
11 encounter in our Medicare age group.

12 One of the issues relates to the pre- and  
13 postoperative astigmatism in that patients were excluded  
14 who had more than a diopter and a half, either pre- or  
15 postoperatively. The product labeling, as I read it, will  
16 put the onus on the physician to ensure that there's not  
17 greater than a diopter and a half of astigmatism. That  
18 will include any astigmatism that might be induced  
19 postoperatively. So I will comment a little bit further on  
20 some product labeling and warnings for physicians as well,  
21 and that we don't have data over a diopter and a half. The  
22 onus, as I read it, is put on the physician to ensure that  
23 there is not more than a diopter and a half.

24 ~~It was interesting that 5 to 11.6 percent of~~

1 patients do not appreciate the bifocality of this lens.  
2 I'm not certain if I read it as 5 percent in one place,  
3 11.6 in the other. I'm not sure which it is, so I would  
4 like a clarification on exactly what percentage of patients  
5 do not appreciate the bifocality of the lens.

6 I think it is important to stress to physicians  
7 that they stress to their patients that this lens does not  
8 lead to a significant increase in intermediate visual  
9 acuity. It is very important to stress to patient and  
10 physician that there is no appreciation of the bifocality  
11 of the lens in pupils that are less than 2.5 diopters. It  
12 is very important for physicians to measure the pupillary  
13 diameter preoperatively to ascertain whether their patients  
14 are apt to get improvement or not.

15 The contrast sensitivity levels that were  
16 demonstrated to be lower under certain conditions I really  
17 don't think are a major problem, at least as I read it as a  
18 clinician. I do think it needs to be stressed to patients  
19 that when driving at night and under low visibility  
20 conditions, they may appreciate a difference, so that they  
21 can make an informed decision prior to surgery as to  
22 whether they want to accept those minimal decreases or  
23 those minimal deficiencies.

24 ~~It should be stressed that 44 percent of the~~

1 patients cumulatively and 27 percent persistently did have  
2 increased problems in driving at night, and that 29 percent  
3 cumulatively and 8 percent persistently -- I'm sorry. That  
4 was the driving at night. The prior number was for halos.  
5 This lead to a 0.7 percent explantation rate. Again, I  
6 think the issues here need to be directed toward informed  
7 consent, both for patient and surgeon.

8           There was only one patient that required  
9 explantation relative to vitreoretinal surgery. I am not  
10 quite certain about this, based on the data that was  
11 presented, as to whether this really is a problem or not.  
12 It doesn't sound like it's an overriding or a major  
13 problem, but, again, something that needs to be stressed  
14 prior to surgery.

15           Decentration may prove to be a bigger problem.  
16 It was 2.5 percent in the U.S. population, 11 in the  
17 international study. This was in a study done by high  
18 volume, presumably highly skilled surgeons in the United  
19 States. I'm not certain that that 2.5 percent decentration  
20 rate will bear out in the normal population of surgeons.  
21 There was at least one patient that had only a millimeter  
22 decentration that led to symptoms sufficient to require  
23 explantation.

24           Decentration is a really big issue here. If

1 this lens is not perfectly centered, not only does one lose  
2 the benefit of the lens, but one potentially has major  
3 problems with the lens. So I think it needs to be stressed  
4 extensively that this lens must be centered either  
5 sulcus/sulcus or bag/bag -- and preferentially bag/bag, of  
6 course -- and that there aren't existing conditions that  
7 the surgeon might anticipate that might lead  
8 postoperatively to decentration of the lens.

9           The emmetropia issue would also seem to be a  
10 big one. If emmetropia is not obtained, then the benefit  
11 of the lens, or many of the benefits of the lens are lost.  
12 Again, this will be stressed or will be in the product  
13 label. The physicians are going to have to understand that  
14 if they don't hit emmetropia, the benefit of the lens is  
15 not going to be achieved, and we don't hit emmetropia 100  
16 percent of the time. So again, this is a warning not only  
17 to patient but to surgeon.

18           I think the distance and near visual acuities  
19 have been talked about enough. I could go into this more.  
20 I think the acuities that are attained with this lens are  
21 acceptable. There are some measurable differences. In one  
22 of the measured differences, it was a 0.33 line difference;  
23 in another it was a 1.5 under dimmer lighting conditions.

24 ~~I think these are all within acceptable range and I won't~~

1 go back through them anymore.

2 I was very surprised. I saw that Roger had 46  
3 percent of monofocal eyes saw J3 or better at near. I had  
4 49. So anyway, somewhere in that 45 to 50 percent of  
5 monofocal lenses seeing J3 at near. That was really quite  
6 a surprise. I'm not quite sure what to say about that.

7 The other remarkable thing that has already  
8 been stated I'm going to restate, and that is that 98  
9 percent of patients with multifocal lenses saw 20/40 at  
10 distance and J3 at near. That really is pretty remarkable,  
11 that with bilaterality the multifocal lens has a  
12 substantially improved visual function over monofocal in  
13 one eye and multifocal in the other.

14 I do have one question, and then I do have  
15 something I'll read briefly. The specific question is, are  
16 there any issues related to doing a YAG capsulotomy with  
17 this lens that the person who's going to be doing the laser  
18 needs to be aware of? There was a 25 percent YAG rate,  
19 which is in an acceptable range. But are there any special  
20 things that we need to know about relative to doing a YAG  
21 and not damaging the lens?

22 Then I do have one paragraph I'm going to read.

23 Multifocal lenses will create a new and much  
24 higher level of expectation on the part of patients. Even

1     though distance visual acuity compares favorably to  
2     monofocal lenses, the higher expectation will exist on the  
3     patient's part above previous levels of expectations not  
4     only with regard to multifocality in near vision, but for  
5     distance vision. We need strong product labeling and  
6     warning for the surgeon because of some of the  
7     characteristics of and expectations with this lens.

8             We've gone from an era of "the doctor knows  
9     best" to one of informed consent. Now we're approaching  
10    one of informed expectations. The concept of caveat emptor  
11    that could be somewhat tied to the era of informed consent  
12    must now include caveat venditor. The implanting physician  
13    must be very aware of the product label and claims, as well  
14    as anticipated outcomes based on data and potential  
15    problems that may arise with this lens that could have gone  
16    unnoticed with monofocal lenses. The surgeon must not only  
17    calculate for emmetropia, but have emmetropia achieved  
18    postoperatively in order to have the patient get full  
19    advantage of this lens.

20            The postoperative astigmatism must not be  
21    greater than 1.5 diopters, including any component that  
22    might have been surgically induced. The lens must be  
23    absolutely centered, not only to get full benefit of the  
24    lens, but to avoid problems with this lens.

1 Patients must be informed that even when  
2 everything is perfect, a percentage will not appreciate the  
3 bifocal characteristics of the lens, and that in such  
4 situations, the decrease in contrast sensitivity and acuity  
5 at low levels of light intensity will still exist.

6 Issues of caveat venditor for the company  
7 should be effectively dealt with in the product labeling.  
8 I would hope that these issues relative to the surgeon will  
9 be aided by a patient brochure that clearly states all  
10 issues and limitations and which the surgeon will be  
11 required to provide to the patient preoperatively.

12 DR. STULTING: Thank you.

13 What I'd like to do, if no one objects, is to  
14 let the other primary reviewers present, and then we'll ask  
15 the sponsor to come up and do a question and answer  
16 session.

17 Dr. Bullimore?

18 DR. BULLIMORE: Thank you, Dr. Chairman.

19 To follow my colleague's example, I'll  
20 paraphrase my own comments. I just quickly want to commend  
21 the sponsor on the level of rigor and accountability that  
22 they've exhibited in this PMA. They're to be commended on  
23 that.

24 ~~As far as the efficacy of the device, the~~

1 presented data suggests that patient satisfaction is good,  
2 and the device appears to achieve what it intended to. In  
3 most patients, supplementary spectacle usage is as might be  
4 predicted.

5           There are some discrepancies in the visual  
6 acuity data. Basically, that found on the patient cohort,  
7 and that what might be expected from theoretic predictions.  
8 This also comes out in the depth of focus data, which are  
9 perhaps more disappointing and less compelling. According  
10 to my interpretations of Figures A8 in the submission, a  
11 clear bifocal effect is observed in three of the 10  
12 patients with small pupils, five of the 10 patients with  
13 medium pupils, and six of the 10 patients with large  
14 pupils. So clearly, there's a great deal between-subject  
15 variability which, as previous speakers have said, should  
16 be reflected in the labeling.

17           As far as safety concerns, I'll speak mainly  
18 about the driving data. Again, I commend the sponsor on  
19 the rigor. I acknowledge that the 66 patients were a  
20 sample of convenience, and of course the visual acuity is a  
21 little better than for the cohort as a whole.

22           I tend to take a fairly pragmatic approach to  
23 the driving data. Overall, I regard the reduction in  
24 performance as typically of the order of 20 to 25 percent

1 when considering response time or distance. This could be  
2 compensated by the patients adjusting their speed by the  
3 appropriate amount. It's therefore disappointing from a  
4 scientific point of view that we're not presented with any  
5 speed data.

6           Getting back to that 20 to 25 percent reduction  
7 in performance, it's interesting that that corresponds to  
8 the one line lost that we see for some of our low contrast  
9 measures. One could argue that that, if you like,  
10 validates the low contrast acuity measures that the FDA has  
11 been asking sponsors to undertake. I think actually the  
12 sponsor is a little conservative about some of their  
13 conclusions. I think the correlations between recognition  
14 distance and contrast testings are actually good. Again  
15 resorting to a pragmatic approach, I don't think getting  
16 bogged down by comparisons of individual conditions, signs,  
17 and comparisons of those give rise to what is particularly  
18 fruitful.

19           So in summary, the sponsor has completed the  
20 appropriate studies in a satisfactory fashion. My general  
21 impression is that the device is safe and effective.

22           Given the generally good preoperative acuities  
23 of the cohort, the generalizability of the results to the  
24 population as a whole must be questioned. This should be

1 addressed in the labeling.

2 Without wanting to question the judgment of the  
3 surgeons and investigators, it should be noted that the  
4 preoperative visual acuities in many cases were actually  
5 better than 20/20. Indeed, looking at Table A5-3, at least  
6 four subjects have visual acuities, preoperative visual  
7 acuities, in the 20/10 to 20/15 range. I think there  
8 should be some clarification whether this device is  
9 intended as a treatment for cataract or presbyopia. This  
10 should be addressed in the labeling, I think.

11 In summary, I would support approval, but there  
12 must be conditions, at least 1 through 9 as listed by Dr.  
13 Eydelman. There should be some comment as proposed by the  
14 sponsor about night driving.

15 Two other remarks I'd like to go on the record  
16 with before I hand over the microphone to my colleague.  
17 First, standardized quality of life instruments should be  
18 used in future studies where appropriate. Instruments such  
19 as the NEI-VFQ and the VF14 have been shown to exhibit good  
20 repeatability and validity. They are appropriate to a  
21 range of diseases, interventions, devices, and procedures.  
22 I suggest that the FDA consider adopting a standardized  
23 quality of life instrument in future trials, so that in 10  
24 years when we do the fourth version of the grid, we can

1 have data among quality of life.

2 Second, for the specification of near visual  
3 acuity, deviation from the Jaeger notation and greater  
4 attention to testing distances is encouraged. I was  
5 confused, as probably some other people in the audience,  
6 when Dr. Steinert -- I apologize for picking on you, sir --  
7 jumped back from J3 to 20/50, and so on and so forth.

8 An observation is, the Jaeger scale doesn't  
9 consist of equal step sizes. Likewise, the use of 20/20 at  
10 near or 20/40 at near assumes a constant test distance. So  
11 therefore, something like the use of an M notation --  
12 which, for those not familiar, is equivalent to the  
13 denominator in the traditional Snellen fraction measured in  
14 meters -- would make the procedure consistent with the  
15 distance visual acuity testing procedures that we now  
16 follow with some rigor. Adopting a notation with which the  
17 investigators are less familiar might even improve the  
18 validity of the data, and avoid some of the paradoxes that  
19 we see between the clinical data and theoretical  
20 predictions and the substudies.

21 DR. STULTING: Dr. Rubin? I'm sorry. Dr.  
22 Bradley is next.

23 DR. BRADLEY: I'll be happy to wait for Dr.  
24 Rubin, but I can go first.

1 I guess I'd be repeating what the previous two  
2 panel members have said, but I was extremely impressed with  
3 the quality and the quantity of the data presented in this  
4 proposal. Trying to get a handle on the safety and  
5 efficacy of multifocal vision is not a simple task. I  
6 think the complexity of the task was reflected in the  
7 complexity of the study that was actually carried out, in  
8 this case by the sponsor. I think their quantity and  
9 quality of data are impressive, and certainly appropriate,  
10 given the nature of the problem that they're dealing with.

11 I have four areas in which I'd like to comment  
12 on. Maybe the simplest one first would be the patient base  
13 for whom this lens is designed. Again, there was a  
14 comment, I think on one of the slides earlier on, that the  
15 patients were those who "desire multifocal vision." It's  
16 hard for me to imagine patients who have never experienced  
17 multifocal vision claiming that they desire it. I think  
18 that's an important thing to think about. Does a patient  
19 come in saying, "Yes, I'd really like to have multifocal  
20 vision"? I mean, is that a patient who desires multifocal  
21 vision? By that definition, I suspect there are no  
22 patients out there for which this lens is appropriate. So  
23 who are the patients you're going to use was the question I  
24 had.

1           That was the patient base. Second, I think  
2 safety is the next issue. I think largely of safety as how  
3 much will distance vision be degraded in order to provide  
4 the increased depth of focus or near vision? I think most  
5 of the data look quite impressive, and it looks as we might  
6 expect, that there is a small reduction in the quality of  
7 distance vision. That small reduction manifests itself in  
8 a lot of things -- visual acuity, contrast sensitivity,  
9 slightly worse performance on the driving test -- but  
10 overall I thought these differences were relatively minor.  
11 That's the main comment on safety.

12           Efficacy. Efficacy I think in terms of how  
13 much near vision does the lens provide? Does it really  
14 provide the patient with what we're essentially claiming it  
15 does? That is, this allows you to see at near. That will  
16 be ideal, I think.

17           There are a number of things that came up with  
18 regard to that. First of all, in trying to decide whether  
19 or not adequate near vision is provided by the lens, the  
20 rule of thumb that was presented here, the J3 at near, it's  
21 nice to have such a simple rule of thumb, but the fact that  
22 whether it was 46 or 49 percent of patients with monofocal  
23 lenses passed that criteria indicates that a stricter  
24 ~~critterion really should have been used, as a rule of thumb,~~

1 because if half the patient base can see perfectly well at  
2 near, by this criterion then obviously bifocal spectacles  
3 would not be very successful, but they are. So it's pretty  
4 clear that that rule of thumb criterion was not an  
5 appropriate choice.

6 Some oddities in the data regarding efficacy.  
7 I was very puzzled when I read the proposal, and also when  
8 I saw the presentation today, when describing the data  
9 obtained with the BAT tester, the statement was made that  
10 at near VA the monofocal VAs were basically equivalent to  
11 the multifocal VAs. That would indicate that no additional  
12 near benefit was provided by the multifocal lens. That was  
13 a bit puzzling. It would be nice to have some answer to  
14 that.

15 Finally, on efficacy, if we look closely at the  
16 data on the through focus data, there are a couple of  
17 things that puzzled me there. The first one, which I think  
18 is the simplest one to address, there was a slide presented  
19 today with a very nice plot. A visual acuity is a function  
20 of lens power, which is a classic through focus visual  
21 acuity plot. We saw a peak acuity at distance, and a  
22 secondary sort of plateau at near, which is exactly what  
23 the lens is designed to do, and what you might expect it to  
24 do.

1           The thing that was different is that on that  
2 slide that was presented, that plateau at near gave acuity  
3 of better than 5 or better than 20/40. Five is the Regan  
4 chart line. I think that's equivalent to 20/40. So it was  
5 providing better than 20/40.

6           Now, the figure that I had originally, which is  
7 Figure V1-16 -- and that's on page V1-273 of the original  
8 proposal -- has a similar shaped curve, but the plateau  
9 occurs at the Regan line score of 4, which I believe is  
10 worse than 20/40. I just wondered what the discrepancy was  
11 there. It would be nice to have a comment on that.

12           The second comment with regard to the through  
13 focus data really is a repeat of what the two previous  
14 panel members have asked you about. That is, when you look  
15 at the individual through focus functions, there are a  
16 considerable number of patients whose through focus data  
17 with the multifocal looks almost identical to the through  
18 focus data with the monofocal. The other panel members  
19 have asked that patients undergoing this surgery and having  
20 this lens implanted should be alerted to the fact that  
21 there is a chance that the lens will not behave as a  
22 multifocal in their eye.

23           I, as a scientist, would be curious to know  
24 why. I wonder if Allergan has some indication of why the

1 lens is not behaving as a multifocal in these eyes, because  
2 it's not a rare occurrence. It seemed to be a relatively  
3 frequent occurrence.

4           So those are the questions regarding efficacy.  
5 Final topic, the brochure and instructions given to the  
6 patient. This I think is a very difficult task for  
7 Allergan, in the sense that we're talking about informed  
8 consent. The question is how do we inform the potential  
9 patient of what they are about to receive in this case? If  
10 they've never experienced multifocal vision, telling them  
11 that their acuity might drop one line, or low contrast  
12 targets might be slightly more difficult to see, or they  
13 might be able to read labels on a medicine bottle at near,  
14 these are the sort of general descriptions that we provide  
15 for other sorts of optical products.

16           But I think with bifocal vision, Allergan  
17 clearly appreciates that those sorts of informed pieces of  
18 information, I guess, for the patients, will be inadequate.  
19 I have to compliment Allergan in coming up with quite a  
20 creative solution to this problem of how to inform the  
21 patient of what they're about to see through this lens.

22           They've come up with a solution which is their  
23 computer modeling, what they call visualizations. There  
24 ~~are some very nice diagrams that they present showing~~

1 examples of what vision will be like with a multifocal  
2 versus what it would be like with a monofocal. I think  
3 this is a very creative and excellent idea.

