

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

OPHTHALMIC DEVICES PANEL
108TH MEETING

Friday, March 5, 2004

9:00 a.m.

Gaithersburg Holiday Hotel
2 Montgomery Village Avenue
Gaithersburg, Maryland

P A R T I C I P A N T S

Jayne S. Weiss, M.D., Chairperson
Sara M. Thornton, Panel Executive Secretary

VOTING MEMBERS:

Arthur Bradley, Ph.D.
Michael R. Grimmett, M.D.
Allen C. Ho, M.D.
William D. Mathers, M.D.
Timothy T. McMahon, O.D.

INDUSTRY REPRESENTATIVE:

Ronald E. McCarley

CONSULTANTS:

Neil M. Bressler, M.D.
Jeremiah Brown, Jr., M.D.
Alexander J. Brucker, M.D.
Frederick J. Ferris, M.D.
Leo J. Maguire, M.D.
Janine A. Smith, M.D.
Walter J. Stark, M.D.

FDA PARTICIPANTS:

A. Ralph Rosenthal, M.D.
Malvina B. Eydelman, M.D.
Joseph N. Blustein, M.D.
Don Calogero, M.S.
Gene N. Hilmantel, O.D., M.D.

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

2 Call to Order

3 DR. WEISS: I would like to call this
4 meeting of the Ophthalmic Devices Panel to order,
5 and we will have introductory remarks from Sarah
6 Thornton, the Executive Secretary of the Panel.

7 MS. THORNTON: Good morning. On behalf of
8 the FDA, I would like to welcome you to the 108th
9 meeting of the Ophthalmic Devices Panel.

10 Before we proceed with today's agenda, I
11 have a few short announcements to make. I would
12 like to remind everyone to sign in on the
13 attendance sheets in the registration area, just
14 outside the meeting room. All public handouts for
15 today's meeting are available at the registration
16 table. Messages for panel members and FDA
17 participants, information or special needs should
18 be directed through Ms. Annemarie Williams who is
19 available in the registration area. The phone
20 number for calls to the meeting area is
21 301-977-8900.

22 In consideration of the panel, the sponsor
23 and the agency, we ask that those of you with cell
24 phones and pagers either turn them off or put them
25 on vibration mode while in this room, and make your

1 calls outside the meeting area.

2 Lastly, will all meeting participants
3 please speak clearly into the microphone and give
4 your name so that the transcriber will have an
5 accurate recording of your comments?

6 At this time I would like to extend a
7 special welcome and introduce to the public, the
8 panel and the FDA staff two new panel consultants
9 who are with us at the table today for the first
10 time.

11 On my right, Dr. Neil Bressler, Professor
12 of Ophthalmology, with an international referral
13 practice in the Retinal Vascular Center at the
14 Wilmer Eye Institute of The Johns Hopkins
15 University School of Medicine; and Dr. Jeremiah
16 Brown, Jr., who is the director of Ophthalmology
17 Research at the Walter Reed Army Institute of
18 Research Laboratory at Brooks Air Force Base in San
19 Antonio, in addition to maintaining a private
20 retina practice with Ophthalmology Associates of
21 San Antonio. Welcome, gentlemen.

22 Will the remaining panel members please
23 introduce themselves, beginning with Rick McCarley?

24 MR. MCCARLEY: Good morning. My name is
25 Rick McCarley. I am President of Ophtec and I am

1 the industry representative.

2 DR. BRUCKER: Alexander Brucker,
3 Philadelphia, Pennsylvania, Professor of
4 Ophthalmology at the University of Pennsylvania
5 Scheie Eye Institute.

6 DR. FERRIS: Rick Ferris, I am the head of
7 the Division of Epidemiology and Clinical Research
8 at the National Eye Institute.

9 DR. BRADLEY: Arthur Bradley, Professor of
10 Vision Science, Indiana University.

11 DR. MCMAHON: Tim McMahon, Professor of
12 Ophthalmology, Department of Ophthalmology,
13 University of Illinois in Chicago.

14 DR. WEISS: Jayne Weiss, Professor of
15 Ophthalmology and Pathology, Kresge Eye Institute,
16 Wayne State University, Detroit.

17 DR. GRIMMETT: Michael Grimmett, Bascom
18 Palmer Eye Institute, University of Miami.

19 DR. MATHERS: Bill Mathers, Professor of
20 Ophthalmology at Oregon Health Sciences University.

21 DR. HO: Good morning. Allen Ho,
22 vitreoretinal surgeon, Wills Eye Hospital, Thomas
23 Jefferson University.

24 DR. SMITH: Janine Smith, Deputy Clinical
25 Director of the National Eye Institute.

1 DR. BRESSLER: Neil Bressler, already
2 introduced.

3 DR. BROWN: Jeremiah Brown.

4 DR. STARK: Walter Stark, Professor of
5 Ophthalmology, Wilmer Eye Institute, Baltimore,
6 Maryland.

7 DR. MAGUIRE: Leo Maguire, Associate
8 Professor, Mayo Clinic, Rochester, Minnesota.

9 DR. ROSENTHAL: Ralph Rosenthal, Division
10 Director, Ophthalmic and ENT Devices.

11 MS. THORNTON: Thank you. I would like to
12 note for the record that the panel consumer
13 representative, Ms. Glenda Such, will not be in
14 attendance today due to illness. Thank you, Jayne.