4 I just wanted to make a couple of comments  
5 about the details of that actual visualization analysis or  
6 procedure you have. The idea of visualization is, in my  
7 opinion with multifocal vision, perhaps the only way that  
8 you can really provide informed consent for this product,  
9 in the sense that how else is the patient going to know  
10 what they're getting into if they've never experienced  
11 multifocal vision? So I think this is a very, very good  
12 idea.

13 However, I think it should be obvious that if  
14 you're going to do a computer simulation of what it will  
15 look like through multifocal optics, the value or the only  
16 way that that simulation can really provide informed  
17 consent for the patient is if the visualization or the  
18 simulation is accurate. There are a couple of things that  
19 make me believe that the simulation, as performed, as  
20 presented to us, has a couple of errors in it. The errors  
21 are fairly easily rectified, I believe. So I believe that  
22 the method will work, but the current approach that is  
23 taken by Allergan is not quite correct.

24 ~~Essentially, the general approach of~~

1 calculating optical transfer function and using these  
2 calculations to compute these multifocal images is the  
3 right way to do it. I think there will be no doubt about  
4 that.

5 A couple of errors. The two errors that I see  
6 in your current method, one may not be that important.  
7 That is that you've seemingly only used the modulation  
8 transfer function as opposed to the complete optical  
9 transfer function. In technical terms, there may be a  
10 phase shift or a position shift that can happen due to the  
11 multifocal optics that might be important. It seems  
12 reasonable to expect that in the simulation.

13 I think much more important, though, you have  
14 effectively -- and I was a bit puzzled by this. I'm still  
15 a bit confused exactly what you did, but somehow you ended  
16 up with your multifocal distance MTFs being superior to the  
17 monofocal distance MTFs. I think everybody would  
18 appreciate that is impossible. I'm getting a questioning  
19 look from over there. Let me just give you the table  
20 reference for that.

21 DR. BULLIMORE: Come back to that.

22 DR. BRADLEY: Yes, I'll come back to the table.  
23 Look here. Multifocal distance MTFs exceed that of  
24 monofocal distance MTFs. It's Table 3-2 on page B-9.

1 That's clearly impossible, and it's due to an error in the  
2 way you calculate these.

3 That error is perpetrated or continued through  
4 to your final analysis of these images. What you end up  
5 doing, effectively, is creating an equal high spatial  
6 frequency content in the multifocal and the monofocal  
7 images, which is a direct result of the earlier error. You  
8 end up with presenting multifocal images as being better  
9 than they really are. I think that's important to rectify  
10 that, but it's easy to rectify, so that's not a problem, I  
11 think.

12 The other thing I personally would like to  
13 see -- and from my own experience with this problem -- is  
14 that the multifocal optics seem to interact with the  
15 optical aberrations of the eye. I think it would be worth  
16 considering including these in your multifocal simulation.  
17 Again, the reason being you're trying to create the most  
18 accurate representation for the patient as possible, in the  
19 sense that you want your patients to be truly providing  
20 informed consent.

21 I think without these simulations, it's going  
22 to be hard for them to do that, so I would encourage you to  
23 work hard to ensure the accuracy of your computer  
24 simulations. I'll finish on that point.

1 I had one point about the driving simulation.  
2 I guess this is a question for Dr. Bloomfield. Is it  
3 possible to get one of those for my son?

4 (Laughter.)

5 DR. BRADLEY: He would really enjoy having one  
6 of those at home.

7 DR. STULTING: Dr. Rubin?

8 DR. RUBIN: In the interest of time, I will try  
9 to extract only the different comments that I have compared  
10 to those that have come before. So I will not spend the  
11 lengthy time I had planned congratulating Allergan on the  
12 very difficult job they did, but move right into the  
13 howevers.

14 (Laughter.)

15 DR. RUBIN: I would like to begin with a  
16 consideration of some weaknesses of the study design that I  
17 think are of consequence and not merely cosmetic. First of  
18 all, the cohort was 99 percent Caucasian, and in one of the  
19 most critical substudies, the multifocal eye/fellow eye  
20 substudy was 81 percent female. I think that it is quite  
21 unfortunate that the study was not better balanced with  
22 respect to gender and race. The sponsor contends that it  
23 is unlikely that there are significant differences  
24 according to these demographic factors. However, it has

1     been shown that African-Americans and Caucasians differ  
2     with respect to glare sensitivity. This may be an issue.  
3     In fact, it may work even in the sponsor's favor.

4             Another issue about the composition of the  
5     cohort, as has been pointed out, the cohort had remarkably  
6     good preoperative vision. For example, depending on where  
7     you looked, 85 percent demonstrating J3 or better near  
8     acuity. On the one hand, this points out the question as  
9     to whether the cohort was representative, but on the other  
10    hand, it points out the utter inappropriateness of the  
11    current standards used for demonstrating effectiveness,  
12    since by the standard of J3 or better near vision, the best  
13    treatment would have been not to remove the cataracts  
14    rather than to have removed them and gotten a lower  
15    percentage in some cases of J3 or better near acuity.

16            Another issue or question that I have that I  
17    think may relate to one of our previous reviewer's  
18    questions about the BAT testing being the same for the  
19    monofocal and the multifocal eye, as I understand it, all  
20    contrast acuity testing was done with spectacle correction  
21    if needed, and therefore, we are unable to determine if  
22    there may have been an interaction between the contrast  
23    sensitivity losses, which we expect, and the defocus that  
24    may have resulted from the multifocal lens design.

1           Finally, the study design was such that there  
2           are no comparisons of the occurrence of visual symptoms, as  
3           far as I could tell, using bilateral monofocal patients  
4           compared to bilateral multifocal patients. Instead, we  
5           must compare the monofocal eye with the multifocal eye  
6           within the cohort. It may be very difficult for patients  
7           to assess symptoms by considering one eye at a time when  
8           the real conditions of importance in daily life are with  
9           both eyes.

10           Moving on to questions of effectiveness, while  
11           it is true that the majority of the participants, the  
12           overwhelming majority, have excellent distance vision and  
13           acceptable near vision, and that many multifocal patients  
14           can function at near without glasses, while few monofocal  
15           patients can, and while it is also true that the average  
16           satisfaction and quality of life are greater in multifocal  
17           patients than monofocal patients, many of the important  
18           issues are obscured by looking solely at average data  
19           comparing averages between groups.

20           We're not interested in what the average  
21           performance is of the group, and whether there's a  
22           statistically significant difference between average  
23           performance. Rather, we are most interested in whether or  
24           not there are significant numbers of patients in one or

1 another group that have an unfortunate or unacceptable  
2 outcome. Looking at the proportions of people, the numbers  
3 of people who, for example, do not achieve the desired  
4 goals would be more illuminating than merely looking at  
5 mean differences. That also applies to the driving study,  
6 as well as the other components of the study.

7           So concentrating then instead on average data,  
8 rather on percentages of people who may fail to achieve  
9 desired goals, we see that, for example, 14 percent of the  
10 multifocal eyes failed to achieve J3 without add. Going  
11 along with this, depending on where exactly you look, 63  
12 percent bilateral multifocal patients use spectacles for  
13 near activities at least some of the time, 40 percent use  
14 spectacles for reading, 19 percent report being unable to  
15 function comfortably at near without spectacles, and 23  
16 percent in the quality of life substudy reported wearing  
17 glasses all or most of the time for near tasks. So some  
18 one-quarter of the patients in the study report wearing  
19 glasses all or most of the time for near tasks.

20           In the issue of safety, contrast acuity and  
21 glare, while we heard that there were very small and  
22 possibly clinically insignificant differences between the  
23 mean contrast sensitivities of the monofocal and multifocal  
24 groups, it is important to note that 15 to 25 percent of

1 multifocal patients lose a clinically significant amount of  
2 contrast sensitivity, or actually contrast acuity, even  
3 with glasses, and that is lose two or more lines. This  
4 occurs even at levels of 25 percent contrast under some  
5 glare conditions, which are not unreasonably low contrast  
6 levels for relating to daily activities.

7           Regarding the driving substudy, I had not  
8 planned to mention very much until some of the data that  
9 were presented earlier this afternoon which raised the  
10 significant question of -- well, sometimes they're called  
11 speed/accuracy tradeoffs. But in this case, they're  
12 distance/accuracy tradeoffs.

13           Because the data were analyzed separately for  
14 the detection recognition percentages and for the  
15 recognition distances, there is a serious possibility,  
16 which I think was illustrated in some of the data presented  
17 by the FDA members, that both a reduction in detection  
18 accuracy and a reduction in detection distance may have  
19 been compounding an effect which, looked at separately, for  
20 either alone, does not seem to be of particular  
21 significance. I think that there needs to be a  
22 multivariate analysis that takes both distance and  
23 detection into account simultaneously.

24           Finally, on the issue of visual symptoms, I

1 think it is again important to point out that there were  
2 significant differences between the multifocal and  
3 monofocal eyes. There are many ways to cut it. The place  
4 that I've chosen to cut it is at those who have reported  
5 severe vision problems, unlike the sponsor who has lumped  
6 together severe and moderate. If we look only at those who  
7 reported severe difficulty, we find that, for example, 11  
8 percent of multifocal eyes reported severe difficulty with  
9 glare versus 1 percent of monofocal eyes. Fifteen percent  
10 of multifocal eyes reported severe difficulty with halos,  
11 versus 6 percent of monofocal eyes. Eight percent of  
12 multifocal eyes reported severe difficulty with blurred  
13 near vision, which is not much different than 6 percent of  
14 monofocal eyes.

15           Given all of these considerations, I think that  
16 there are some changes that need to be made in labeling to  
17 make it clear that, while the device is generally effective  
18 and safe for most patients, there are a significant number  
19 of patients for whom the benefits will not be recognized,  
20 and for whom some safety issues may be raised. I think it  
21 was already mentioned, and I would reiterate, that there  
22 needs to be careful avoidance of any suggestion of benefit  
23 at intermediate working distance. Such suggestions do  
24 ~~currently exist by the way the examples are worded in the~~

1 current labeling. I think that needs to be eliminated.

2 Unless and until the visualization examples can  
3 be determined to be valid, which they have not and there  
4 may be errors with them, and unless they can be extended  
5 not only to the best case, which I believe is what we have  
6 now, but to a cross-sample of representative cases, I don't  
7 think that these visualization examples should be included.  
8 That is, unless they can be validated.

9 I think that there needs to be a clear  
10 indication of the probability that the multifocal benefit  
11 will not be realized. That is, the proportion of people  
12 for whom it will not be realized, and the visual cost of  
13 multifocal optics, in terms of excess severe symptoms of  
14 halo, glare, and the like.

15 DR. STULTING: Thank you.

16 It is 3:50. We need to structure our  
17 discussion from this point onward so we can get finished  
18 with our business and leave at a reasonable time. I  
19 suggest that we ask the sponsors to return to the table,  
20 and we ask them questions, but we restrict those questions  
21 to issues that would impact on our decision to recommend  
22 approval or disapproval.

23 Having heard the four primary reviews, it  
24 sounds to me as if the sentiment at this point is toward

1 approval, but with various conditions. If we're going to  
2 approve this, I think we need to reserve enough time today  
3 to make sure that those conditions are appropriately  
4 discussed. I don't want that to be left at the end without  
5 good discussion.

6 So if there are no objections to that kind of  
7 process, I'd like to move on with it, and open the floor  
8 for questions of the sponsor that are of material interest  
9 in the approval or no approval decision. So the floor is  
10 open.

11 Marian?

12 DR. MACSAI: Marian Macsai. I have a question  
13 for the sponsor. It's not clear to me, some things in this  
14 study. If 83 percent of the patients could see J3  
15 preoperatively, and 19 percent of the patients were unable  
16 to function at near without spectacles, are those 19  
17 percent including the 17 percent who couldn't see J3  
18 before? Or did people who could see J3 before they had  
19 surgery, without anything, without any surgery, end up not  
20 able to see J3 after placement of this multifocal IOL? Do  
21 you understand the question?

22 DR. STEINERT: I need a little clarification.  
23 The people who couldn't see J3 post-op that's not --

24 DR. MACSAI: Without glasses, without glasses.

1 DR. STEINERT: Without glasses, yes. Now, I  
2 don't think we have the data on seeing J3 uncorrected,  
3 except for myopes pre-op. There were no uncorrected pre-op  
4 visual acuity --

5 DR. MACSAI: No, with correction pre-op. I  
6 guess what I want to know is, 83 percent of these people  
7 could see J3 before they had surgery.

8 DR. STEINERT: With correction.

9 DR. MACSAI: With correction. Then they have  
10 surgery, so that they can see J3 without correction. Now,  
11 19 percent are unable to function without correction. So  
12 who are those 19 percent? Were they better off with their  
13 add before surgery or not? Does anyone else understand  
14 this question? Do you get it?

15 DR. STULTING: Do you want us to vote?

16 (Laughter.)

17 DR. MACSAI: Do you get it? What I want to  
18 know is, were the patients better off, because the way I  
19 read this study they weren't.

20 DR. STEINERT: If I could address the bigger  
21 issue, because it concerned all of us about these good  
22 preoperative visions, which I really think is the  
23 underlying question here. We did not anticipate, let me  
24 just say, that it would be so many people who had high

1 contrast acuities as good as they were. The entry criteria  
2 for patients in this study was distance vision worse than  
3 20/40 best corrected, or worse than 20/40 with glare, or  
4 patients who complained about their quality of vision in a  
5 way that was attributable to cataract. As you know, that's  
6 very multifactorial. That obviously opened up this group  
7 of patients.

8           Near vision was not an entry criteria pre-op.  
9 Near vision was not measured uncorrected preoperatively.  
10 There is no patient, other than somebody who picked up a  
11 post-op pathology, but correct me if I'm missing something  
12 here, but I believe no patient, other than the macular  
13 pathology patients, saw better preoperatively with glasses  
14 than postoperatively with glasses. They didn't lose  
15 anything through this, the near vision.

16           DR. MACSAI: They didn't lose anything in the  
17 measurements of near vision, but they may have in contrast  
18 sensitivity and driving function, from what I'm gathering  
19 from this study.

20           DR. YAROSS: If I may, this is Marcia Yaross.  
21 What may help with your question -- I believe you were  
22 talking about the percentage of patients preoperatively  
23 that saw worse than J3 with correction.

24           DR. MACSAI: Yes.

1 DR. YAROSS: In terms of the population -- and  
2 this is in Table 2 of the physician labeling, on page MD-  
3 5 -- with additional add, after surgery in the final data,  
4 that's actually 99 percent that saw J3 or better. So if we  
5 compare with correction pre-op to with correction post-op  
6 with additional add, in the best-case population it was  
7 99.5 percent that saw J3 or better.

8 DR. MACSAI: So it improved from 83 percent to  
9 99 percent?

10 DR. YAROSS: Yes.

11 DR. BRADLEY: When you qualified that with  
12 additional add.

13 DR. YAROSS: That's correct, which is the  
14 apples and apples comparison, I believe.

15 DR. BRADLEY: So with the multifocal, you've  
16 given them the additional add, if needed.

17 DR. YAROSS: If needed. Without that, it was  
18 87.9 percent.

19 DR. BRADLEY: Of course, if you give them the  
20 additional add, you are essentially testing their distance  
21 vision.

22 DR. YAROSS: Right, but what I'm saying is, we  
23 don't have the number right now uncorrected preoperatively  
24 for that comparison.

1 DR. MACSAI: The second question I have for you  
2 is that, though this is called a multifocal Array lens, it  
3 appears to be a bifocal lens, because the intermediate  
4 distances, the monofocal and multifocal did the same. So  
5 really it's like a bifocal, not a multifocal, unless I  
6 misunderstood.

7 DR. STEINERT: This is Roger Steinert again.  
8 We are not claiming that there is an additional incremental  
9 benefit at intermediate distance compared to a monofocal  
10 lens. The difficulty in terminology is that, for example  
11 in spectacles, the word "bifocal" implies a bimodal with a  
12 gap in the middle.

13 There's no gap here. It's not down, up, down.  
14 There's no incremental blur at arm's length and out there  
15 compared to monofocal or compared to anything. It comes  
16 down flat. There's the minimal, and you saw it on the  
17 through focus curve, the minimum slightest hump there, but  
18 there is good retention of functional vision out at arm's  
19 length at intermediate distances. So that is the reason  
20 for choosing the terminology of multifocal instead of  
21 bifocal.

22 DR. BULLIMORE: I'm going to take exception to  
23 that. When we first showed maybe the second slide of your  
24 presentation, you plotted the power distribution across the

1 lens. It's an optical measure. There's not a question of  
2 functionality or patient perception. It's a staircase  
3 function. I mean, it's a step function. It goes from +3.5  
4 to 0, +3.5 to 0. It's a bifocal.

5 DR. STEINERT: Doctor, actually I'm not the  
6 optical expert on this. You are correct that there is more  
7 of the near at the +3.5 intraocular power than there is at  
8 any other place. Absolutely, that's dominant of the near  
9 portion, but the step function is that it wasn't a vertical  
10 slope. It was a slant to that. As you go in the  
11 transition of these ripples, there is some intermediate  
12 range there.

13 DR. TARANTINO: This is Nick Tarantino  
14 speaking. In addition, in the central 2 millimeter portion  
15 of the lens, there is some intermediate as well as distance  
16 in that portion as well, if you recall.

17 DR. BULLIMORE: Would you care for the record  
18 to actually sort of put a figure on that, because certainly  
19 looking at your power profiles, I would guess that it's a  
20 very small fraction of the lens is designed to be  
21 significantly different from either 0 or +350.

22 DR. YAROSS: There are tables in the first part  
23 of Section 6, which I believe is in -- yes, that's not the  
24 exact one. But basically, the amount for intermediate in

1 centered can vary, again depending on pupillary aperture,  
2 from roughly 8 percent -- well, for a centered lens, at 2  
3 millimeter aperture, we're showing about 16 percent of the  
4 light to intermediate; with a 3 millimeter aperture, about  
5 11 percent of the light to intermediate; with a 5  
6 millimeter aperture, 11 percent of the light to  
7 intermediate.

8 DR. BULLIMORE: So to repeat my previous  
9 statement, it's not a third. It doesn't even approach the  
10 third. So you have close to 90 percent of the light being  
11 distributed between the two primary foci.

12 DR. YAROSS: We did try to make sure that the  
13 bulk of the light went -- that the largest percentage  
14 always went to distance, then near. Then intermediate is  
15 30.

16 DR. STULTING: This was a topic for discussion  
17 some years ago. Would one of FDA's staff care to comment  
18 on what the resolution was as far as nomenclature?

19 MS. LOCHNER: If I recall, I think at the time  
20 years ago when this was discussed, there were many sponsors  
21 sponsoring bifocal or multifocal IDEs, some companies were  
22 calling them bifocals, and some companies were calling them  
23 multifocals. The consensus of the panel at the time was  
24 that it did not matter to them whether they were called

1 either.

2 Now, if you can separate that issue of what  
3 they're called with what any potential claims in the  
4 labeling themselves would show -- and I think, as AMO has  
5 said, they're not claiming any intermediate vision -- the  
6 question gets back to the increased depth of focus, but at  
7 the time, we had a discussion about the terminology of  
8 multifocal versus monofocal, with the understanding that  
9 none of the lenses were designed to have enough energy at  
10 the intermediate focal plane.

11 DR. TARANTINO: I can also address the criteria  
12 that was used for the endpoint of intermediate vision. We  
13 had, after looking in the literature, determined that the  
14 typical resolution required is somewhere in the vicinity of  
15 about 20 to 22 minutes of arc is the typical intermediate  
16 target. That's taken from an ANSI document, as well as an  
17 article by Sheddy, which indicated from visual display  
18 terminals.

19 That would relate to somewhere in the vicinity  
20 of about a 20/80 type of image. What we decided is that we  
21 thought that we would go lower to 20/60. About 20/60 is  
22 the intermediate vision requirement that we determined  
23 would allow for intermediate vision. Based on that, we  
24 were able to show that we hit this point, and that's one of

1 the bases that we have for our multifocality.

2 DR. BRADLEY: Just a comment, that if the goal,  
3 by using the name "multifocal," is to avoid using the term  
4 "bifocal," that seems reasonable to me. I guess the  
5 panel's concern, though, is that the patient will be misled  
6 into thinking that there is some special property of this  
7 lens that will bring into focus intermediate distant  
8 objects. Obviously, the lens doesn't have that power, so  
9 that's the problem.

10 DR. MACSAI: Right. It makes it like a  
11 variable addition in bifocal. My concern is that it gives  
12 one the impression that the lens is equal to a variable  
13 addition in bifocal.

14 DR. STULTING: Woody?

15 DR. VAN METER: I agree that it could be  
16 confusing to call this a multifocal lens. We've made a  
17 number of mistakes with bifocal contact lens fitting in the  
18 past. Historically, we've used multifocal and bifocal,  
19 bifocal to mean two, and multifocal to refer to an aspheric  
20 lens that actually does provide a more continuous  
21 transition between distance and intermediate.

22 Mr. Chairman, if I may add a couple of other  
23 comments that concern me, I see three potential problems  
24 with this lens, and I'm not sure if they're safety or

1 efficacy issues. One is, in contact lens fitting over the  
2 last 10 years, success rates under the best of  
3 circumstances, using experienced fitters with contact lens  
4 wearers who have worn contact lenses for a long time and  
5 become presbyopic, have ranged between 60 and about 80  
6 percent in best published series. The 80 percent success  
7 rate usually comes from a segmented lens that can clearly  
8 translate between distance and near. The simultaneous  
9 bifocal lenses tend to achieve a lower success rate, and  
10 actually are among the poorer patient satisfaction  
11 percentages, usually about 60 percent in the best series.

12           What this means is there are about 40 percent  
13 of patients who have been dissatisfied with their  
14 simultaneous bifocal contact lenses and chosen not to wear  
15 them. Usually the reason they quit is because of decreased  
16 near vision. It's often because they think the lack of  
17 near vision is complicated some by the problems with  
18 distance, like driving and glare sensitivity, that we've  
19 seen.

20           So I think the fact that potentially it's  
21 easier to take out a bifocal lens than it is a lens  
22 implant, and this is a serious problem in my thinking, that  
23 we're going to subject patients to something that they  
24 can't easily get rid of if they don't like it.

1           A second point is the driving simulation  
2 studies. You would expect some of the most sensitive tests  
3 to more clearly show a difference between these two lenses  
4 than tests that might not be sensitive. For example, there  
5 was a statistically significant difference demonstrated on  
6 a clear night in recognition time of objects on the road,  
7 and on sign recognition. The sign recognition was  
8 statistically significant in cases of fog, and fog is where  
9 you lose contrast. The third one is detection distance of  
10 objects on the road. I believe that all three of these  
11 would suggest that there's a potential driving problem for  
12 elderly patients that have these lenses implanted.

13           The third issue that I have is there are some  
14 things out of the surgeon's control, complications that are  
15 going to happen even though you try to avoid them, such as  
16 lens decentration, erroneous power calculations,  
17 postoperative astigmatism that might exceed 1.5 diopters,  
18 and a small pupil size, that have to be included into the  
19 overall evaluation of this lens. This is discounting the  
20 fact that retinal procedures will be more difficult,  
21 diabetic lasering will be more difficult, and there's a  
22 potential loss of near vision that many patients are going  
23 to experience.

24           ~~Perhaps these problems can be overcome in the~~

1 informed consent, but I think it's difficult for us to say  
2 that this lens does it all, when you can get many of the  
3 same effects by undercorrecting a monofocal intraocular  
4 lens implant by a half or three-quarters of a diopter, and  
5 patients will still have acceptable vision at distance and  
6 at near.

7 DR. STULTING: Other comments or questions?

8 Dr. Ferris?

9 DR. FERRIS: I have a comment about this issue  
10 of multifocal versus bifocal, because I think I agree with  
11 Mark. As I looked at what was presented, it looks like  
12 you're attempting to get essentially bifocal, and you've  
13 done a good job of providing some intermediate vision.

14 But Arthur said earlier that patients don't  
15 come to him and say they want multifocal vision. Slightly  
16 revised, I think all the patients I see over age 45 or 50  
17 say, "I want multifocal vision." What they mean by  
18 multifocal vision is, "I want my vision to be the way it  
19 used to be."

20 The problem I have, I guess coming from an area  
21 where there are a lot of implied claims -- ocuvites, eye  
22 caps, Nutrivision, Eye Guard, and so on -- the multifocal  
23 sounds like an implied claim. I think it's very important  
24 that we proceed down the path of investigating new ways and

1 developing new ways to provide both distance and near  
2 vision. We're never going to do it if we don't approve  
3 products. I just am worried, as Dr. McCulley said, that we  
4 don't oversell it. In our zeal to sell the product, that  
5 we don't oversell it. So that's the caveat.

6 DR. McCULLEY: Actually, to come up with my  
7 little Latin phrase, I had to call three different  
8 attorneys before I got an answer. Everyone knows caveat  
9 emptor.

10 PARTICIPANT: That's expensive.

11 (Laughter.)

12 DR. McCULLEY: They were friends. Maybe that's  
13 why it took so long.

14 Caveat emptor is buyer beware, but caveat  
15 venditor is seller beware. I am very much in favor of  
16 approval of this lens, but I think that things have to be  
17 made very clear, by the company, to the physician. I'm  
18 concerned about the physician in this situation not fully  
19 understanding what is implied with this lens. The things  
20 that Woody stated are the same things I stated, pupillary  
21 size, astigmatism, centration, emmetropia being hit, and so  
22 on. The physician must be very informed himself about what  
23 he or she then is going to then be informing the patient  
24 about. I think that this can be dealt with, but I think it

1 has to be dealt with very explicitly, and not left to  
2 chance.

3 DR. YAROSS: If I may comment, Mr. Chairman, we  
4 certainly agree that the physicians and patients need to be  
5 well informed. We've been working with FDA, and will  
6 continue to work with FDA, to try and come up with the  
7 best, most balanced presentation to achieve that end.

8 DR. STULTING: Dr. Sugar?

9 DR. SUGAR: In this same regard, it seems from  
10 the patient cohort preoperatively that the surgery was done  
11 prophylactically to prevent them from getting cataracts.  
12 My concern is that this lens, with the implication of its  
13 multifocality, will lower the threshold for surgery because  
14 physicians who, even if you write it out, and patients may  
15 request -- that the physician may feel, and the patient may  
16 expect, that somehow you're going to make it like it used  
17 to be, like Rick Ferris said. That's a serious concern,  
18 and I don't know how any wordings can avoid that. I don't  
19 think that that should be reason not to approve the lens,  
20 but it's a concern.

21 Spencer Thornton this morning said that this  
22 would save money for the government, which is not our task  
23 to decide here. I suspect that it won't. A significant  
24 proportion, 43 percent of the patients, still wore glasses

1 a significant portion of the time, and more patients maybe  
2 will have surgery because of this.

3 That aside, the question was asked about YAG  
4 lasers, non-sequitur. What about YAG lasers doing this?  
5 Can you focus the laser between zones? Do you get pitting?  
6 Do you have difficulty maintaining your focus with the  
7 laser?

8 DR. STEINERT: This is Roger Steinert. To  
9 answer the YAG laser question, Joel -- and I was going to  
10 talk to Jim after --

11 DR. McCULLEY: I assume you don't want to  
12 address the other one.

13 DR. STEINERT: No, I can say anything you want.

14 (Laughter.)

15 DR. STEINERT: But I thought that was the  
16 directed question. There were no reports of the clinicians  
17 who did YAG posterior capsulotomy of any lens damage, to  
18 their extent of deciding what that meant. The technique is  
19 identical. There is no modification. There is no  
20 interference that anyone has perceived from the variable  
21 focus in terms of focusing the YAG.

22 I personally have done only one YAG laser on a  
23 patient with an implanted Array lens, but found no effect  
24 at all in doing that patient.

1 DR. MACSAI: Marian Macsai. Roger, is there a  
2 minimal size YAG opening that's required to achieve the  
3 benefits of this lens? Has that been looked at?

4 DR. STEINERT: Well, it hasn't been examined in  
5 a rigorous way, Marian, but I think that it is fair to say  
6 that you presumably would want to do what you presumably do  
7 now, which is to make the opening the size of the pupil, as  
8 long as it's not outrageously big, because otherwise you're  
9 going to be denying some of the more peripheral optics. If  
10 you restrict it, and you made a 1.5 millimeter opening, it  
11 will be purely the center area, for example.

12 DR. MACSAI: I guess what I'm asking is, do you  
13 need to dilate these patients before you do a YAG so that  
14 you get the opening bigger than the pupil, so you can get  
15 the effect, or no?

16 DR. STEINERT: I don't think you have to alter  
17 your technique at all. If you're used to doing them  
18 undilated, unless it's a particularly small pupil for some  
19 reason, no, you would not have to.

20 DR. STULTING: Go ahead.

21 DR. BULLIMORE: I would actually like to get  
22 some input from the sponsor on the question of is this a  
23 treatment for presbyopia? It's been raised by myself, and  
24 now Dr. Sugar. Are we going to see patients with 20/15 and

1 20/10 acuities being operated on at the age of 50 just to  
2 cure their presbyopia? Or is there going to be specific  
3 labeling to cover the issues for cataract surgery only?

4 DR. YAROSS: The indications for use that we've  
5 proposed are a modification of standard class indications  
6 for use that were in fact discussed this morning. It's for  
7 subjects for the visual correction of aphakia, and subjects  
8 60 years of age and older, in whom a cataractous lens has  
9 been removed, plus. Then the plus is in terms of those  
10 additional benefits that we believe will be achieved, but  
11 certainly our indications are for the same cataractous  
12 population that is currently addressed by monofocal lens  
13 indications.

14 DR. BULLIMORE: I have one other sort of  
15 safety-related question. There was a news item maybe three  
16 weeks ago. The NTSB, National Transportation Safety Board,  
17 attributed a Delta incident, an accident with one of their  
18 aircrafts last year, to a pilot inappropriately wearing the  
19 monovision contact lenses. I wonder whether there is any  
20 regulations on the statute at the moment that would relate  
21 to the prescribing of this lens in a pilot, truck driver,  
22 or similar person.

23 Dr. Rosenthal, are you aware of any?

24 DR. ROSENTHAL: I am not.

1 DR. BULLIMORE: Is that something we should  
2 consider, at least, adding to the labeling? Are there any  
3 professions you want to discourage?

4 DR. MACSAI: I think that raises a significant  
5 safety issue, not a labeling issue.

6 DR. STULTING: There is already a line in the  
7 labeling that addresses people who have to have excellent  
8 visual acuity for their tasks.

9 DR. MACSAI: No, but if what you're saying is  
10 that with this lens you're unable to safely drive, operate  
11 an airplane, drive a truck, that's a safety issue. That's  
12 not a labeling issue. You can't control when the fog sets  
13 in, and you can't control when it starts to rain.

14 DR. RUIZ: But they have criteria that they  
15 check them for in order to qualify to be a pilot or a truck  
16 driver and so on. If they pass it, they pass it.

17 DR. BULLIMORE: That was not where I was going.  
18 Are we satisfied that there are adequate statutes within,  
19 say, the FAA, et cetera, that would cover this eventuality?

20 DR. MACSAI: Well, I'm not talking about just  
21 the FAA. I'm talking about a car. After you have cataract  
22 surgery, you don't have to retake your driver's license  
23 test.

24 ~~DR. STULTING: Well, I think it's appropriate~~

1 for us to ask whether or not people can drive safely with  
2 this.

3 DR. MACSAI: Right. That's what I'm asking.

4 DR. STULTING: If that's a concern, then we  
5 need to discuss it.

6 Along those lines, one of the questions that  
7 rose in my mind as I reviewed this, and have listened to  
8 the discussion today, is you can drive legally in Florida  
9 if you have 20/70 vision in one eye. I didn't see any  
10 comparison in here about what happens to your performance  
11 on the simulator if you have a normal eye, but your visual  
12 acuity is only 20/60, or 20/60 in one eye. I also didn't  
13 see any data about what happens to normal people at the age  
14 ranges, except for the fact that you don't see so much  
15 difference between the lenses as you grow older.

16 My suspicion is that age effects and reduced  
17 vision effects that are still within the realm of legal  
18 driving in most states will cause effects that are at least  
19 as big as what we saw between multifocal and monofocal. Do  
20 you have that data or have you seen it?

21 DR. YAROSS: I think regarding the question of  
22 different acuity levels, we had a minimum acuity required  
23 for inclusion in the driving substudy. So we can't  
24 directly address that question.

1 DR. STULTING: Just as a general comment, if  
2 you had an opportunity to do this again, I would suggest  
3 putting a few people in there who were 80 years old, but  
4 still had 20/20 vision, and a few people who were 40 or 50  
5 years old, but had 20/60 best corrected, and run them on  
6 the simulator so that we could understand where those bars  
7 would fall under those circumstances, because those are  
8 people that are already out on the roads with us and are  
9 driving legally.

10 PARTICIPANT: Do you want that in the grid as  
11 well?

12 DR. STULTING: This should be on the grid.

13 Other questions? Don?

14 DR. CALOGERO: I can potentially address that a  
15 little.

16 DR. STULTING: Great.

17 DR. CALOGERO: I tried to do an analysis, and I  
18 looked at their data, and I took a subgroup of the ones  
19 with the worst VAs, and compared them to the group with the  
20 best VAs, something like 20/10s versus 20/30s. There's no  
21 predictive value. In a lot of cases, the ones with the  
22 best VAs were performing worst in terms of these night  
23 tasks.

24 ~~Then we have the experience from the European~~

1 literature, in terms of we've got the German driving  
2 experience. In the German driving experience in Germany,  
3 the licensing requirements, especially for certain  
4 occupations, are very severe. They do fields. They do low  
5 contrast acuities. The multifocal subjects in Germany are  
6 failing the licensing testing at a rate of about 15 percent  
7 higher than the monofocal subjects.

8 Then additionally, from the literature in  
9 Europe, we find that the best performers are actually the  
10 subjects that still have their crystalline lens. They  
11 outperform the ones with even the monofocal lens, and then  
12 the multifocal are, of course, below that.

13 Those are my comments.

14 DR. STULTING: That's interesting. In Germany,  
15 you don't have quite as much time to avoid the --

16 (Laughter.)

17 DR. STULTING: -- road hazards. I can vouch  
18 for that.

19 Karen?

20 DR. BANDEEN-ROCHE: Karen Bandeen-Roche. Just  
21 following up on the driving issue, I am very concerned  
22 about how to communicate to patients what their  
23 expectations about driving can be. This includes not only  
24 task by task for the performance, but some valid way of

1 considering the data as a whole, both in terms of the  
2 tradeoff between distance and correctness, and also across  
3 tasks. In particular, what is a realistic, reasonable risk  
4 that a person will end up essentially so impaired that they  
5 will have difficulty driving?

6 So the two parts of that question is do you  
7 have any analysis to address that issue? Secondly, I think  
8 we do need to think about how to communicate that to  
9 patients fairly in a brochure.

10 DR. YAROSS: In terms of difficulty driving at  
11 night, there was subject perception of difficulty driving  
12 at night in the quality of life data. We can pull that  
13 data if that's what you're interested in.

14 I'm not quite sure --

15 DR. BANDEEN-ROCHE: That's really from the  
16 simulation. So in other words, on a most simple level,  
17 what would be the proportion of patients who fail enough  
18 signs that they would be a hazard on the road, at some  
19 reasonable tradeoff between distance and correctness?  
20 That's just a simple example.

21 I think ultimately analysis needs to go well  
22 beyond that. Even if the task-by-task comparisons are not  
23 very large, if there is 20 percent of these patients who  
24 fail a whole lot of things, that's being masked because

1 we're looking at everything task by task, then that's a  
2 concern.