15 Conflict of Interest Statement

16 I would now like to read the conflict of
17 interest statement for today's meeting. The
18 following announcement addresses conflict of
19 interest issues associated with this meeting, and
20 is made part of the record to preclude even the
21 appearance of an impropriety.

22 To determine if any conflict existed, the
23 agency reviewed the submitted agenda for this
24 meeting and all financial interests reported by the
25 committee participants. The conflict of interest

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

9 Therefore, a waiver has been granted to
10 Dr. Alexander Brucker for his interest in a firm at
11 issue that could potentially be affected by the
12 panel's recommendations. The waiver allows him to
13 participate fully in today's deliberations. Copies
14 of this waiver may be obtained from the agency's
15 Freedom of Information Office, Room 12A-15 of the
16 Parklawn Building.

17 We would like to note for the record that
18 the agency took into consideration certain matters
19 regarding Drs. Alexander Brucker, Neil Bressler,
20 Frederick Ferris, Michael Grimmett, Allen Ho and
21 Jayne Weiss. They reported interests in firms at
22 issue but in matters not related to today's agenda.
23 The agency has determined, therefore, that they may
24 participate fully in all discussions.

25 In the event that the discussions involve

1 any other products or firms not already on the
2 agenda for which an FDA participant has a financial
3 interest, the participant should excuse himself or
4 herself from such involvement and the exclusion
5 will be noted for the record.

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

12 DR. WEISS: Thank you. We are going to
13 now have branch updates, Karen Warburton.

14 Branch Updates

15 MS. WARBURTON: Good morning. I would
16 like to present one item of interest from our
17 Branch. One of the device types that the VEDB
18 reviews is the ophthalmic sponge, which is used
19 during LASIK surgery. We have recently become
20 aware of Medical Device Reports, or MDRs, that
21 identified an association between ophthalmic
22 sponges and diffuse lamellar keratitis. Testing of
23 a sample of ophthalmic sponges from a lot
24 associated with a cluster of DLK cases showed
25 significantly higher levels of bacterial endotoxin

1 than a different lot. Additional MDRs have also
2 reported an association between microkeratomes and
3 DLK, although most of those reports did not
4 implicate endotoxin per se.

5 Endotoxin has been shown to cause DLK in a
6 rabbit model and there have been reports in the
7 literature implicating endotoxin from sterilizer
8 water reservoirs as a cause of DLK outbreaks.
9 Additionally, a variety of other etiological
10 factors have been suggested. However,
11 endotoxin-contaminated ophthalmic sponges have not
12 previously been identified as a possible cause of
13 DLK. Endotoxin-contaminated water used during
14 device manufacture is a potential source.
15 Historically, FDA has not required that ophthalmic
16 sponges or other devices used in LASIK surgery be
17 pyrogen or endotoxin free, and they are typically
18 not labeled as such, although many may, in fact, be
19 endotoxin free.

20 Our Branch is working with other Center
21 offices to make the ophthalmic community aware of
22 this potential cause of DLK through letters to
23 professional organizations and letters to the
24 editor in journals which we anticipate will be
25 published in the near future. We hope to encourage

1 reporting of DLK to FDA through MDR reporting, and
2 to stimulate both user and FDA investigation into
3 these outbreaks so that we can better understand
4 the role that ophthalmic devices and endotoxin in
5 particular play in DLK, and make changes in our
6 product review policies if necessary. That
7 concludes my update. Are there any questions?

8 DR. WEISS: Seeing no questions, thank you
9 very much, Karen. We will now begin the open
10 committee session with the general issues
11 discussion and the FDA team presentation. Dr.
12 Eydelman?

13 FDA Team Presentation

14 DR. EYDELMAN: Good morning.

15 [Slide]

16 Today's discussion is centered around
17 clear lens extraction for the correction of
18 presbyopia. I want to thank Dr. Blustein, Don
19 Calogero and Gene Hilmantel for organizing today's
20 presentation and preparing all the materials.

21 [Slide]

22 Clear lens extraction--or CLE as we will
23 be referring to it for the rest of the day--for the
24 correction of presbyopia is an intraocular surgical
25 procedure where non-cataractous lens is removed and

1 replaced with a multifocal intraocular lens,
2 allowing for both distance and near vision. The
3 sole purpose of this procedure is for refractive
4 correction.

5 [Slide]

6 There are several points I wanted to make
7 sure panel members are clear on. CLE is not
8 currently approved in U.S. for any indication. It
9 has been performed, as all of you know, as an
10 off-label practice for several years but mainly in
11 eyes with high refractive errors.

12 [Slide]

13 There are currently no standards or
14 guidances available for clear lens extraction with
15 IOL implantation.

16 [Slide]

17 There is currently only one multifocal IOL
18 approved in U.S., but there are quite a few under
19 investigation. Only two IOLs are approved for
20 improving near vision acuity in presbyopic
21 patients, and that is the AMO Array and the CMC
22 Vision. Several different devices utilizing quite
23 various approaches are under investigation. Again,
24 there are no standards or guidances for devices
25 solely intended for the correction of presbyopia.

1 [Slide]

2 An estimated 1.5 billion people worldwide
3 have presbyopia. Therefore, devices approved for
4 the correction of presbyopia will have a very
5 significant public health impact.

6 [Slide]

7 The challenge that faces us today is in
8 trying to design a study which will be least
9 burdensome for establishing safety and efficacy of
10 the device for the correction of presbyopia while
11 making sure that the significance to public health
12 impact due to improper trial design is considered.

13 [Slide]

14 We want to make sure that we address all
15 the appropriate aspects of the appropriate study
16 design. So, today we will ask for your
17 consideration on the control population;
18 inclusion/exclusion criteria; acceptable adverse
19 event rates; sample size; study duration; variables
20 to be investigated; efficacy endpoints and quality
21 of life assessment.

22 [Slide]

23 The goal, of course, is designing an
24 appropriate clinical trial for evaluation of clear
25 lens extraction for the correction of presbyopia.

1 The first step in pursuing that goal was
2 identification of all relevant adverse events and
3 their anticipated time course. In order to address
4 that, we did quite an extensive literature search
5 which Dr. Blustein will summarize for you.

6 [Slide]

7 DR. BLUSTEIN: Initially we looked for
8 studies that related specifically to clear lens
9 extraction for presbyopia. There were very few
10 articles that addressed this topic. There were two
11 that we found, Dick and associates and Packer and
12 associates, that dealt with clear lens extraction
13 for presbyopia. Both studies were using the Array
14 multifocal IOL.

15 [Slide]

16 Dick and associates--their study was a
17 prospective study with 25 patients. They were
18 bilateral CLE with MIOL. The average patient age
19 was 51, with a range of 44-62. The preop spherical
20 equivalent ranged from minus 25.5 to plus 5.75
21 diopters. Follow-up was at 6 months and the
22 outcomes for efficacy were very good, 100 percent
23 binocular uncorrected visual acuity of 20/30 and J4
24 or better. However, 48 percent of the patients
25 complained of star bursts and 36 percent complained

1 of halos.

2 [Slide]

3 Packer and associates, in a retrospective
4 study of 68 eyes and 36 patients--their study was
5 not limited to just clear lens extraction but 34
6 percent of the eyes had received additional
7 procedures for astigmatism. The average age was 58
8 years old and the range was from 45-81. Preop
9 spherical equivalent ranged from minus 7.5 to plus
10 6.5 diopters. Follow-up was at 3 and 6 months.
11 The outcomes--again, there was good efficacy with
12 94 percent binocular uncorrected visual acuity of
13 20/40 and J5 or better. Close to 6 percent had
14 symptomatic posterior capsular opacities requiring
15 YAG capsulotomies. There were no complication
16 rates and there were no reports or assessment of
17 visual symptoms.

18 [Slide]

19 Clear lens extraction with monofocal
20 IOLs--because there was limited information for the
21 multifocals we looked at what was done with
22 correcting other refractive procedures with clear
23 lens extraction so we looked at three areas for
24 ametropia, hyperopia and myopia.

25 [Slide]

1 Vicary and associates, in a retrospective
2 study of 138 cases with average patient age of
3 close to 49 years of age, ranging from 22-69 years
4 of age, with a range of preop spherical equivalent
5 of minus 23.75 to plus 11.62 diopters, with an
6 average follow-up time of 5 months, with a range of
7 2-26 months, reported on the following outcomes:
8 They had uncorrected visual acuity at 3 months with
9 90 percent at 20/40 or better and close to 50
10 percent had 20/20 or better. Retinal detachment at
11 5 months, there was one case so that gave a rate of
12 0.7 percent. Uveitis, again one case with the same
13 rate. Posterior capsular opacification requiring
14 YAG capsulotomies was at 8 percent. Additional
15 refractive surgeries were performed in 7 cases.