3 DR. YAROSS: Well, again, by design some of the  
4 tasks were intended to be difficult enough that some would  
5 fail, because you need that to have the resolution to pick  
6 up differences. So again, it's hard for us to set the  
7 arbitrary criteria, other than the types of conclusions  
8 we've drawn, which is that where differences have been  
9 found, as Dr. Bloomfield pointed out, in most of the cases  
10 they do appear to be within the range of safe driving.

11 We do agree that both physicians and potential  
12 patients need to be informed about these differences, and  
13 that subjects should be cautioned to exercise due care in  
14 driving, and be aware of the fact that they may have more  
15 difficulty in recognizing traffic signs, particularly in  
16 poor light or poor visibility conditions.

17 DR. RUBIN: This is Gary Rubin. I think that  
18 the comment that the data demonstrate that while there are  
19 differences in the driving situation, that most of these  
20 differences are well within what is operationally  
21 significant, is a misleading statement, because there are a  
22 proportion of individuals for whom that is not true.

23 What we need to know is what are the proportion  
24 of individuals who are operating outside of operational

1 safety in the multifocal group and the monofocal group? If  
2 it's a significantly higher number of people -- not just  
3 average difference in detection ratios, but if there's a  
4 significantly higher number of people who would fail,  
5 according to some criteria, then that becomes a safety  
6 issue.

7 DR. YAROSS: I think where we attempted to look  
8 at that was in the collision rates. There was no  
9 significant difference found in the collision rates. That  
10 is one place where we did attempt to analyze that, because  
11 that's clearly a significant measure.

12 DR. RUBIN: But if I recall correctly, for some  
13 of the avoidance tasks, 50 percent of the people didn't  
14 detect the obstacles. Is that correct?

15 DR. BLOOMFIELD: It's probably worth saying,  
16 though, we were selecting things that were difficult to  
17 see. Now, these include some hazards like a traffic cone  
18 and a ball where, if you don't see them, it's sort of a  
19 nuisance if you actually hit them. But when we go to  
20 hazards that are in fact rather dangerous, they tend to be  
21 more noticeable. They're things like the car that pulls  
22 onto the road, and then weaves out to the left. That's an  
23 object where it becomes very serious if you don't see that  
24 one.

1           So actually, what's very difficult to do is to  
2 talk about which of the things that you should require  
3 people to do, because, for example, if there are things  
4 like the ball, and they fail to detect it at night, it's  
5 true it's a hazard, and they may be upset if they bump into  
6 it, but it probably doesn't matter at all. So from the  
7 point of view of danger, we have to look very carefully at  
8 which of these things we can include in that criteria.

9           DR. MACSAI: There are two different issues,  
10 though, from what you've said. One is the danger to the  
11 driver of suffering harm by impacting on a large object  
12 with a collision. But the other is the danger to the  
13 object with which they collide. For example, a person or a  
14 small child in the road, they're not going to be as big as  
15 a car. They may not be seen in time to be avoided. Since  
16 we are charged with protecting public safety, this sounds  
17 like a safety issue.

18           DR. BLOOMFIELD: I think this is a safety  
19 issue, but it's a safety issue for everybody driving in low  
20 light level at night. It's not specifically to people who  
21 have had this kind of surgery. There is a danger for  
22 anybody who is driving in these particular situations,  
23 whether they're patients in this study or not, in hitting  
24 things like this ball. I don't think this is something

1 that distinguishes between -- this doesn't seem to be to be  
2 an appropriate comparison to make here, with things like  
3 the ball.

4 DR. MACSAI: Then I guess I need more  
5 clarification, because if your 15 percent of multifocal IOL  
6 patients are not passing their driver's tests, and 94  
7 multifocal patients hit or can't avoid a ball, versus 120  
8 mono -- I mean, the feet, the distance was 94 for  
9 multifocal versus 120 for monofocal --

10 DR. BLOOMFIELD: This is a difference in  
11 detection, but not in avoidance.

12 DR. MACSAI: You need to detect before you can  
13 avoid.

14 DR. BLOOMFIELD: That's right, but we found  
15 that there were significant differences in detection  
16 distance, but not in avoidance behavior. If you look at  
17 the last column there, there's no difference in the ability  
18 to avoid the hazards.

19 DR. STEINERT: This is Roger Steinert. If I  
20 could just hopefully not muddy things further, but maybe  
21 even help a little, from a clinical point of view, we  
22 struggle with this all the time. The problem is what  
23 you've bumped into. You're totally correct. We are now  
24 beyond the frontier, because no one knows.

1           Anybody who practices medicine, or anybody who  
2 studies this scientifically, knows full well that 20/40  
3 high contrast vision in Massachusetts, or 20/70 in Florida,  
4 is an inadequate test of somebody's visual ability to  
5 drive. There is no test whatsoever of any of the other  
6 critical functions, like decisionmaking and reflexes, and  
7 motor strength, and mentation, as you just indicated,  
8 Marian.

9           It would be wonderful to have some kind of a  
10 simulation that was the equivalent of what jet pilots have  
11 to do to get back in the saddle again, but we're way over  
12 the edge of what we know. We have no standards whatsoever.  
13 In the European study that was just referenced, we don't  
14 know how many other variables are going on, including which  
15 multifocal lens did they have? What are the pathologies  
16 present? We've just got unanswerable things that are  
17 beyond where we are in July, 1997.

18           DR. FERRIS: Excuse me, Mr. Chairman?

19           DR. STULTING: Yes?

20           DR. FERRIS: It strikes me that we can't get  
21 past this, other than it's a concern. It seems to me  
22 obvious by your presentations that the people with the  
23 multifocal lens overall did a little bit worse than the  
24 ~~people with the monofocal lens. That doesn't say how they~~

1 would have done compared to when they had cataracts in  
2 their eyes and they were still driving around, or how much  
3 testosterone was running around in teenagers. I mean,  
4 there are all these other factors, as everybody has alluded  
5 to.

6 I don't see how you can do more than just warn  
7 the physicians and the patients that, if you have this kind  
8 of lens in your eye, you're going to have to be a little  
9 bit more careful than you would be otherwise. We can't  
10 tell them they can't drive, or that they can't have this  
11 lens because of that, because by all the tests that have  
12 been done, they seem to be able to avoid these objects.  
13 They don't see them quite as quickly, but they can avoid  
14 them. If they slowed down, they would be able to avoid  
15 them.

16 DR. STULTING: Look, I want to focus this a  
17 little bit. We've used up 40 of our minutes. Now, I want  
18 to try to get finished by 5 o'clock.

19 Let's talk about issues that would impact on  
20 the approval/disapproval process. What I'm hearing now is  
21 recurrent and repeated expressions of concern about one  
22 thing or another. If you have concerns, just figure out  
23 whether they are things that can be addressed in the  
24 labeling or not. If you think they are things that can be

1 addressed in the labeling, then we'll address them later.

2 Dr. Soni?

3 MS. THORNTON: Excuse me. Doyle, is this the  
4 end of the questioning of the sponsor period?

5 DR. STULTING: I don't think so. Do people  
6 have other questions that they would like to address?

7 DR. VAN METER: Mr. Chairman, before we get off  
8 of the question, could I just ask for clarification?  
9 Earlier I was trying to make the point that some of the  
10 driving simulation tests were more sensitive than others.  
11 Am I correct in assuming that, for instance, recognition  
12 time on a clear night is a fairly sensitive issue that  
13 might accurately discern a difference between monofocal and  
14 multifocal lenses? The second difference was sign  
15 recognition in fog. The third difference where you found  
16 the significant difference was in detection distance.  
17 Would not, for instance, detection distance be much more  
18 sensitive than avoidance behavior?

19 DR. STULTING: Is this something that would  
20 reflect on whether you would approve or disapprove?

21 DR. VAN METER: It's just a yes or no question.

22 (Laughter.)

23 DR. STULTING: That wasn't what I asked, but at  
24 ~~the risk of continuing, can you say yes or no?~~

1 DR. BLOOMFIELD: When they're driving in fog,  
2 this is a more difficult task. You might expect that to be  
3 more sensitive. We didn't necessarily find that the harder  
4 tasks were more sensitive. That is what we might have  
5 expected. That didn't happen.

6 DR. STULTING: Sarita, you had your hand up a  
7 little bit. Go ahead.

8 DR. SONI: Moving off to another topic, since  
9 pupil size and decentration of the lens is important,  
10 wouldn't it make more sense to put it as a number 12  
11 precaution, rather than burying it in your clinical data?  
12 This is going to labeling. You have, under labeling, under  
13 "Precautions," you have 12 items listed. Pupil size seems  
14 to be a real important issue. If you want to address it  
15 and make sure that people, physicians and patients, see  
16 that, then I think it would be more appropriate to put it  
17 under precautions.

18 DR. STULTING: Any other pertinent comments?  
19 Yes, Dr. Bradley?

20 DR. BRADLEY: Perhaps to reiterate what Dr.  
21 Rubin said earlier, one of the problems we're having with  
22 the data is that we're seeing, for example with the  
23 driving, that mean performance is a bit lower. The  
24 question keeps coming up, well, do we have a safety issue

1 here? It's very difficult for us to judge that. There are  
2 two things that you might be able to do which would allow  
3 us to evaluate whether or not there is a safety issue.  
4 Both have been suggested.

5 First of all, convert the mean data to what  
6 proportion of people's performance falls below some  
7 criteria that will give us an idea of that proportion of  
8 the patients who have multifocals who are going to suffer  
9 potential hazard. I think that's a very good idea.

10 But the question is what standard do we adopt?  
11 The suggestion has been made by Dr. Stulting that we have  
12 some out there that we could use, or you could use. There  
13 are people driving around who are 80 years old that have  
14 20/20 acuity, and those who are 40 years old that have  
15 20/60 acuity.

16 If these people are allowed to drive, then  
17 presumably if your subjects with the multifocal perform  
18 better than people who are already driving, then you could  
19 argue that in fact, if there is a hazard here, it is small  
20 enough to allow these people to drive. That might allow us  
21 as a panel to be able to say, yes, the hazard or the risk  
22 here is sufficiently small.

23 DR. STEINERT: This is Roger Steinert. Dr.  
24 Bloomfield just told me, those patients have never been

1 tested. No one knows the answer.

2 DR. BRADLEY: Scary.

3 DR. STULTING: Any other questions?

4 DR. RUIZ: Let me just ask, I assume some of  
5 the patients who had the monofocal lenses underperformed  
6 some of the patients who had the multifocal lenses.

7 DR. YAROSS: Absolutely.

8 DR. RUBIN: But that's not the issue. The  
9 issue is the percentage of people who have multifocal  
10 lenses. We have distributions.

11 DR. RUIZ: They gave us the percentage.

12 DR. RUBIN: That was only for the avoidance.  
13 We could take the driving distance. You  
14 proposed what is a reasonable -- or what was it? -- the  
15 reasonable distance to be able to stop or something like  
16 that?

17 DR. BLOOMFIELD: It's not the reasonable  
18 distance to stop. It's the time required to react.

19 DR. RUBIN: Right. You could compute that for  
20 each subject under each condition from your data.

21 DR. BLOOMFIELD: You can do that based on the  
22 speed they traveled at, and the distance at which they saw  
23 whatever it was. That's true.

24 ~~DR. STULTING: Does anybody else have comments~~

1 or questions?

2 (No response.)

3 DR. STULTING: Okay. I'm going to let the  
4 sponsor leave the table if there are no other questions for  
5 the sponsor, and I'm not going to let them come back.

6 (Laughter.)

7 DR. STULTING: Is that clear? So we're  
8 finished with the sponsor, right? Last chance.

9 You all can leave. Thank you.

10 We have this list of questions that we have to  
11 somehow get into the record. What I'm going to do is take  
12 them out of order, so that they don't interfere with  
13 ordinary thought patterns and science, and the way we ought  
14 to do business.

15 Let's look at number 4 first. You have these  
16 in your packets, so please pull them out. It's P960028.  
17 Let's look first at number 4.

18 The question is, "Do the safety and  
19 effectiveness outcomes support approval for the proposed  
20 indications?" I would add to that, for understanding that  
21 if you vote yes, that means that there are some  
22 circumstances under which you think it should be approved.  
23 That may be a conditional approval, where you have labeling  
24 requirements, et cetera, et cetera.

1                   Recall, as well, Ms. Thornton's reading this  
2 morning of what an approval vote means and what a  
3 disapproval vote means, as you say yes or no to this. So  
4 it can be approved with conditions, is what I'm saying.

5                   Is there anybody who is unclear about what  
6 we're supposed to do? We're supposed to answer this  
7 question. Those who believe the answer to question number  
8 4 is yes, please raise your hands, of those that are  
9 legally voters.

10                   (Show of hands.)

11                   DR. STULTING: I count six yes.

12                   Those who believe the answer to question number  
13 4 is no, please raise your hands.

14                   (Show of hands.)

15                   DR. STULTING: Three. It was six yes, and  
16 three no, by my count. Who abstained?

17                   (Show of hands.)

18                   DR. STULTING: That's one. We're still one  
19 person short.

20                   DR. RUIZ: I didn't vote.

21                   DR. STULTING: Everybody who thinks they can  
22 vote, put your hands up.

23                   (Laughter.)

24                   (Show of hands.)

1 DR. STULTING: That's 11.

2 Now, of those who just had their hands up,  
3 those who believe the answer to question 4 is yes, please  
4 put your hand up once again.

5 (Show of hands.)

6 DR. STULTING: Eight. Now we have eight yes.

7 (Laughter.)

8 DR. STULTING: We'd better stay away from the  
9 driving simulator.

10 (Laughter.)

11 DR. STULTING: Those who believe the answer to  
12 question 4 is no, please raise your hands.

13 (Show of hands.)

14 DR. STULTING: That's three. Okay. We have  
15 eight yes, and three no.

16 Is it appropriate for us to take that as a  
17 recommendation for approval? Do we now have to have a  
18 formal motion?

19 MS. THORNTON: You have to have a motion.

20 DR. STULTING: The Chair would entertain a  
21 motion that we recommend this PMA for approval.

22 DR. McCULLEY: So moved.

23 DR. STULTING: Could I have a second?

24 DR. RUBIN: Second.

1 DR. STULTING: I understand that this sounds  
2 like the same question, and I believe it's the same  
3 question, too, but we have to have the record reflect it  
4 differently.

5 DR. SUGAR: Does this preclude approval with  
6 conditions?

7 DR. STULTING: No. What I'd like to do to make  
8 it real clear for the record what we're approving and what  
9 the conditions are is first to approve it, and then add one  
10 at a time the conditions, so we state them very clearly for  
11 the agency and for the record.

12 MS. THORNTON: As amendments to the motion.

13 DR. STULTING: Well, by parliamentary  
14 procedure, you can't do that.

15 DR. SUGAR: You can't approve the motion and  
16 then amend it. You have to amend it before you approve it.

17 DR. STULTING: That's right.

18 Would it be acceptable to you if we -- like I  
19 say, these cause a lot of trouble. You can't do that until  
20 you have the conditions, and you can't answer this before  
21 the conditions are stated out.

22 DR. McCULLEY: How are we going to resolve  
23 this?

24 ~~DR. STULTING: Well, there's no way to resolve~~

1 it. That's why I've got a problem.

2 Would you withdraw the motion so we can do this  
3 better?

4 DR. McCULLEY: Would it make your life easier?

5 DR. STULTING: Yes, please.

6 DR. McCULLEY: I'll withdraw my motion.

7 DR. MACSAI: I have a motion. I have a motion.  
8 I move that we disapprove this PMA.

9 DR. STULTING: Is there a second?

10 DR. VAN METER: Second.

11 DR. STULTING: It's been moved and seconded  
12 that we disapprove the PMA. No discussion?

13 (No response.)

14 DR. STULTING: Those in favor of the motion,  
15 please raise your hands.

16 (Show of hands.)

17 DR. STULTING: That's two for disapproval.

18 Those opposed?

19 (Show of hands.)

20 DR. STULTING: That's nine opposed, so the  
21 motion fails.

22 Can we direct our attention to additional  
23 questions? Let's try at this point --

24 DR. ROSENTHAL: Number 1, please. I would

1 appreciate it, Mr. Chairman, if you could go through them.

2 DR. STULTING: Number 1 is, "Do you believe the  
3 sponsor has adequately defined and demonstrated an  
4 'increased depth of focus' as stated in the labeling?"

5 Those who believe they have, please raise your  
6 hands.

7 (Show of hands.)

8 DR. STULTING: That's five yes.

9 Those opposed?

10 PARTICIPANT: There were more than five.

11 DR. STULTING: Okay, if I missed it, those in  
12 favor, please raise your hands.

13 (Show of hands.)

14 DR. STULTING: Seven for.

15 Those opposed, please raise your hands.

16 (Show of hands.)

17 DR. STULTING: That's two -- three against.

18 Those abstaining?

19 (Show of hands.)

20 DR. STULTING: One abstained.

21 DR. BRADLEY: Mr. Chairman?

22 DR. STULTING: Yes.

23 DR. BRADLEY: Just a point of clarification for  
24 me. Clearly, there was an increased depth of focus for

1 some people, and not for others. I voted no because it was  
2 not for others. I could have voted yes because it was for  
3 some. I was a bit unsure of how to vote.

4 DR. ROSENTHAL: Could we have a very brief  
5 discussion on the issue for those who voted no, so we may  
6 have the issue laid out before us? In the final discussion  
7 with the sponsors, we need to know.

8 DR. STULTING: Okay. We will poll the table.  
9 We will go around and let everyone who voted explain their  
10 position.

11 DR. BULLIMORE: Mr. Chairman, if we do this for  
12 every question, we're going to be here until 8 o'clock.

13 DR. STULTING: That's exactly my understanding,  
14 which is why I would like --

15 DR. ROSENTHAL: No, I don't need that. I only  
16 need the ones you disapprove. If you approve, you approve.  
17 But if you disapprove, I'd like to know why.

18 DR. BULLIMORE: Well, can we do that when we  
19 vote on approval with conditions, which is where we're  
20 heading? Can we take these questions in a fairly sort of  
21 cursory manner? Then, once we've gone through them, as  
22 requested by Dr. Rosenthal --

23 DR. ROSENTHAL: But I would like a  
24 comprehensive discussion of why people voted against some

1 of the issues, so that when we come to lay out the  
2 labeling, discuss the labeling, with the sponsor, we have a  
3 full comprehensive understanding of the panel's feeling  
4 about the issues that have been asked, so you could give  
5 your feeling about.