16 [Slide]

17 For clear lens extraction for hyperopia
18 there were several studies that were performed in
19 U.S., England, Belgium, India and Greece. They
20 overall reported good efficacy in these studies.
21 The sample sizes were relatively small, ranging
22 from 18 to 50 eyes. Patient age ranges were from
23 19-86, and this is across all these studies. The
24 preop spherical equivalent ranged from plus 2.75 to
25 plus 13 diopters. The follow-up was anywhere from

1 1-60 months in these patients.

2 [Slide]

3 The complications reported for the clear
4 lens extraction for hyperopia collectively in these
5 studies were that for posterior capsular
6 opacification requiring YAG capsulotomy ranged from
7 5.6 percent to 54 percent in these studies.
8 Posterior capsular tears at the time of surgery
9 ranged from close to 3 percent to a little over 5
10 percent. Two cases required IOL exchange. Then,
11 there were single case events reported of iris
12 prolapse, iridodialysis, corneal burn and malignant
13 glaucoma. The malignant glaucoma case occurred two
14 years after implantation. Endothelial cell loss
15 was reported for one study after 12 months at 7.38
16 percent.

17 [Slide]

18 Then we looked at clear lens extraction
19 for high myopia. There are several reported
20 studies with high efficacy. The problems with
21 these studies is that there are short follow-up
22 times that are associated with them and also
23 exclusion of lost to follow-up on patients.

24 [Slide]

25 Colin and associates had a 7-year

1 follow-up of their study of clear lens extraction
2 for high myopia. There were 52 eyes in 30
3 patients. Preop spherical equivalent average was
4 minus 16.9 diopters and the axial length in 64
5 percent was greater than 29 mm. Average patient
6 age was 36, a little over 36 years of age, with a
7 range of 22-51 years of age. They had performed
8 laser pre-treatments on anyone who had suspicious
9 lesions for future retinal detachments, treating
10 lattice, retinal tears and retinal holes. The
11 results of this study showed that close to 60
12 percent were within 1 diopter of emmetropia and
13 approximately 85 percent were within 2 diopters of
14 emmetropia.

15 [Slide]

16 Colin and associates reported the retinal
17 detachment rate at 4 years and then again at 7
18 years. At 4 years it was 2 percent and at 7 years
19 it was 8.1 percent. This points out the importance
20 that retinal detachments can occur later in the
21 postop period.

22 [Slide]

23 In this study 75 percent of the retinal
24 detachment had YAG capsulotomies prior to the
25 retinal detachments. One eye had YAG one year

1 before the retinal detachment and two eyes had YAG
2 two years before the retinal detachment. In the
3 four eyes that had retinal detachments the best
4 corrective visual acuity ranged from 20/30 to
5 20/200 and the visual acuity in the fellow eye
6 ranged from 20/30 to 20/100 in the untreated eye.

7 [Slide]

8 The slide on the right shows the posterior
9 opacification with YAG capsulotomies. At 4 years
10 it was approximately 37 percent and 61 percent
11 after 7 years. So, again, this is to illustrate
12 that complications of posterior opacification can
13 occur beyond the follow-up time, short follow-up
14 time. So, after 7 years there was a significant
15 number that also had complications of
16 opacification.

17 [Slide]

18 The mean time to YAG in this study was a
19 little bit over 48 months, ranging from 9-75
20 months. Close to 37 percent within 4 years of
21 clear lens extraction had significant posterior
22 capsular opacification and 61 percent within the 7
23 years. The odds ratio of retinal detachment after
24 clear lens extraction and YAG versus no YAG was
25 2.0. Other complications that were reported in

1 Colin's study were subfoveal choroidal
2 neovascularization in one eye which occurred 9
3 months after surgery, and there was a decrease in
4 best corrected visual acuity in that eye from 20/50
5 to 20/200.

6 [Slide]

7 Ripandelli and associates were reporting
8 from the refractive surgeons studies. They were
9 reporting from the retinal surgeons perspective.
10 They reported on retinal detachment secondary to
11 clear lens extraction for high myopia. they saw 53
12 eyes in their practice. The preop spherical
13 equivalent average was minus 19.5 diopters, ranging
14 from minus 14 to minus 29. Patient age was an
15 average of 37.5, ranging from 25-58 years of age.
16 This is in Italy, this practice. Laser pre-clear
17 lens extraction was performed in close to 58
18 percent of these eyes. The time after clear lens
19 extraction to the retinal detachment average was
20 2.25 years and ranged anywhere from 1 month to 4
21 years. YAG capsulotomies had been performed in a
22 little bit over 25 percent of these patients.
23 Then, macular involvement was in 100 percent of the
24 eyes that had been operated on.

25 [Slide]

1 Twelve eyes were lost to follow-up because
2 they didn't come back for surgery even though that
3 was recommended. For retinal detachment repair, 88
4 percent had the retina reattached; 41.5 percent had
5 proliferative vitreoretinopathy; 34 percent had
6 posterior retinal breaks. The results are that 22
7 percent had best corrected visual acuity of 20/60
8 or better. One patient had hand motion in one eye
9 and 20/100 in the other. The pre-clear lens
10 extraction visual acuity in this patient was 20/20
11 and 20/25.