6 DR. BULLIMORE: Can we defer that to the end,  
7 though?

8 DR. ROSENTHAL: Yes.

9 DR. STULTING: That was actually the way I  
10 wanted to do it to start with, but I wasn't able to quite  
11 proceed with that. So if it's okay with you, we will do  
12 these in a cursory manner, and then at the end, we'll --

13 DR. ROSENTHAL: Exactly.

14 DR. STULTING: -- do the discussion. I'll give  
15 then FDA staff an opportunity to ask about any issues that  
16 they do not feel will be clear in the transcript part.

17 DR. ROSENTHAL: Fine. Thank you.

18 DR. STULTING: Question number 2. "Both depth  
19 of focus testing and Jaeger near acuity testing were  
20 performed on 25 cohort subjects. While 18 subjects  
21 achieved J1 or better in the uncorrected near acuity  
22 testing, only three of these subjects had a near peak on a  
23 depth of focus curve which was greater than or equal to  
24 20/25. Do you think the sponsor's explanation for this

1 discrepancy is adequate and should it be included in the  
2 labeling?"

3 Those of you who believe the answer to this  
4 question is yes, please raise your hands.

5 DR. RUBIN: That's two questions here.

6 DR. STULTING: We'll do them one at a time.

7 The first question is, "Do you think the  
8 sponsor's explanation for this discrepancy is adequate?"  
9 That will be the question that we're going to address now.  
10 Those of you who think the answer is yes, put your hands  
11 up, please.

12 DR. MACSAI: Excuse me, Dr. Chairman. I don't  
13 think I heard an explanation from the sponsor about this  
14 discrepancy.

15 DR. BULLIMORE: You should probably vote no,  
16 then.

17 DR. MACSAI: Perhaps I missed it in the  
18 discussion, and one of my colleagues could clarify this for  
19 me.

20 DR. STULTING: Would anyone like to continue to  
21 discuss this?

22 DR. MACSAI: Or explain it to me, because I  
23 missed it.

24 DR. RUBIN: I can give my answer and the reason

1 I was prepared to vote yes, or did you want to hear their  
2 answer?

3 DR. MACSAI: We're asking about the sponsor. I  
4 was wondering if you heard an explanation from the sponsor?

5 DR. RUBIN: Yes, that's what I meant. I heard  
6 an adequate explanation. Adequate for me means, I don't  
7 think it's an issue.

8 DR. MACSAI: Could you tell me what that was?

9 DR. RUBIN: No. I mean, because I don't think  
10 it's an issue, I'm not waiting for an answer.

11 DR. ROSENTHAL: I think what you're saying, Dr.  
12 Rubin, is you're not worried about the question.

13 DR. RUBIN: I'm not worried about the question.

14 DR. ROSENTHAL: Okay.

15 DR. RUBIN: The way it's stated here. I think  
16 it comes up elsewhere.

17 DR. ROSENTHAL: Okay. Fine.

18 DR. STULTING: Is everybody prepared to express  
19 their opinion on this question? Those who believe the  
20 answer to that is yes, please raise your hands.

21 (Show of hands.)

22 DR. MACSAI: There was no answer.

23 DR. McCULLEY: I concur with what Dr. Rubin  
24 said.

1 DR. STULTING: That's three who think the  
2 answer is yes. Those who think it's no, please raise your  
3 hands.

4 (Show of hands.)

5 DR. STULTING: That's three.

6 Those abstaining?

7 (Show of hands.)

8 DR. STULTING: That's five abstained.

9 The next subquestion is, "Should it be included  
10 in the labeling?" Those who think the answer is yes,  
11 please raise your hands.

12 (Show of hands.)

13 DR. RUBIN: No. Since I don't believe that the  
14 issue is clear in this formulation, I don't think it should  
15 be in the labeling. The discrepancy between these two  
16 things is a complicated issue, and I don't think it's a  
17 labeling issue. That's just my opinion.

18 DR. BULLIMORE: Call for the question.

19 DR. ROSENTHAL: Excuse me. I gather what  
20 you're saying is, you don't feel it should be included in  
21 the labeling or excluded from the labeling.

22 DR. RUBIN: Right.

23 DR. ROSENTHAL: It's a non-issue.

24 DR. RUBIN: As formulated here, yes.

1 DR. McCULLEY: How would you formulate it to  
2 make it an issue?

3 DR. RUBIN: Well, I'm not quite sure what  
4 they're getting at. I'm not sure what the issue is that  
5 the FDA is really trying to get at. But here, to me, the  
6 fact that there's a discrepancy between two things isn't  
7 necessarily -- there are lots of reasons it could be.

8 MS. BOULWARE: That was the question, the fact  
9 that there was a discrepancy between the near acuity  
10 testing with the Rosenbaum card, and the near peaks seen in  
11 the depth focus data. The fact that there was a  
12 discrepancy, the explanation that the sponsor provided, did  
13 you feel that it was an adequate explanation?

14 If this was a discrepancy, if you thought that  
15 either the clinical near acuity results were overestimated,  
16 overstated, were perhaps more than are supported by the  
17 depth of focus data, or perhaps the depth of focus data did  
18 not adequately reflect what was really happening in the  
19 clinical setting, perhaps what was in the labeling should  
20 be adjusted to reflect this. That's what we were trying to  
21 get at with this question.

22 DR. VAN METER: Mr. Chairman, this is almost  
23 the same thing as number 1, in that some patients did not  
24 receive an increased depth of focus. Some of them did, but

1 some of them do not. I see that intimately tied to  
2 question number 1.

3 DR. STULTING: Yes, I believe you're right.

4 DR. RUIZ: There isn't any explanation, is  
5 there, that anybody knows of?

6 DR. STULTING: It didn't actually ask whether  
7 there was a valid explanation. It just asked if the  
8 sponsor's explanation was adequate, and should it be  
9 included in the labeling?

10 DR. BULLIMORE: Can we vote on the second --

11 DR. STULTING: I've tried to do that. I'll be  
12 glad to move forward --

13 DR. BULLIMORE: Call for the question.

14 DR. STULTING: -- to do anything except vote.

15 The second question is, "Should it be included  
16 in the labeling?" Those who think the answer is yes, put  
17 up your hands, please.

18 (Show of hands.)

19 DR. STULTING: Those who think the answer is  
20 no, put your hands up, please.

21 (Show of hands.)

22 DR. STULTING: That's eight. That's zero  
23 yeses, eight no.

24 ~~Those abstaining, please?~~

1 (Show of hands.)

2 DR. STULTING: Three abstentions.

3 Question number 3, "Do the results of contrast  
4 sensitivity and glare testing, and the reports of  
5 optical/visual phenomena, provide reasonable assurance of  
6 safety and effectiveness?"

7 Those who think the answer is yes, please raise  
8 your hands.

9 (Show of hands.)

10 DR. STULTING: That's six yes.

11 Those who think the answer is no, please raise  
12 your hands.

13 (Show of hands.)

14 DR. STULTING: That's four no.

15 Those who abstain, please raise your hands.

16 (Show of hands.)

17 DR. STULTING: That's one.

18 Number 5 is "Do the indications, warnings, and  
19 precautions in the current draft physician and patient  
20 labeling adequately reflect the data and experience from  
21 the driving simulation substudy?"

22 Those who think the answer is yes, please raise  
23 your hands.

24 DR. McCULLEY: What about 4?

1 DR. STULTING: We already did 4. We did that  
2 first. We're voting on number 5, and we're doing yeses.

3 (Show of hands.)

4 DR. STULTING: I see one hand.

5 Those who think that it's a no, put your hands  
6 up.

7 (Show of hands.)

8 DR. STULTING: Seven.

9 Abstentions, please.

10 DR. McCULLEY: I'm abstaining. I need  
11 reiteration to --

12 DR. STULTING: You mean you don't understand  
13 the question?

14 DR. McCULLEY: I'd like to have someone state  
15 -- no, I understand the question. I don't remember what's  
16 in the labeling.

17 DR. STULTING: Well, eventually, we'll do that  
18 because it'll be down here. We'll get to it.

19 Number 6. "Do you feel that the following  
20 information should be communicated to the physician and  
21 patient? If so, in what manner?" So now we have to do two  
22 answers to each of these questions. We will first discuss  
23 whether we feel the information should be communicated, and  
24 then we will vote on in what manner it should be

1       communicated.

2                       The first one is "The same degree of near  
3       benefit was not achieved by all patients." Do you think  
4       that should be communicated? If yes, please hold your hand  
5       up.

6                       (Show of hands.)

7                       DR. STULTING: That's 11 yeses.

8                       In what manner?

9                       DR. RUBIN: In writing.

10                      (Laughter.)

11                      DR. McCULLEY: I think, you know, adequate  
12       product labeling, and to insure that the physician has  
13       gotten it, so that the patient then gets it, a required  
14       patient brochure.

15                      DR. STULTING: Well, that would be my opinion,  
16       and that is question 7, which is what I wanted to do  
17       second, but I've been forced to go down through the list  
18       here, and so that's what I'm doing.

19                      DR. McCULLEY: Well, that's my answer to how.

20                      DR. STULTING: Then what you can say on each of  
21       these is by the physician and patient brochures, and then  
22       we can move through them.

23                      DR. McCULLEY: Probably. But I think that it's  
24       a required patient brochure, adequate product labeling and

1 a required patient brochure, would be my answer probably to  
2 all of these. Certainly, to that one.

3 DR. RUIZ: Mr. Chairman?

4 DR. STULTING: Yes, sir.

5 DR. RUIZ: Can I make a statement? Isn't it  
6 covered by the fact that we're going to very clearly and  
7 explicitly state that some of these people will not be able  
8 to read?

9 DR. STULTING: Yes, sir, I believe it is, and I  
10 wanted to cover number 7 before going through these, but I  
11 was asked not to do it by FDA staff, and so that's why  
12 we're taking the time to do this. I'm sorry.

13 DR. McCULLEY: I respect both views, but I  
14 think that's the answer that I would use for this, and we  
15 can still answer 7. It might have some other implications,  
16 but my answer to these in general is going to be what I  
17 said, adequate product labeling and a required patient  
18 brochure.

19 DR. STULTING: Well, let's just say that really  
20 quickly, so we can move along.

21 DR. McCULLEY: I just said it.

22 MS. LOCHNER: Can I just make one other  
23 distinction? If there are any of the items, either in the  
24 ~~list in number 6 or additional items you may come up with,~~

1 the other thing that we would want to know is do you want  
2 to see it put into a warning? Do you want to see it put  
3 into the data tables? Do you want to just see it as a note  
4 somewhere in the clinical study section? So keep that in  
5 mind as also what we're looking for.

6 DR. STULTING: Say those again. Warning --

7 MS. LOCHNER: There are just various places  
8 throughout the label you can put this. You can put it as a  
9 warning.

10 DR. STULTING: Tables.

11 MS. LOCHNER: You could put it as text in the  
12 clinical section describing the visual acuity data tables,  
13 so we want -- and precautions. You know, we want to know  
14 the level of importance that you place on the different  
15 statements as well.

16 DR. McCULLEY: Well, maybe it would be  
17 reasonable -- I still say the same thing, labeling and  
18 brochure, and I would say on this first one it would be  
19 warning. So if we did it that way, if we went this --

20 MS. LOCHNER: It's that type of --

21 DR. McCULLEY: -- and said what level you  
22 wanted, that might --

23 MS. LOCHNER: That's I think what we're getting  
24 at for "If so, in what manner?" If you just want it

1 downplayed more, a statement in the clinical section of the  
2 label, or if you want it to have the importance of a  
3 warning.

4 DR. VAN METER: Since we are here as a  
5 multifocal lens and since it is advertised as a multifocal  
6 or bifocal lens, I think a warning would be very  
7 appropriate.

8 MS. LOCHNER: Thank you.

9 DR. VAN METER: Because that's why you would  
10 use the lens.

11 MS. LOCHNER: Thank you.

12 DR. STULTING: And you think it should go in  
13 the physician and the patient?

14 DR. VAN METER: Yes.

15 DR. McCULLEY: Yes, sir.

16 DR. STULTING: It's been sort of suggested that  
17 this be a warning and that it appear in both the physician  
18 and the patient materials. Let's see if that's a  
19 consensus. Those who would agree with that, put your hands  
20 up.

21 (Show of hands.)

22 DR. STULTING: Eleven yes, and so we're  
23 recommending a warning in both the physician and the  
24 patient materials.

1           The next one is "The imaging quality and depth  
2 of field through the multifocal IOL may potentially impact  
3 vitreoretinal surgery." Do you think that that should be  
4 communicated to the physician and patient?

5           DR. McCULLEY: Yes.

6           DR. STULTING: Those who say yes?

7           (Show of hands.)

8           DR. STULTING: That's 11 yeses.

9           In keeping with the request, would you like to  
10 have this go -- I'm sorry.

11          DR. BRADLEY: I abstained on that one.

12          DR. STULTING: Sorry. Yes 10, and one  
13 abstained.

14          We need to figure out where to put it and how  
15 to emphasize it then. Do you think it should go in the  
16 patient thing or the physician thing or both?

17          DR. McCULLEY: Both.

18          DR. STULTING: Both.

19          DR. McCULLEY: In a warning.

20          DR. STULTING: I'm hearing a consensus being  
21 both and a warning.

22          DR. RUIZ: What's it going to mean to the  
23 patient?

24          DR. McCULLEY: They will have been adequately

1 informed, so if their surgeon has to take their lens out,  
2 they've been warned.

3 DR. STULTING: Let's see. How can we do this  
4 most efficiently? Who thinks that this ought to be in the  
5 physician document?

6 (Show of hands.)

7 DR. HIGGINBOTHAM: I didn't hear the question.

8 DR. STULTING: We're dealing with 6b, and we've  
9 decided that it belongs in the communication, and we're  
10 asking whether it needs to be in the physician or the  
11 patient letter. We're discussing now the physician one.  
12 Do you think it ought to be in the physician one?

13 (Show of hands.)

14 DR. STULTING: Ten yes.

15 Are you abstaining?

16 DR. BRADLEY: Yes.

17 DR. STULTING: Ten yes, 10 for the physician,  
18 and one abstention.

19 Are you abstaining because you think it ought  
20 to be somewhere else?

21 DR. BRADLEY: No.

22 DR. STULTING: Okay.

23 How many think that this ought to be in the  
24 patient information document?

1 (Show of hands.)

2 DR. STULTING: That's seven yes.

3 You wanted the level, too. I forgot to do that  
4 for physician. Let's do it for the patient first. That's  
5 what level. Do you want it in text, tables, warning, what  
6 level? Big black letters? That's what you want to know,  
7 right?

8 PARTICIPANT: It's a warning.

9 DR. RUIZ: Why? It's not going to apply to but  
10 1 percent of --

11 DR. STULTING: It seems that the thing that I  
12 have heard most spoken is warning, so let's vote on  
13 warning, and we'll see if there's a lot of dissension. If  
14 there is, then we'll discuss it a little bit and figure out  
15 whether it ought to be somewhere else.

16 Those who think it belongs in the warning,  
17 please say yes. No, no. Put your hand up.

18 (Show of hands.)

19 DR. STULTING: That's six yes for warning.

20 How many think it ought to be in text?

21 (Show of hands.)

22 DR. STULTING: Did I do that right? Did I ask  
23 warning?

24 ~~There were six that believe that it ought to be~~

1 as a warning. Those who didn't believe that it ought to be  
2 as a warning and still believe that it ought to be  
3 included, where do you think you ought to put it?

4 DR. GREENIDGE: Is one option text?

5 DR. STULTING: Yes.

6 DR. GREENIDGE: Text.

7 DR. STULTING: Text, and the minority wanted it  
8 as text.

9 We need to go back to the physician. Do you  
10 think it ought to be in the physician as a warning? How  
11 many think it ought to be a warning for the physicians?

12 (Show of hands.)

13 DR. STULTING: That's eight.

14 PARTICIPANT: Nine.

15 DR. STULTING: Nine as a warning.

16 Those who think it ought to be something else?

17 (Show of hands.)

18 DR. STULTING: Nine as a warning, one as a  
19 text, and anybody else have an opinion? And probably an  
20 abstain.

21 The next one is "The clinical study involved  
22 patients with potential visual acuities of 20/30 or better;  
23 no data are available on the performance of the multifocal  
24 lens in patients with lower potential visual acuity and/or

1 ocular pathologies."

2 Do you think that should be communicated to the  
3 physician? Those who believe yes, hold your hands up.

4 (Show of hands.)

5 DR. STULTING: That's 11 yes.

6 And at what level? Everybody who thinks it  
7 ought to be as text, please raise your hand.

8 (Show of hands.)

9 DR. STULTING: That's 11 as text.

10 Do you think it should be communicated to  
11 patients? Those in favor or think yes?

12 (Show of hands.)

13 DR. RUBIN: Excuse me. Question?

14 DR. STULTING: Yes.

15 DR. RUBIN: If the patient does not meet this  
16 criteria -- I thought it wasn't in cases of patients who  
17 didn't meet this criteria, and therefore would there be a  
18 purpose in informing them?

19 DR. McCULLEY: Yes.

20 DR. RUBIN: Okay. That way, you'll get  
21 around --

22 DR. STULTING: Those who think yes?

23 (Show of hands.)

24 DR. STULTING: That's 11 yes.

1                   Those who believe it should be in text?

2                   (Show of hands.)

3                   DR. STULTING: I see 10.

4                   Are you voting, Woody?

5                   DR. VAN METER: I'm voting for warning.

6                   DR. STULTING: I see. So it would be 10 for  
7 text and one for a warning.

8                   D is "An analysis of the lens design predicts  
9 that patients with pupil diameters less than 2.5  
10 millimeters may have a lesser degree of near benefit." Do  
11 you think that needs to be communicated to the physician?

12                   DR. RUBIN: Point of clarification. I think  
13 that should be changed to "will not have the benefit" or  
14 something much stronger.

15                   MS. THORNTON: Could you speak into the  
16 microphone, please?

17                   DR. RUBIN: I would propose that that be  
18 changed to "An analysis of the lens design predicts that  
19 patients with pupil diameters less than 2.5 millimeters  
20 will not have any benefit." "Predicts that patients will  
21 not have any benefit" -- is that correct? Okay. "May not  
22 have any benefit."

23                   DR. STULTING: Malvina, you're shaking your  
24 head. Does FDA have some requirement that directs what we

1 need to say here?

2 Dr. Drum?

3 DR. DRUM: This is Bruce Drum, FDA. The  
4 problem is the pupil size interacts with the centration of  
5 the lens. If the lens is decentered even a little bit,  
6 then a 2 millimeter pupil may still hit a significant  
7 portion of the near zone, so you may have a distribution of  
8 people, some of whom will not see any near benefit and some  
9 see only partial near benefit.

10 It's a complicated issue. The question is how  
11 should we communicate this to the patient and the  
12 physician.

13 DR. STULTING: Do you accept that, Dr. Rubin?  
14 Do you still want --

15 DR. RUBIN: I still wouldn't want to say  
16 "lesser degree." I would still say "may not have any near  
17 benefit."

18 DR. STULTING: That's kind of a compromise.  
19 That's "may not have any" --

20 DR. RUBIN: "Near benefit."

21 DR. STULTING: "Near benefit." Is that  
22 acceptable to everybody? How about on the panel?  
23 Everybody happy with that? FDA happy with that?

24 All right. It's been recommended this be

1 changed to "less than 2.5 millimeters may not have any near  
2 benefit." Obviously, we think that that should be  
3 communicated, or we wouldn't have paid any attention to  
4 rewording it. Do you think it needs to go to the  
5 physician?

6 (Show of hands.)

7 DR. STULTING: We're going to say yes, it goes  
8 to the physician, right? Woody, are you abstaining or are  
9 you voting yes or are you voting no?

10 DR. VAN METER: I'm abstaining.

11 DR. STULTING: That's yes 10, abstain one.

12 Those who think it ought to be as a warning?

13 (Show of hands.)

14 DR. STULTING: As a warning, 10.

15 PARTICIPANT: Eleven.

16 DR. STULTING: Eleven for a warning, so  
17 consensus is it should be communicated to the physician as  
18 a warning.

19 Do you think it should be communicated to the  
20 patient?

21 (Show of hands.)

22 DR. STULTING: Eleven think that the patient  
23 needs to know.

24 ~~On what level do we need to let them know it?~~

1 As a warning or text? As a warning? Those in favor of a  
2 warning?

3 (Show of hands.)

4 DR. STULTING: That's eight who say yes.

5 Those who say no?

6 (Show of hands.)

7 DR. STULTING: That's one.

8 Abstaining? Two of you put up your hands,  
9 please.

10 (Show of hands.)

11 PARTICIPANT: I voted no.

12 DR. STULTING: So I miscounted it. How many  
13 no? Two no. Sorry. The count, then, is eight for a  
14 warning, two for something else, and one abstention.

15 Now we're on to 6e. "There are no data on the  
16 performance of the multifocal lens in patients with final  
17 postoperative astigmatism exceeding 1.5 diopters."

18 Do we think that should go to the physician?  
19 If so, please hold your hand up.

20 (Show of hands.)

21 DR. STULTING: That's 11 yes, think it goes to  
22 the physician.

23 And at what level?

24 DR. McCULLEY: Doyle, this is one of those that

1 I think really needs to be highly stressed to the  
2 physician, because it is in there that it's going to be to  
3 the patient not 1.5, and that the physician has to  
4 understand that it's also at the end of recovery from  
5 surgery, that they've got to understand that if they induce  
6 astigmatism -- well, they've got to avoid inducing  
7 astigmatism if they can, or they're going to have to face  
8 the piper if they do.

9 DR. STULTING: So the recommendation is for  
10 including it into the physician labeling and emphasizing it  
11 significantly, so that they understand that even induced  
12 postoperative astigmatism will make the level of  
13 performance less than optimal.

14 Does everybody agree on that?

15 DR. SUGAR: We don't know that it will. That  
16 it may.

17 DR. STULTING: May make the performance less  
18 than optimal. I can that as a matter of faith that if you  
19 have three or four doctors, astigmatism probably won't work  
20 as well, but we can put "may" in there.

21 DR. McCULLEY: You can well bet it's not going  
22 to work as well.

23 DR. GREENIDGE: But they don't have data.

24 DR. STULTING: I don't have true data that if I

1 stand on the railroad track and a train hits me, I'm going  
2 to die, but I'm pretty sure that's what's going to happen.

3 (Laughter.)

4 DR. BULLIMORE: Call for the question.

5 DR. STULTING: We can let it be made to reflect  
6 our lack of data about 1.5 diopter.

7 Is that agreeable to everybody and acceptable?

8 (Show of hands.)

9 DR. STULTING: Is anybody opposed to that?

10 (No response.)

11 DR. STULTING: Is anybody abstaining from that?

12 (No response.)

13 DR. STULTING: Then that's 11 yeses.

14 Then we need to figure out if that needs to go  
15 to the patient. Do you think the patient would understand  
16 this?

17 DR. VAN METER: No, and I think it's a  
18 potential liability issue, too.

19 DR. STULTING: In that if the patient reads  
20 this and they don't get a good result, that it probably was  
21 their surgeon's fault.

22 DR. RUIZ: I don't think they can understand as  
23 well as they are about the pupil.

24 ~~PARTICIPANT: They understand the pupil better~~

1 than --

2 DR. STULTING: It's been voiced from a couple  
3 of corners that this should not be in the patient brochure,  
4 so let's vote on that. Those who think it belongs in the  
5 patient brochure, put your hands up, please.

6 (Show of hands.)

7 DR. STULTING: Three.

8 No, please put your hands up.

9 (Show of hands.)

10 DR. STULTING: Seven.

11 Abstentions?

12 (Show of hands.)

13 DR. STULTING: One.

14 DR. RUIZ: It certainly could be used as an  
15 explanation to a patient if they didn't achieve the result  
16 they wanted and they had 2 diopters of astigmatism.

17 DR. STULTING: We're down to 6f. "Limited data  
18 are available on subjects with poor preoperative best  
19 spectacle corrected visual acuity."

20 Do we think that this should be communicated to  
21 physicians? How many think yes?

22 (Show of hands.)

23 DR. STULTING: No?

24 (Show of hands.)

1 DR. STULTING: Is that a yes that you just  
2 missed? Okay. So that is yes would be 10.

3 Abstentions?

4 (No response.)

5 DR. BRADLEY: Woody's in the bathroom.

6 DR. STULTING: Yes. That's nine yeses, one no,  
7 and one absence.

8 DR. RUIZ: Mr. Chairman, that's the same thing  
9 as 6c, isn't it?

10 DR. SUGAR: It's just people who had denser  
11 cataracts than were in the study. Isn't that right?

12 DR. STULTING: So that goes with the  
13 physicians. It's recommended for inclusion in physicians.

14 At what level should we include it? As text?  
15 Those in favor of text?

16 (Show of hands.)

17 DR. STULTING: Those opposed to that  
18 recommendation?

19 (No response.)

20 DR. STULTING: And those abstaining?

21 (No response.)

22 DR. STULTING: Maybe I miscounted. Did  
23 everybody who's sitting here vote yes? Then that's 10  
24 yeses, and a miscount previously.

1                   Now, we're at 7. "Is there additional  
2 information you believe should be included in the physician  
3 or patient labeling?" Let's open the floor for inclusion  
4 of those things.

5                   DR. McCULLEY: I think something in the  
6 labeling for the physician to be warned relative to the  
7 absolute necessity of achieving centration to achieve  
8 maximal benefit of the lens, and potential detriment from  
9 the lens if it's not centered, and that emmetropia must be  
10 achieved to obtain maximal benefit of the lens. Two for  
11 the physician.

12                  DR. STULTING: Is that one thing or several  
13 things?

14                  DR. McCULLEY: It's two, centration and  
15 emmetropia.

16                  DR. STULTING: Need for centration and the need  
17 for emmetropia. I think emmetropia's already in there,  
18 unless I'm incorrect.

19                  DR. McCULLEY: No, it's not.

20                  DR. STULTING: For the physician?

21                  DR. McCULLEY: No, it's not -- or it may be.

22                  DR. STULTING: Well, it'll take less time to  
23 vote on it than it will to look it up.

24                  DR. McCULLEY: Yes.

1 DR. STULTING: The need for centration and the  
2 need for achievement of emmetropia. In other words, you  
3 mean that the lens power calculations need to be set for  
4 emmetropia, as opposed to myopia?

5 DR. McCULLEY: And emmetropia must be achieved  
6 to get the maximum benefit of the lens.

7 DR. STULTING: So calculated and achieved  
8 emmetropia.

9 DR. ROSENTHAL: This is already designated on  
10 page --

11 DR. STULTING: That's what I thought. Okay.  
12 So that one's already in there.

13 DR. McCULLEY: It's adequately in there?

14 DR. ROSENTHAL: It says, "This lens is designed  
15 for optimum depth of focus when emmetropia is targeted."

16 DR. McCULLEY: My point with this is that needs  
17 to be stressed very strongly to the surgeon, that he must  
18 target and achieve emmetropia to have maximal benefit of  
19 the lens. I think that just burying it in the text is not  
20 adequate in this situation.

21 DR. STULTING: Those in favor of that proposal,  
22 please say yes, or if you have any questions about it, we  
23 can deal with that. I didn't mean to push this through,  
24 ~~but I'm just trying to get it done.~~

1           The proposal is that the physician labeling  
2           include a warning about the needs for centration and the  
3           possibility that the lens won't function well if it  
4           decenters, and the need to calculate for and achieve  
5           emmetropia or the lens won't deliver as it's designed to  
6           deliver.

7           DR. GREENIDGE: It's just that my concern is  
8           how many warnings we're putting there, and if you have 17  
9           warnings whether or not you'll read any of them.

10          DR. McCULLEY: You better read them all.

11          DR. GREENIDGE: And how do we distinguish some  
12          warnings so that they're read? I hope you understand what  
13          I'm saying.

14          DR. MACSAI: You mean red the color or read --

15          DR. STULTING: Well, that's what we're being  
16          asked to recommend.

17          DR. GREENIDGE: So I guess my question was, is  
18          this a red warning or a black warning?

19          DR. MACSAI: This is a red warning, R-E-D, not  
20          R-E-A-D. Or both.

21          DR. McCULLEY: I vote for strong warning on  
22          that, both of them.

23          DR. STULTING: It's been suggested and proposed  
24          that these be included as strong warnings of the

1 appropriate typeface that would match that recommendation  
2 and that level. Those in favor, please raise your hands.

3 (Show of hands.)

4 DR. STULTING: Eleven yes.

5 The floor is open for other labeling  
6 inclusions.

7 DR. RUIZ: Mr. Chairman, it seems like it's a  
8 good opportunity just to list all these warnings under a  
9 separate title there. That would, I think, catch the  
10 attention of the physician.

11 DR. STULTING: So it was suggested that we put  
12 these all listed under one set of warnings.

13 Anything else that people need to go in?

14 DR. McCULLEY: I have a question. Does the  
15 labeling adequately address the lack of improvement in  
16 intermediate distance? And does it adequately -- I guess  
17 it does adequately address halos, glare, decreased night  
18 driving, low illumination function ability.

19 DR. MACSAI: But I would think you want to  
20 include the percentages there, not just that you can have  
21 them, but that 15 percent, for example, had severe halos  
22 and 11 percent had severe glare. Those are very high  
23 percentages.

24 DR. STULTING: I thought those were in there.

1 DR. McCULLEY: I guess the point is that we do  
2 think it ought to be very well stated in the labeling, and  
3 I think that it also needs to be very well stated for  
4 physician and patient that there's no benefit in  
5 intermediate distance.

6 DR. STULTING: I thought that the glare numbers  
7 were already in there. Am I not correct about that?

8 DR. RUBIN: Mr. Chairman, I think that the  
9 glare numbers that are in there possibly are misleading, in  
10 that they have combined severe and moderate, which  
11 diminishes the difference between the two groups. I think  
12 if we stick with severe --

13 DR. STULTING: Yes, you made that point before.  
14 It was on my notes to get back to.

15 How can we develop a consensus here? It's been  
16 recommended that the percent of patients who experience  
17 severe optical symptoms be included in the physician  
18 labeling. Would that be the right wording, do you think?  
19 That would be glare and halos and double vision and things  
20 like that. We're now talking about physician labeling. We  
21 can talk about patient in a minute.

22 Is that a consensus? Any other suggestions?  
23 Those who believe that ought to be on there, please raise  
24 your hands.

1 (Show of hands.)

2 DR. STULTING: Ten.

3 Art, are you abstaining?

4 DR. BRADLEY: I was distracted, Doyle.

5 DR. STULTING: Ten yeses and one distracted.

6 (Laughter.)

7 DR. BRADLEY: I was trying to see if I was  
8 going to miss my flight.

9 DR. STULTING: So to clarify it for the agency,  
10 there was concern about the way these things were  
11 tabulated. If you tabulate frequencies that are high by  
12 combining moderate and severe, then the differences appear  
13 to be less, and what we want to do is emphasize the number  
14 who have significant severe ones.

15 DR. SUGAR: They're specifically in here.

16 DR. STULTING: That's what I thought.

17 DR. SUGAR: Yes. It says no difficulty,  
18 moderate, severe.

19 MS. THORNTON: Can you use the microphone? The  
20 transcriber and summary writer can't hear.

21 DR. RUBIN: I would direct your attention to  
22 page PT-7, unless I'm looking at the wrong thing. "Revised  
23 June 17th, 1997."

24 ~~DR. SUGAR: I'm talking about the physician~~

1 one, which is MD-15.

2 DR. RUBIN: I'm sorry.

3 DR. STULTING: Is anybody unhappy with what is  
4 in MD-15? Then maybe what we're talking about is putting  
5 it in the patient brochure.

6 DR. RUBIN: I'm sorry. You're correct on that.

7 DR. STULTING: Do you think it ought to be in  
8 the patient brochure? Is there general consensus that it  
9 needs to be in the patient brochure, the severe symptoms?  
10 Those who believe yes, please raise your hand.

11 (Show of hands.)

12 DR. STULTING: Was that 11? Okay. So we think  
13 this ought to go in the patient.

14 DR. ROSENTHAL: I understand your concern in  
15 putting the severe complications in the patient brochure,  
16 but a table of that complexity may not be in the best  
17 interest. We can assure you we'll put the severe  
18 complications on.

19 DR. STULTING: That would be my interpretation  
20 of what was being recommended.

21 DR. ROSENTHAL: Fine. Thank you very much.

22 DR. STULTING: That it be pared down.

23 DR. ROSENTHAL: Okay. Thank you very much.

24 ~~DR. STULTING: While we're on this, I notice~~

1 that the patient brochure also doesn't say that somewhere  
2 around 1 percent of the lenses were actually removed  
3 because of visual symptoms, and I personally think that  
4 ought to be in there, too.

5 Is there consensus on that? Is there anybody  
6 who would vote no or abstain?

7 (No response.)

8 DR. STULTING: Then that's 11 yeses to include  
9 the removals.

10 Let's see. There were some other comments,  
11 too. Intermediate distance. The point that intermediate  
12 distance is not necessarily improved by the lens. Should  
13 that go in the patient brochure, that's what you're asking  
14 about?

15 DR. McCULLEY: Physician and patient.

16 DR. STULTING: Physician and patient?

17 DR. SONI: I think for the patient we can  
18 probably add that to the table of comparisons. Under range  
19 of vision and under monofocal, it says required for near  
20 work and intermediate. We can probably add intermediate in  
21 there just to clarify that intermediate doesn't improve  
22 that much more.

23 DR. VAN METER: Is this an appropriate place to  
24 discuss whether to call it a bifocal lens or a multifocal

1 lens?

2 DR. STULTING: Not right this instant. We'll  
3 get to it in a minute. We're talking about the  
4 intermediate distance, so let's put that in, and then we'll  
5 talk about what to call it.

6 DR. FERRIS: Doyle, can I just make a comment  
7 -- this is Rick Ferris -- about what's in the patient  
8 brochure and what's in the physician brochure? I think we  
9 need to be careful about any kind of paternalistic approach  
10 that patients won't understand this. I also think it's  
11 important to not overload the patient brochure with a whole  
12 bunch of stuff that patients won't understand, and the  
13 suggestion that I make as a compromise to that is the bulk  
14 of the patient brochure ought to be aimed at the things  
15 that patients are interested in, but I think an appendix or  
16 something of these are warnings and information that were  
17 given to your physician of a more technical nature, but  
18 that they're there someplace, might be considered.

19 I'm not sure exactly how to best do this, but  
20 I'm a little bit concerned about the idea that you tell a  
21 physician something, but you appear to be keeping it a  
22 secret from the patient. I'm not sure that's a good idea.

23 DR. MACSAI: I think you can make a patient  
24 brochure quite detailed, as they have been made for PRK,

1 and we shouldn't underestimate the ability of our patients  
2 to understand and be concerned about these possible  
3 consequences or side effects. So I have no problem with it  
4 being quite complicated.

5 DR. STULTING: I think the concern is just like  
6 when you and I get a whole bunch of mail during the day.  
7 You know, we're going to select stuff that we're going to  
8 read and stuff that we're not, and if they get a huge one  
9 that's got relevant and irrelevant stuff, they'll have a  
10 hard time sifting out what they need. I agree with you,  
11 but I do think that the issue is not really protecting them  
12 from information, but selecting information that we can  
13 communicate to them efficiently, and stuff that matters.

14 DR. ROSENTHAL: Mr. Chairman, we do have a  
15 group we work with in the agency on patient information,  
16 and I think they will probably have similar feelings that  
17 the panel has about these issues. I frankly would like to  
18 defer it to them in the final makeup of the label or  
19 patient brochure.

20 DR. STULTING: Okay.

21 DR. ROSENTHAL: The language.

22 DR. STULTING: Let's see. We were on the  
23 intermediate thing. I think we got distracted before we  
24 finished that.