12 [Slide]

13 O'Brien and associates reported that for
14 clear lens extraction for high myopia the efficacy
15 is certainly encouraging, that this seems to be
16 very beneficial in terms of correcting the
17 refractive error. However, the potential
18 complications still outweigh the risks.

19 [Slide]

20 Literature review for clear lens
21 extraction--there was only one study with long-term
22 follow-up. That was the Colin study that followed
23 for 7 years. The rates of retinal detachment
24 continue to increase postop, 2 percent at 4 years
25 and then 8 percent at 7 years. Lack of long-term

1 retinal detachment rates post clear lens extraction
2 is a concern. So, we did a little literature
3 search on retinal detachment rates post cataract
4 extraction.

5 [Slide]

6 About 40 percent of all retinal
7 detachments occur post cataract extraction.
8 Patient-dependent risk factors include age, gender,
9 refractive state, fellow eye, status of the
10 posterior vitreous. Those are patient-dependent
11 risk factors.

12 [Slide]

13 Surgeon-dependent risk factors include
14 surgical technique, whether it is intracapsular or
15 extracapsular, phacoemulsification and also
16 incision size, capsulotomy and maintaining anterior
17 chamber depth. Intraoperative complications are
18 also risk factors--torn posterior capsule or
19 vitreous loss.

20 [Slide]

21 Then, postoperative risk factors include
22 trauma and YAG capsulotomy.

23 [Slide]

24 Norregaard and associates had a
25 population-based Danish study which looked at all

1 cataract inpatient surgeries done from 1985 to 1987
2 with 4-6 years follow-up and patient age of 50 or
3 over. They used a reference group of a cohort that
4 was age matched, gender matched and had no previous
5 intraocular surgery.

6 [Slide]

7 The 4-year retinal detachment risk after
8 cataract surgery for various surgical techniques
9 was shown to be 3.2 percent for extracapsular
10 without IOL; 2.8 percent for intracapsular cataract
11 extraction without IOL; and 0.93 percent for
12 extracapsular without IOL. The reference group had
13 retinal detachment rate of 0.21 percent.

14 [Slide]

15 The 4-year retinal detachment risk after
16 extracapsular cataract extraction with IOL was
17 stratified by age. There were increasing rates
18 with decreasing age, 2.43 percent for the age group
19 of 50-59 years of age; 60-69 years of age, 1.51
20 percent; 0.82 percent for 70-79 years of age; and
21 80 and above was 0.47.

22 [Slide]

23 This relative risk for retinal detachment
24 stratified by age, with the reference group having
25 no intraocular surgery, shows that there is a

1 significant relative risk in the younger age
2 groups. In the 50-59 group, they are over 20 times
3 more likely to have a retinal detachment having had
4 surgery; for 60-69 they are 12.5 times more likely
5 to have retinal detachment; 70-79, close to 7 times
6 more likely; and even 80 and older still, close to
7 4 times more likely to have retinal detachment when
8 no surgery was performed.

9 [Slide]

10 Javitt and associates, did a U.S.
11 population-based study looking at all Medicare
12 beneficiaries having cataract extraction in the
13 year 1984, with a sample size of over 300,000 and
14 they excluded the younger age Medicare
15 beneficiaries and only included the 66 and older
16 group. Extracapsular extraction was done in 60
17 percent of these patients; intracapsular was done
18 in 31 percent; and phacoemulsification in 9
19 percent. They followed this in the database for
20 rehospitalization for retinal detachments over 4
21 years.

22 [Slide]

23 In their study, they showed that the risk
24 factors were dependent on race, with whites being
25 1.7 times more likely to have a retinal detachment

1 than Blacks and with the various surgical
2 techniques the intracapsular having the greatest risk
3 and phacoemulsification the lowest. The younger
4 age is also at greater risk for retinal detachments
5 compared to the older, and we will go into that a
6 little bit more.

7 [Slide]

8 For 4-year retinal detachment risk after
9 cataract surgery stratified by age, they found 2.2
10 percent for 65-69 years of age patients; 1.3
11 percent for 70-79 year-old patients; 0.6 percent
12 for 80-89; and 0.2 percent for 90 and above.

13 [Slide]

14 When you look at the relative risk, the
15 65-69 year age group were 18 times more likely to
16 have retinal detachment than the no surgery group;
17 70-79 years old, close to 11 times more likely to
18 have retinal detachment; 80-89, 5 times more
19 likely; and 90 or above, 1.67 times more likely to
20 have retinal detachment.

21 [Slide]

22 Javitt did another study. This was based
23 on a 5 percent sample of Medicare beneficiaries.
24 They looked at inpatient and outpatient surgeries
25 between 1986 and 1987. The sample size was over

1 57,000, and they looked at 3-year follow-up for
2 retinal detachment.

3 [Slide]

4 The cumulative 3-year retinal detachment
5 rate was 0.81 percent, which was a rate similar to
6 the previous inpatient study. Also, they showed
7 that younger patients were more at risk than older
8 patients.

9 [Slide]

10 This is from the 3-year retinal detachment
11 risk after extracapsular cataract extraction,
12 showing 0.95 percent for the 65-69 year-old group;
13 0.51 percent for the 70-79 year-olds; 0.24 percent
14 for the 80-89 year-olds; and 0.08 percent for the
15 90 and above.

16 [Slide]

17 Looking at the slide on your right,
18 summarizing the Danish study and the earlier Javitt
19 study, they found one-year rates for retinal
20 detachment with extracapsular with IOL and for the
21 Danish study it was 0.42 percent and the 4-year
22 rate was 3.2 percent for extracapsular without IOL
23 and then 0.93 percent for extracapsular with IOL.

24 In the Javitt study the one-year rate for
25 combining extracapsular cataract extraction whether

1 it was with or without IOL was 0.3 percent and for
2 phacoemulsification it was 0.4 percent. The 4-year
3 rate was 0.9 percent for extracapsular cataract
4 extraction and 1.17 percent for
5 phacoemulsification.

6 [Slide]

7 The relative risk for retinal detachment
8 at one year in the Danish study, extracapsular
9 cataract extraction with IOL was 14 times more
10 likely to have retinal detachment than no surgery.
11 At 4 years, extracapsular cataract extraction with
12 IOL was 26.67 times more likely to have retinal
13 detachment than no surgery; and extracapsular
14 cataract extraction with IOL was 7.75 times more
15 likely.

16 In the U.S. study at one year
17 extracapsular cataract extraction was 10 times to
18 have a retinal detachment, and with
19 phacoemulsification it was 13.3 times more likely
20 to have a retinal detachment. At 4 years the
21 relative risk for retinal detachment with
22 extracapsular cataract extraction was 7.5 times and
23 for phacoemulsification was 9.75 times.

24 [Slide]

25 Rowe and associates reported on cumulative

1 retinal detachment rates after extracapsular
2 cataract extraction and phacoemulsification. It
3 was a population-based study in Olmstead County,
4 Minnesota. It was an incidence study. They looked
5 at retinal detachment diagnosed between 1976 and
6 1995. The retinal detachment rates were adjusted
7 for age and gender and they were compared with
8 non-surgical retinal detachment rates.

9 [Slide]

10 The cumulative retinal detachment rates
11 after extracapsular cataract extraction and
12 phacoemulsification at 2 years was 0.36 percent
13 compared to 0.034 percent with no surgery. At 5
14 years it was 0.77 percent compared to 0.13 percent
15 with no surgery. At 10 years it was 1.29 percent
16 compared to 0.25 percent with no surgery.

17 [Slide]

18 Looking at this as relative risk, at 2
19 years it is 10.59 times more likely to have a
20 retinal detachment with cataract surgery; at 5
21 years it was 5.92 times more likely; and at 10
22 years it was 5.16.

23 [Slide]

24 DR. EYDELMAN: In light of the literature
25 summary that you just heard, the first question we

1 would like you to consider is do you recommend a
2 control population for studies of clear lens
3 extraction for the correction of presbyopia, or do
4 you believe that the study subject's own
5 preoperative data is sufficient for comparison?

6 [Slide]

7 If you do recommend a control population,
8 which one of the following do you believe to be
9 appropriate? Is it historical control, active
10 control or some other control? Active control
11 would imply concurrent enrollment in a study of
12 subjects with no previous ocular surgery. For
13 historical control that you would obtain from the
14 literature, there are several options, subjects'
15 status post CLE for correction of presbyopia or
16 those that have had a composite of all different
17 refractive indications; subjects' status post
18 cataract extraction or those that had no previous
19 ocular surgery. Those are, obviously, all choices
20 we would like you to consider.

21 [Slide]

22 Any time we define an appropriate study
23 population for the investigation the real issue is
24 identifying patients for whom risk/benefit
25 assessment warrants enrollment in such a study.

1 [Slide]

2 Therefore, the question we ask you is
3 should the clinical study inclusion/exclusion
4 criteria limit subject enrollment based on the
5 criteria listed below? If yes, we would like you
6 to discuss the appropriate ranges of each limiting
7 criteria for inclusion in the study.

8 [Slide]

9 Under (a) is refractive error and axial
10 length, and we would like you to consider each one,
11 the hyperopia and its associated refractive range;
12 emmetropia; myopia with its range; (b) subject's
13 age.