1 DR. SONI: Can I go into that one?

2 DR. STULTING: Sarita.

3 DR. SONI: Yes. I think that whole question  
4 about intermediate vision can be and should be addressed in  
5 the comparison table that the sponsor has put together. A  
6 number of places, the word "intermediate" is left out.

7 Let's go back to what I was talking about  
8 earlier, range of vision and under monofocal. It talks  
9 about vision. "The IOL generally gives good distance  
10 vision, but glasses are usually required for near work."  
11 It should probably say "near and intermediate work," and  
12 then when you move over to the multifocal text, it talks  
13 about "The IOL is designed to give you vision at both far  
14 and near distances like the natural lens of the younger  
15 eye." That's what Arthur doesn't want, and I certainly  
16 don't want that in there, which implies clear vision all  
17 the way through, so that should be taken out.

18 So in this particular comparison table, I think  
19 there are a lot of errors, especially to do with  
20 intermediate vision, that need to be really looked at  
21 carefully. We can go through them one at a time or we can  
22 just leave it with the agency.

23 DR. McCULLEY: Bottom line was that comparing  
24 monofocal to the multifocal lens, there was no difference

1 in intermediate vision, so we just leave it to them to be  
2 certain that that is effectively communicated and labeled  
3 for physician and patient.

4 DR. STULTING: I agree with you. I have  
5 serious concerns about some of this wording here, and I  
6 actually think these are more important for us to focus on  
7 than some of the things that we've been looking at. I  
8 really think that we ought to get into some of that before  
9 we leave today.

10 Since you've brought it up, maybe everybody  
11 should pull out patient page 7 of the most recent labeling,  
12 which is in this thin thing -- that's Volume 1 of one -- at  
13 the end, and we're looking at the table, which is what you  
14 brought up, over there under the Array.

15 "The IOL is designed to give you vision at both  
16 far and near distances like the natural lens of the younger  
17 eye. The IOL generally gives good distance vision, but it  
18 may not be quite as sharp as with a monofocal. You can  
19 expect near vision to be better than with a monofocal IOL,  
20 but there may still be some circumstances where" -- you  
21 know, to me, I think that's misleading in a couple of ways.  
22 I don't think you should mention that it's like the natural  
23 lens and I'm not convinced that it's better than monofocal  
24 at near.

1 DR. BULLIMORE: I move that we strike the words  
2 "like the natural lens of the younger eye."

3 DR. BRADLEY: Second.

4 DR. RUIZ: Mr. Chairman, do we need to do this  
5 or can't the agency do that?

6 DR. STULTING: Well, apparently we do.

7 DR. RUIZ: I think they've gotten the message  
8 of whatever Dr. Rosenthal wants.

9 DR. STULTING: Is that what you want?

10 DR. BRADLEY: I would also make a modification  
11 of the third sentence, instead of "You can expect near  
12 vision to be better than with a monofocal IOL," to "Most  
13 people can expect near vision to be better."

14 PARTICIPANT: Some.

15 DR. BRADLEY: I think it's more than 50  
16 percent, so I think that is most.

17 DR. BULLIMORE: I accept Dr. Bradley's friendly  
18 amendment.

19 DR. STULTING: Which was?

20 DR. BULLIMORE: That the final sentence should  
21 begin "Most patients can expect."

22 DR. STULTING: Is there general agreement about  
23 that? Do people object to that? Does anyone object to  
24 that? If so, please say something.

1 (No response.)

2 DR. STULTING: I don't hear anything, so the  
3 transcript will reflect the comments there.

4 I actually think that this is important for us  
5 to get the labeling right because --

6 DR. ROSENTHAL: Absolutely.

7 DR. STULTING: That's what I was trying to do  
8 since we started, looking at the --

9 DR. ROSENTHAL: I realize that.

10 DR. STULTING: Because I thought we were going  
11 to approve it, and what we really need to do is make sure  
12 that people understand how to use it and what the risks are  
13 that they're facing, so as far as I'm concerned this is the  
14 most important thing that we've done today.

15 DR. MACSAI: Can I go on to the next part of  
16 glasses?

17 DR. STULTING: Absolutely.

18 DR. MACSAI: You know, this is somewhat  
19 dependent on what the person's doing during the day. For  
20 example, if they're drawing insulin into their syringes,  
21 there is not a high probability that they will be able to  
22 do this without glasses. The data showed that 24 percent  
23 of patients still required an add for near tasks, and 43  
24 percent still wore glasses. This is very misleading.

1 DR. BANDEEN-ROCHE: Even as stated, I believe  
2 it's misleading because I believe that was the number for  
3 always, right? For the always category. It was not? Then  
4 maybe the overhead was -- exactly what category is that  
5 for?

6 DR. YAROSS: That was occasionally plus always.

7 DR. MACSAI: It's not reflected in the data.  
8 In the data, I understood that 14 percent of patients still  
9 required an add to achieve J3 vision, and 24 percent were  
10 still requiring an add for near tasks, so 92 percent would  
11 be a misleading number.

12 DR. BRADLEY: Could we recommend to the FDA  
13 that they insure that statistic is correct when it's posed  
14 in this brochure and move on?

15 DR. STULTING: So the recommendation is that  
16 the number be verified and that it include percentages.  
17 Can we stop with that? Okay.

18 I guess, while we're on it, any other comments  
19 about this page?

20 DR. FERRIS: But this percentage of  
21 occasionally, I think that's very much a matter of  
22 interpretation of the question. I think a lot of elderly  
23 people think they use their reading glasses occasionally.

24 I think the reason this is 92 percent, and the reason we're

1 having the discussion here, is because I don't think there  
2 are 92 percent of this population who don't need add, so I  
3 think the agency needs to look at it and reflect -- I worry  
4 about numbers. That's my quirk. I'm not sure we need  
5 numbers, but it looks to me like a significant number of  
6 people are going to need additional help for near work.

7 DR. STULTING: Down at halos and glare, I found  
8 this one to be, once again, unbalanced and misleading. On  
9 the right, they talk about visual aberrations with a  
10 multifocal, and it says you may get accustomed to them, you  
11 may continue to notice them, but you also may have to have  
12 the lens come out because of it, and that happens in 1  
13 percent of eyes. I would recommend that be put in. Any  
14 objections to that?

15 DR. MACSAI: I would agree with that, and I  
16 would also say that the data they showed on the screen  
17 didn't show that with a monofocal there was a 29 percent  
18 chance of -- is that 29 percent correct?

19 DR. McCULLEY: Forty-nine. Forty-nine saw J3.

20 DR. MACSAI: No, I'm sorry. We're talking  
21 halos and glare for the monofocal.

22 DR. BULLIMORE: If you look at Table 10 on page  
23 MD-15, it's 26 for moderate halos, 6 for severe halos in  
24 the monofocal group, so that comes out to 28.5.

1 DR. RUBIN: We already discussed switching that  
2 to the severe anyway, I think.

3 DR. FERRIS: But that's the point, because here  
4 the implied relative risk is something like a 40 percent  
5 increased risk on the one hand, and then severe it's a  
6 doubling of risk, and so I think the important point here  
7 is to concentrate on the severe, because that's where  
8 you've got a two or three times risk. When you look at  
9 this moderate plus severe, it makes it look like, well,  
10 you've got a little bit more risk, but not a lot.

11 DR. MACSAI: That's what I meant to say.

12 DR. BULLIMORE: We've already voted on that.

13 DR. STULTING: The recommendation is that all  
14 of those things that we said about severe and how to report  
15 them belong in these boxes. Is that consensus? Okay.

16 Let's see. There were some other things that  
17 we had about the labeling before. There was a comment.  
18 Dr. Bradley, you complained about the way they calculated  
19 and did their pictures, right?

20 DR. BRADLEY: Yes. I think it would be  
21 mandatory really for the computer simulations, the  
22 visualizations for the patient, to be both theoretically  
23 and empirically verified. It's my judgement that they are  
24 ~~theoretically in error, and Dr. Rubin pointed out that they~~

1 have not been validated. Obviously, if they are incorrect,  
2 they will mislead the patient into what to expect after  
3 surgery.

4 DR. STULTING: When you say validated, can you  
5 explain what that would be?

6 DR. BRADLEY: There are two levels. One is in  
7 theory and the theory seemed to me incorrect at the moment  
8 and I know they can correct that. I can advise them, if  
9 they would be interested.

10 Empirically, how do you validate? Actually,  
11 you have to put lenses in people's eyes, and essentially,  
12 if you have a monofocal cohort, you can have them look at  
13 your simulation with their monofocal eye and look at their  
14 monofocal simulation with their bifocal eye. The question  
15 is, do they look the same? If they don't, then your  
16 simulation is in error. I believe that's the way to do it.

17 DR. STULTING: Does everybody understand this  
18 and agree with it? The proposal is for correction of the  
19 theoretic formulas in the computer simulations with  
20 validation using the monofocal/multifocal groups, people  
21 who had implants of each kind.

22 Any other discussion on that? Is there general  
23 agreement that that be part of the recommendations?

24 ~~Anybody objecting, please speak.~~

1 (No response.)

2 DR. STULTING: No speaking parts, so we will  
3 consider that a unanimous approval.

4 DR. SUGAR: One other thing on the  
5 visualization --

6 MS. THORNTON: Joel, could you use the  
7 microphone?

8 DR. SUGAR: Sorry. Joel Sugar. Page H-6, with  
9 the visualization of the nighttime halos and glare, it says  
10 they are reported 10 percent more frequently with the  
11 multifocal implant. The relative risk for severe is two  
12 and a half times. I think that that's a more accurate  
13 statement.

14 DR. STULTING: So the recommendation, then, for  
15 Figure 4 is to express it in the frequency of severe.

16 DR. SUGAR: Yes.

17 DR. STULTING: And give the two percentages,  
18 rather than a difference. Is that correct?

19 DR. SUGAR: Or the relative risk, yes.

20 DR. STULTING: Or the relative risk, how many  
21 times more frequent it is.

22 Is there general agreement on that  
23 recommendation? Okay. There was no objection to that.

24 DR. BRADLEY: I could add one additional

1 recommendation regarding the simulations. Once the  
2 programming's set up, it's very easy to put any number of  
3 objects or images through the simulation, and it's my  
4 experience that the quality of bifocal vision can be --  
5 let's say varies with the actual object that you're looking  
6 at, and a particular one that patients often report having  
7 trouble with is high contrast letters that they're reading  
8 at near. It might be good to give a simulation of that.

9 DR. STULTING: I actually had something that's  
10 a little bit like that. I had some concerns about page 4,  
11 because one of the alternatives is not here, and that is  
12 monofocal with reading glasses, so they don't get a  
13 comparison of what it would be like if they had a monofocal  
14 with glasses, and I think that ought to be in there to  
15 fairly present it.

16 Is there any disagreement on that among the  
17 panel? Can we take that as a recommendation? I don't hear  
18 any disagreement being voiced.

19 DR. BRADLEY: I thought that would be a good  
20 idea, in the sense that, as AMO has suggested, there is a  
21 tradeoff here, and we've seen the benefit by going from  
22 monofocal IOL at near, which is defocused, to multifocal.  
23 It'd be nice to see the cost, in the sense of what you  
24 would lose.

1 DR. VAN METER: Mr. Chairman, on page 7 at the  
2 end, in bold type --

3 MS. THORNTON: Dr. Van Meter, would you speak  
4 into the microphone?

5 DR. VAN METER: Woodford Van Meter. On page 7,  
6 patient page 7, the last sentence under low contrast  
7 driving is "You may have more difficulty recognizing  
8 traffic signs," et cetera. Might that be amended so you  
9 say "You may need to take extra care when driving,  
10 especially in poor light conditions"?

11 DR. STULTING: Does anybody object to that  
12 recommendation?

13 DR. BRADLEY: Good idea.

14 DR. STULTING: Anything else that people  
15 believe belongs in the labeling or things that are in the  
16 labeling that need to come out or that are  
17 misrepresentations of the lens?

18 Karen?

19 DR. BANDEEN-ROCHE: I just have two more  
20 things. One is I think very minor. One page MD-8, the  
21 contrast sensitivity results are introduced, but I don't  
22 see any summary. It's just the tables on the next page and  
23 there's not a summary, so it'd be helpful if a summary like  
24 ~~had accompanied the other tables could be added.~~

1           The second one I think is much, much more  
2           important, and that involves the recommendations that were  
3           made several times about including some information about  
4           driving that summarized the potential for not being able to  
5           drive effectively, comparing multifocal and monofocal  
6           lenses.

7           DR. STULTING: Are you talking about the bar  
8           graphs that we saw with recognition and distances on them  
9           or something else?

10          DR. BANDEEN-ROCHE: I'm talking about a  
11          recommendation that was made, I think very effectively, by  
12          Dr. Bradley, I think it was, about a method that might be  
13          used to summarize -- or maybe it was Dr. Rubin. I forget,  
14          but one method that was forwarded was a percentage of  
15          participants who were not able to stop the car in  
16          simulations fast enough to satisfy standard safety  
17          requirements. It doesn't have to be that, but just some  
18          summary statistic describing a more global measure of risk  
19          of not being able to drive appropriately.

20          DR. CALOGERO: Excuse me. Would you be looking  
21          for, say, one example --

22          MS. THORNTON: Don?

23          DR. CALOGERO: This is Don Calogero. Would you  
24          be looking for, say, one example to put in the labeling?

1 Because we could go into the test data that the company's  
2 performed. Obviously, we can find one example where it  
3 would be an unsafe situation for the multifocal and would  
4 be safe for the monofocal, but that's not truly  
5 representative of the entire body of data.

6 DR. BANDEEN-ROCHE: No, I feel very strongly  
7 that it shouldn't be an item by item sort of comparison,  
8 but this bears on the discussion that we had about needing  
9 to summarize the data in some way that effectively gives  
10 people some way to assess their risk of having a really bad  
11 driving outcome. I thought the summary statistic of  
12 percentage of people in the simulation who would not have  
13 stopped in a safe distance -- maybe a mean over tasks --  
14 was one good idea. It would not have to be that one, but I  
15 just feel that as it is I'm not sure the patients are  
16 getting a fair assessment of kind of a catastrophic risk.

17 DR. RUBIN: Gary Rubin. So you said possibly a  
18 mean over task, the mean percentage of patients over task,  
19 or something like that, is more of a summary statistic?

20 DR. CALOGERO: In the FDA presentation, we had  
21 done some of those analyses, and Dr. Drum had done one  
22 analysis where he looked at the percentage that actually  
23 had failed or had success in recognizing various objects or  
24 hazards within 100 feet. The implication was if you were

1 going faster than 30 miles per hour you didn't have  
2 sufficient time to react and stop in this 100 feet. Some  
3 sort of analysis like that could be added to the labeling.

4 DR. STULTING: Has a sense of the committee and  
5 the comments been transferred adequately do you think?

6 DR. ROSENTHAL: Yes, it has, but I would like  
7 to get back to one issue which has to do with the  
8 indications, which was actually number 1, which I was  
9 pushing you on and which we never really got. I'd like to  
10 refer you to page 3 of your indications for use in your  
11 packet. Page 3, "Indications for Use." It follows the  
12 questions. If you could just look at that, it follows the  
13 questions you've just been considering in your packet.

14 DR. STULTING: It's the thing that got left  
15 out.

16 MS. THORNTON: Yes. It's the thing I faxed to  
17 you that I told you I'd provide in your packet. It's about  
18 two paragraphs at the top of the page.

19 DR. ROSENTHAL: It's "Indications for Use." It  
20 has to do with the issue of multifocal bifocal depth of  
21 focus. It says, in the second part, "The AMO Array  
22 multifocal lenses are indicated for those patients who  
23 desire increased depth of focus," et cetera.

24 ~~Now, do you feel that the sponsor has~~

1 adequately defined and demonstrated an increased depth of  
2 focus? This is the issue you've been talking about with  
3 intermediate distance, with multifocal versus bifocal, and  
4 we need to have a sense of feeling from the panel how best  
5 they should discuss the issue of increased depth of focus.

6 DR. BULLIMORE: Dr. Chairman, I believe we  
7 voted seven to three in favor of that first question. What  
8 else do you want us to do?

9 DR. ROSENTHAL: You believe they've adequately  
10 defined and demonstrated?

11 DR. BULLIMORE: According to my notes, we took  
12 a vote in favor, seven to three, in terms of question 1.

13 DR. ROSENTHAL: And yet, you said at another  
14 time that they did not demonstrate any improvement in  
15 intermediate distance.

16 DR. McCULLEY: Right. Yes. I think we've said  
17 that we think that they've demonstrated good function at  
18 distance, good function at near, but stress that they have  
19 not demonstrated any increase in function in any  
20 intermediate zone with this lens.

21 DR. RUIZ: And that they have not demonstrated  
22 even with near in 100 percent cases --

23 MS. THORNTON: Dr. Ruiz, I can't hear you.

24 ~~DR. RUIZ: I think that has been demonstrated~~

1 that it increases the depth of focus, that a certain  
2 percent of people, greater than 50 percent -- what is the  
3 percentage? Seventy? -- can read without spectacles at  
4 near. It's been demonstrated.

5 DR. McCULLEY: Well, with bilateral multifocal,  
6 it's 98 percent could see J3.

7 DR. MACSAI: With add.

8 DR. McCULLEY: Without anything. Without  
9 anything --

10 DR. RUIZ: So it has been demonstrated. It's  
11 not 100 percent.

12 DR. McCULLEY: Ninety-eight with bilateral  
13 multifocal lenses. I don't like the multifocal, but  
14 multifocal lenses is more than one, so it's multi, I guess,  
15 but that 98 percent of patients with bilateral multifocal  
16 lenses saw 20/40 or better at distance and J3 or better at  
17 near, and that is --

18 DR. SUGAR: And that's at MD-6. It's 82.6  
19 percent.

20 DR. STULTING: Are we correct in quoting that,  
21 Malvina?

22 DR. MACSAI: No, it's not right with add.

23 DR. STULTING: Bruce, you want to add some  
24 information?

1 DR. DRUM: Bruce Drum, FDA. I'd like to try to  
2 clarify the problem that we're having with this set of  
3 issues. It seems to us that there's, if not an actual,  
4 than an implied implication from increased depth of focus  
5 to saying that there's an improvement in intermediate  
6 function. In other words, it's not clear how you can have  
7 an increased depth of focus without some effect on  
8 intermediate function. Even if you can define it in such a  
9 way that technically you have an increased depth of focus,  
10 it gives the implication to the patient and the physician  
11 that there's an improvement in vision throughout a range  
12 from distance to near, and so that's why we're asking the  
13 question about the increased depth of focus as part of the  
14 indications.