14 [Slide]

15 (c) Degree of accommodative loss, and in
16 that discussion we would like you to consider based
17 on what measurement you are making your
18 recommendations; (d) preoperative endothelial cell
19 count; and (e) any other factors, such as BCVA.

20 [Slide]

21 As you heard from Dr. Blustein, there are
22 several numbers that are reported in the literature
23 but all the literature essentially concurs that
24 subjects with no surgery have much less chance than
25 those that do undergo a lens extraction.

1 [Slide]

2 With that in mind, we would like you to
3 consider what should be the primary safety endpoint
4 for the study?

5 [Slide]

6 Another consensus from the literature is
7 that the younger subjects do, indeed, have higher
8 cumulative RD rates and that is basically due to
9 the vitreoretinal interface characteristics and the
10 fact that the risk continues to increase over time
11 and these subjects have essentially a greater
12 number of years left to life after the lens
13 extraction.

14 [Slide]

15 So, is retinal detachment primary safety
16 endpoint?

17 [Slide]

18 After clear lens extraction with MIOL
19 subjects might experience visual symptoms requiring
20 IOL exchange. Therefore, endothelial cell
21 densities should be adequate to withstand
22 additional surgery. From the literature review you
23 have heard only one number, 7.38 percent
24 endothelial cell loss at 12 months after CLE.
25 However, these losses are really consistent with

1 operative losses themselves.

2 [Slide]

3 Several years ago Don Calogero, myself and
4 Dr. Aresnoff, from Toronto, performed a
5 meta-analysis of a literature review to try to
6 determine what is the operative endothelial cell
7 loss secondary to cataract surgery. There we
8 determined that 8.9 percent endothelial cell loss
9 is seen secondary to extracap and 7.4 secondary to
10 phaco. These are losses that were secondary to
11 operative loss itself, i.e., the range was 2-6
12 months.

13 [Slide]

14 There is no long-term data on endothelial
15 cell loss after clear lens extraction.
16 Furthermore, there is very limited data on
17 long-term loss after cataract surgery. We all know
18 from the last several panel meetings that Bourne
19 et. al. reported 0.6 percent CLE loss for eyes
20 without any surgery. However, I don't think all of
21 you might be aware of the fact that Bourne has also
22 performed a study showing that after cataract
23 surgery itself there is a 2.5 percent cell loss
24 that continues annually. Now, this was at 10-year
25 follow-up of a rather small cohort, 64 eyes, and

1 surgeries were performed from '76 to '82, both
2 extracap and intracap, and some of the subjects
3 were left aphakic. So, the accuracy of that number
4 with respect to modern surgery is questionable, but
5 the fact that there is continuous loss secondary to
6 cataract extraction itself seems to be implicit.

7 [Slide]

8 In light of that, is endothelial cell loss
9 perhaps a primary safety endpoint, or if not a
10 primary, should it be a safety endpoint?

11 [Slide]

12 Once you discuss what should be the
13 primary safety endpoint, we would like you to
14 concentrate on the acceptable adverse event rate
15 associated with this safety endpoint.

16 [Slide]

17 The next question that we would like you
18 to consider is sample size and follow-up
19 appropriate for clear lens extraction studies. Not
20 to give you a blank screen, we did several sample
21 size assessments so you have something to work
22 with.

23 The slide on the left summarizes
24 statistics that we ran for the sample sizes that
25 would be required for maximum allowable RD rate per

1 year. Here we assume a historical control rate of
2 0.01 percent annual RD. So, in the first column we
3 have different study duration options, 1 year, 2
4 years, 3 years. Just to give you an example, if we
5 assume that the maximum allowable RD rate per year
6 should be 0.3 percent, a study design would require
7 321 subjects. That is how this table reads. If
8 you have any questions later I can describe it
9 further.

10 [Slide]

11 We also ran sample size statistics for
12 endothelial cell loss. There are two tables, this
13 and the next slide. This one is assuming a fixed
14 historical rate of 0.6 percent annual cell loss.
15 Again, in the first column you have one, two or 3
16 year study duration. Across, 1,000, 1,200, 1,400
17 and 1,500 are some of the cell densities that we
18 assumed for you to choose from as the minimum cell
19 density that you would like subjects to have at age
20 75. As a reference, down below, in the yellow, I
21 put down that the normal ECD at age 75 is 2,400
22 with a standard deviation of 500. So, once again
23 just to try to explain to you how this table works,
24 if you say that you would like for a subject at age
25 75, after having clear lens extraction performed

1 somewhere in their 40s, to end up with 1,200 cells,
2 for a one-year study that would require 319
3 subjects and for a three-year study only 26
4 subjects.

5 [Slide]

6 As I showed you before, this is the same
7 table but now assuming active control, i.e., you
8 would enroll patients who are not operated and you
9 measure their cell loss. With the same examples,
10 one year for 1,200 would be 638 and for three years
11 it would be 48.