15 DR. MACSAI: May I suggest that if you remove  
16 the first five words of that statement, you eliminate the  
17 issue.

18 DR. BULLIMORE: Yes. In spite of what I said  
19 earlier, I could support taking it out of the indications,  
20 but we were asked the question had they shown it. If you  
21 want it out of the indications, I could support that.

22 DR. STULTING: Help me with understanding this.  
23 To me, depth of focus means the distance at which objects  
24 are within some acceptable focus parameter, 20/40 or

1 better, 20/20 or better, or something, that it's the  
2 distance range at which you achieve that acuity.

3 DR. DRUM: Right.

4 DR. STULTING: Ordinarily, we consider that to  
5 be contiguous.

6 DR. DRUM: Right.

7 DR. STULTING: But in this case, it may not be,  
8 because you've got an improvement here, an improvement out  
9 there, and no improvement in the middle.

10 DR. DRUM: Right.

11 DR. STULTING: So what you're concerned about  
12 is the fact that it's not contiguous and people might infer  
13 that.

14 DR. DRUM: Right. The depth of focus implies  
15 an improvement over the entire range.

16 DR. RUIZ: Why do you have to use the term?

17 DR. DRUM: You can define depth of focus -- in  
18 fact, the standard definition of the depth of focus is that  
19 you achieve at least a certain acuity, but in this case the  
20 criterion that you pick may have a big effect on the  
21 result. If you choose 20/40, you may just barely skim  
22 under the depth of focus curve through the entire range,  
23 but if you go to 20/35, suddenly there's no difference  
24 between mono and multifocal, and so I think it's

1 misleading.

2 DR. MACSAI: May I make a proposal?

3 DR. STULTING: I think I understand the issue.

4 Does everybody else understand the issue?

5 DR. MACSAI: Yes. May I make a proposal?

6 DR. STULTING: It's been suggested that we  
7 remove the first five words.

8 DR. MACSAI: That's right. That's what I'd  
9 like to suggest.

10 DR. STULTING: Would everybody agree on that?  
11 Six words.

12 DR. MACSAI: Six.

13 DR. RUIZ: So read it, Mr. Chairman.

14 DR. STULTING: I'm sorry. It's six words.

15 We're going to remove the first six words, so that it reads  
16 "increased near vision without reading add versus a  
17 comparable monofocal IOL."

18 DR. SONI: I don't think we need the word  
19 "increased" either, actually. "The AMO Array multifocal  
20 lenses are indicated for those patients who desire near  
21 vision without reading add."

22 DR. STULTING: Well, you're probably right, I  
23 would guess.

24 ~~DR. BULLIMORE: I guess it's how we define near~~

1 vision. If the patient's happy with J10, then they still  
2 have -- I think we have to imply that there's some value  
3 added here, and I think the word "increased" should stay,  
4 but I think we're down to the point of semantics, and would  
5 be happy to defer to our eminent colleagues over there.

6 DR. STULTING: That suggestion wasn't met with  
7 enthusiasm. As we get longer, we take fewer votes.

8 Now, we do need to go back. We promised that  
9 we would go back and talk about the feeling that people had  
10 who voted no on these other topics.

11 Are there any other issues that we need to deal  
12 with labeling now?

13 DR. ROSENTHAL: I don't think we need --

14 DR. McCULLEY: We need a motion for the PMA.

15 DR. ROSENTHAL: For the PMA. I don't think we  
16 need that anymore.

17 DR. STULTING: What I suggest that we do,  
18 eventually, when we get finished with this, then we can  
19 make a motion for the PMA to be accepted with the  
20 conditions that are included in the transcript or reflected  
21 in our discussions.

22 DR. ROSENTHAL: Correct.

23 DR. STULTING: Is that right?

24 DR. ROSENTHAL: Correct, and we are now happy

1 with all your discussions of all the points, albeit in the  
2 order that we had asked them.

3 (Laughter.)

4 DR. McCULLEY: I move what he said. I move  
5 what he said.

6 DR. STULTING: The agency has expressed  
7 pleasure with the discussions so far. Is there anybody on  
8 the panel who is uncomfortable in any way or displeased or  
9 has some degree of displeasure or feels like something else  
10 needs to be said?

11 DR. MACSAI: We haven't discussed bifocal  
12 versus multifocal wording, but I don't know that we can.  
13 We didn't finish.

14 DR. STULTING: We need to handle that, I guess.

15 Donna, what I was actually asking you was if  
16 there was some standard or some rule or some determination  
17 had already been put in place at the agency, or is this  
18 still up for discussion? Bifocal versus multifocal.

19 DR. RUIZ: Mr. Chairman, it seems like, in  
20 keeping with the fear of using the term "depth of focus,"  
21 that bifocal fits this better than multifocal.

22 MS. LOCHNER: I do think we're at a crossroads  
23 here. We have had a policy that we've allowed companies to  
24 use the term "multifocal" during their investigational

1 studies, but I do feel we're at a point where this could  
2 potentially be the first lens that's approved for  
3 marketing, and so I think any recommendation you have in  
4 this regard would be appreciated.

5 DR. FERRIS: Well, especially since down the  
6 road there's likely to be a multifocal.

7 DR. STULTING: If we make a decision, we need  
8 to set a specific criterion on it so it's clear what we did  
9 and why we did it, and so that everybody else can play by  
10 the same rules, it seems to me. I fear that that would  
11 lead to a big discussion about optics and exactly what  
12 portion needs to be in focus, and what portion of the optic  
13 needs to be devoted to this, that, and the other. You  
14 know, if you have a trifocal, is that a multifocal, et  
15 cetera? But I guess we need to deal with it.

16 DR. BULLIMORE: Mr. Chairman, I think multi  
17 implies more than one. I think the concerns that were  
18 raised about multifocal really pertain to intermediate  
19 vision and claims pertaining to increased intermediate  
20 vision. My sense is that we've adequately taken care of  
21 that in the labeling. I would, for one, be prepared to let  
22 the term "multifocal" stand in the name of the device and  
23 move on.

24 DR. STULTING: Woody?

1 DR. VAN METER: I would like to dissent,  
2 because I think other designs may become available in the  
3 future and for the consumer, patients as well as  
4 physicians, I think it would helpful to differentiate a  
5 potentially -- for instance, an aspherical design, which  
6 would give you a smooth intermediate range, should be  
7 differentiated from a trifocal or bifocal or multifocal  
8 lens. It might not be appropriate to discuss that here,  
9 but it probably should be discussed at some point. I  
10 foresee confusion if other lens designs that are also  
11 multifocal lenses become indistinguishable to either the  
12 patient or the physician.

13 DR. STULTING: Well, one of the concerns that  
14 we've expressed is that multifocal implies some advantage  
15 over bifocal. It's entirely possible that a lens such as  
16 you are describing would not truly be advantageous, and so  
17 the issue becomes as to whether you should assign a name  
18 that we're concerned about implying functionality to a lens  
19 that may not be more functional.

20 DR. VAN METER: With contact lenses, there is  
21 definitely difference in function and satisfaction with  
22 patients that are provided with intermediate range over  
23 bifocal range. Again, it's a labeling issue, and as long  
24 as patients realize that this lens is not designed to give

1 intermediate distance, it's fine.

2 DR. STULTING: I was listening to your  
3 comments, but I'm not sure that they are pertinent and  
4 translatable, because an intraocular lens implant doesn't  
5 move relative to the pupil, we hope, and a contact does.

6 DR. VAN METER: However, the simultaneous  
7 design of contact lenses, which effectively don't move --  
8 most soft bifocal lenses don't move on the cornea.

9 DR. STULTING: But the comparison one does.

10 DR. RUIZ: Mr. Chairman?

11 DR. STULTING: Go ahead.

12 DR. RUIZ: There's probably been two hours'  
13 worth of discussion today on not saying that there's any  
14 intermediate focus here, that there are two foci. One's  
15 distance and one's near. That means bi.

16 DR. STULTING: There are also people who would  
17 say bi is multi because that's more than one, so there are  
18 a lot of arguments here.

19 DR. RUIZ: At this point, it means two.

20 DR. STULTING: Joel, do you have some wisdom  
21 for us?

22 DR. SUGAR: No, I haven't yet, but the term  
23 "array" also implies a spectrum of, rather than two, so the  
24 ~~Array plus multifocal is a reinforcing of the multiplicity.~~

1 I would like to let them use the term "array" because  
2 that's not our job, but to make it bifocal.

3 DR. STULTING: Other comments?

4 DR. BRADLEY: Just a comment on the technical  
5 definition of bifocal versus multifocal. As you saw with  
6 this lens design, it's not 100 percent either near or  
7 distance. There is some intermediate foci, if you want to  
8 think about it that way, and that's true for just about  
9 every design. The only one that I know that does not have  
10 that would be a birefringent lens, but all the ones that  
11 are either defractive or use this zone approach always have  
12 some boundary zone.

13 So it becomes a matter of degree. Well, how  
14 much of the pupil area has to focused at intermediate  
15 distance for it to be called multifocal? It becomes a  
16 difficult matter of degree, I think, and I don't know --

17 DR. SUGAR: It needs to be more than they have.

18 DR. STULTING: My blurred memory of the  
19 previous discussion is now coming into better focus.

20 (Laughter.)

21 DR. STULTING: I can remember flat lens  
22 discussion, why it was such a disaster.

23 Can we get some guidance? Do you want a real  
24 recommendation about this? I think that it's going to

1 amount to an up/down vote, because there are a number of  
2 arguments for one side and another, and everybody pretty  
3 much knows them I think at this point.

4 MS. LOCHNER: If you want to see the labeling  
5 reflected with one word or the other, you have to make a  
6 recommendation. If it's not something you feel is  
7 important enough to change the labeling, we'll just take  
8 your comments under advisement, but if you want to see the  
9 lens advertised a certain way or labeled a certain way, we  
10 need your recommendation in that regard.

11 DR. BRADLEY: I recommend that they be allowed  
12 to use multifocal, but it be very clear in the patient  
13 information brochure that this does not imply anything but  
14 a near add, basically.

15 DR. BULLIMORE: I second.

16 DR. STULTING: Is there further discussion of  
17 this point?

18 DR. SONI: Well, why do we want to do that?  
19 Because everything we've done this afternoon, we've tried  
20 to stay away from that. We've tried to eliminate the word  
21 "intermediate" or at least address that issue. So why not  
22 make it very clear what this lens is?

23 DR. MACSAI: Why not take a vote?

24 DR. STULTING: Does anybody feel that they have

1 some pertinent information that's not already been brought  
2 to the floor?

3 DR. BULLIMORE: Yes. I don't want to cloud the  
4 issue any further, but I'm sure there must be ANSI  
5 standards for what are progressive spectacle lens or  
6 bifocal spectacle lens or multifocal spectacle lenses.  
7 Donna's shaking her head. Okay. I was wrong.

8 DR. RUIZ: Let's take a vote.

9 DR. FERRIS: Just a quick comment. It seems to  
10 me that it wouldn't be inappropriate to say that this was  
11 -- if they want the AMO Array near and distance silicone  
12 posterior, rather than multifocal, and as a semanticist, I  
13 actually think that multiple probably usually in normal  
14 context means more than two.

15 DR. STULTING: If there is no one here that  
16 feels that their opinion can be swayed, then we should  
17 probably vote. Is that the case? All right. Those of you  
18 who believe that this lens should be labeled as a  
19 multifocal, please raise your hand.

20 (No response.)

21 DR. BRADLEY: Could we allow the vote to be on  
22 whether to let Allergan choose what name?

23 DR. STULTING: Those who believe that the vote  
24 should be that the lens should be labeled as a bifocal

1 lens, please raise your hand.

2 (Show of hands.)

3 DR. STULTING: I saw eight hands for bifocal,  
4 and that means that there were three abstentions. Would  
5 those who abstained please state your position? Dr.  
6 Bullimore? That's one abstaining. Dr. Bradley?

7 DR. BRADLEY: Yes, I abstained for the reasons  
8 I've already said.

9 DR. STULTING: Karen?

10 DR. BANDEEN-ROCHE: I abstained for exactly Dr.  
11 Bradley's reasons.

12 DR. STULTING: There were three abstentions and  
13 eight who felt that it should be a bifocal. Is that clear  
14 enough?

15 Are there any other comments about the PMA?  
16 Any other thoughts about the labeling? I think I've gotten  
17 everything that was on my notes taken care of. Anybody  
18 from the FDA that would like to see us touch on other  
19 things or things that are not clear that we need to bring  
20 out?

21 DR. ROSENTHAL: No, sir.

22 DR. STULTING: Eve?

23 DR. HIGGINBOTHAM: To be consistent with our  
24 ~~earlier discussion this morning in terms of the capsular~~

1 bag versus sulcus, can we just adapt the same kind of  
2 wording for this lens?

3 DR. ROSENTHAL: The answer is yes.

4 DR. STULTING: Let's see. We can entertain a  
5 motion now, sort of in the form that it be approved with  
6 the labeling suggestions and the conditions placed on it,  
7 including the one that just recently was made, and that is  
8 that the verbiage regarding capsule and bag fixation be  
9 attached to this one just like the one from this morning.

10 DR. McCULLEY: I'd like to make a motion for  
11 approval along those lines.

12 PARTICIPANT: Second.

13 DR. STULTING: Officially, the motion has been  
14 made and seconded that we recommend conditional approval  
15 with the conditions that were attached in the discussion.  
16 Those in favor, raise your hands, please.

17 (Show of hands.)

18 DR. STULTING: That's 10 yes.

19 Those opposed?

20 (Show of hands.)

21 DR. STULTING: That's one opposed.

22 We need to go around the table and state your  
23 support for your vote, whichever way it may have been.

24 Joel?

1 DR. SUGAR: I voted yes because I think we've  
2 adequately discussed the conditions and the reasons why  
3 those conditions should be there. With those conditions, I  
4 think it's acceptable.

5 DR. BANDEEN-ROCHE: Yes, I agree. I believe  
6 that safety and efficacy has been demonstrated, subject to  
7 all of the conditions that have been discussed.

8 DR. SONI: I agree with both of them.

9 DR. RUBIN: I agree for the same reason.

10 DR. HIGGINBOTHAM: Ditto.

11 DR. McCULLEY: Same.

12 DR. BRADLEY: I voted yes because I think, with  
13 the recommendations we have made, it's possible for  
14 patients to give their informed consent to become  
15 multifocal or bifocal, whatever we want to call it.

16 DR. BULLIMORE: All of the above.

17 DR. GREENIDGE: All of the above.

18 DR. MACSAI: I voted to disapprove this PMA for  
19 the AMO Array Multifocal Intraocular Lens because, despite  
20 a skewed, perhaps noncataractous, patient population, the  
21 benefits do not appear to outweigh the risks. If the  
22 benefits of this lens are J3 vision at near, as said by the  
23 sponsors, and the pre-op vision at near was J3 in 83  
24 percent of patients and improves to 99 percent with add

1 postoperatively, the 16 percent increase in near vision is  
2 not sufficient to warrant the possible risks.

3           These risks include 15 percent severe halos, 11  
4 percent severe glare, decreased acuity with low contrast,  
5 decreased ability to detect signs, roadway hazards, and  
6 driving in fog. These risks present a potential safety  
7 problem for multifocal IOL patients when they are driving  
8 and to other drivers or pedestrians.

9           The lens is really a bifocal lens. There is no  
10 improvement in intermediate distance and there is only a  
11 two-line improvement, which could equally be achieved by  
12 calculating the power of the IOL to undercorrect the  
13 patient by 0.5 to 1.0 diopter. Doing so does not carry the  
14 risks of with safety to driving. Fourteen percent of the  
15 patients still require add to achieve J3 vision at near, 24  
16 percent still require add for near tasks, and 43 percent  
17 still wear glasses.

18           I would feel more comfortable with approval of  
19 this PMA if the pre-op vision of the cohort was not 70  
20 percent 20/40 at distance and 83 percent J3 with  
21 correction, so that a more significant benefit could be  
22 demonstrated. Also, the potential safety issue regarding  
23 multifocal patients driving needs further clarification and  
24 analysis.

1 DR. VAN METER: Woodford Van Meter. I voted  
2 for conditional approval. The objective data presented  
3 suggest to me that the improvement in near vision does not  
4 easily outweigh the loss of distance vision and associated  
5 complications, most noticeably driving. In the average  
6 cataract population, troubled driving is probably a serious  
7 concern and what makes people have cataract surgery. The  
8 difficulty with driving under adverse conditions bothers me  
9 because these patients had cataract surgery for that very  
10 reason.

11 Medical problems that may require surgical  
12 intervention of the posterior pole and the potential  
13 adverse effect of decentration, power calculation areas,  
14 pupil size, and astigmatism all raise questions about both  
15 safety and efficacy to me. However, there are a  
16 substantial number of patients who have benefitted from  
17 this lens and have done well. I believe that this lens  
18 should be available for judicious use in carefully selected  
19 patients with appropriate informed consent.

20 DR. STULTING: Is everybody happy?

21 That should conclude today's proceedings. I'll  
22 remind you to please leave your documents from today's  
23 discussions here in this room and FDA staff will pick them  
24 up. Don't leave things that you want to have tomorrow,

1 because they will disappear overnight.

2 Are there any other announcements?

3 (No response.)

4 DR. STULTING: Okay. The meeting is adjourned.

5 Thank you very much.

6 (Whereupon, at 6:06 p.m., the meeting was  
7 recessed, to reconvene at 8:00 a.m. on Friday, July 11,  
8 1997.)

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