12 [Slide]

13 So, the question is in order to adequately
14 determine the rates of all the adverse events and
15 complications of concern, what do you feel is the
16 appropriate sample size and follow-up period for a
17 CLE study for the correction of presbyopia prior to
18 the submission of the PMA?

19 [Slide]

20 I stress "prior" because the next question
21 deals with post-market studies. To clarify, the
22 post-market process can detect, identify and
23 describe new or previously undetected medical
24 device hazards. It also has the advantage of using
25 real-world medical device experience to confirm the

1 safety profile of the device that was established
2 in the pre-market submission and it could be a
3 condition of approval.

4 [Slide]

5 In light of that, do you believe a
6 post-market study is indicated? If so, what is the
7 appropriate type of study, sample size and length
8 of follow-up for such a study?

9 [Slide]

10 Acceptable adverse event rates for
11 posterior chamber IOLs at one year following
12 cataract extraction are in the FDA grid. The
13 updated FDA adverse event rates are listed for you
14 on the left, and I will spare you going through
15 them. Are these rates applicable for correction of
16 presbyopia in non-cataractous eyes for CLE at one
17 year postop? Again, we are comparing one year to
18 one year but adverse events that were historically
19 acceptable after cataract surgery now to eyes which
20 have not had cataracts.

21 [Slide]

22 Should the acceptable adverse event rates
23 be adjusted for the study duration recommended? If
24 yes, how? Furthermore, do additional adverse
25 events need to be collected? If so, what should be

1 their acceptable rates?

2 [Slide]

3 FDA believes that all multifocal IOLs'
4 safety and efficacy profiles will have to be
5 established in a cataractous population prior to
6 initiation of a clinical trial in a non-cataractous
7 population. MIOL performance in a cataractous
8 population will, therefore, be known for all tests
9 and sub-studies outlined in ANSI draft standards
10 for MIOLs.

11 [Slide]

12 On the slide on the left I summarized for
13 you in the first column all the measurements that
14 are recommended to be performed on all study
15 populations. In the column on the right are those
16 that are done in sub-studies. Just to clarify, it
17 is best spectacle corrected visual acuity at
18 distance; near visual acuity with distance
19 correction; uncorrected visual acuity at distance;
20 uncorrected visual acuity at near; pupil size; lens
21 stability; and subject survey. The sub-studies are
22 defocus curves; fundus visualization; far contrast
23 sensitivity; and functional performance.

24 [Slide]

25 Which sub-studies do you recommend for

1 inclusion in the clear lens extraction protocol for
2 evaluation of performance in this non-cataractous
3 population? A) is functional performance and the
4 functional performance study determines deficits in
5 functional vision secondary to optical effects or
6 multifocal IOLs. An example is a driving
7 simulation study which was performed for MIOs.

8 B) is contrast sensitivity and the current
9 recommendation is for grading contrast sensitivity
10 tests to assess threshold for spatial gradings.

11 C) is defocus curves and defocus
12 evaluation comparing clinical performance to the
13 theoretical lens design. What is done is that a
14 subject's best spectacle corrected visual acuity at
15 distance is obtained for the subject, and then the
16 subject is defocused in 0.5 diopter steps to minus
17 5 diopters.

18 D) is fundus visualization and the current
19 recommendation is for the investigators to rate the
20 clarity of the retinal image through multifocal
21 versus monofocal IOLs.

22 Then there is the endothelial cell
23 evaluation and I think you all know about that by
24 now, and any others that you might recommend.

25 [Slide]

1 The only current performance efficacy
2 endpoint for aphakic posterior chamber IOLs, from
3 the FDA grid once again, is post-operative BCVA of
4 20/40 or better in 92.5 percent of the subjects.
5 Is this applicable to non-cataractous eyes
6 undergoing CLE for the correction of presbyopia?

7 [Slide]

8 Question 7 B), are the predictability--75
9 percent of eyes with MRSE plus/minus 1 diopter and
10 50 percent with MRSE plus/minus 0.5 diopter and
11 UCVA endpoint of 85 percent with 20/40 or better,
12 outlined in FDA's draft guidance for refractive
13 implants, applicable for this scenario?

14 [Slide]

15 Do we need to establish a performance
16 efficacy endpoint for UCVA at near in this
17 population of subjects who are undergoing surgery
18 for the correction of presbyopia? If yes, what do
19 you recommend?

20 [Slide]

21 What additional performance efficacy
22 endpoints, if any, need to be set?

23 [Slide]

24 Something that you all need to consider is
25 whether a general population of presbyopes without

1 cataracts will be tolerant of potential optical
2 aberrations associated with MIOLs.

3 [Slide]

4 How do you recommend that we evaluate
5 patient's quality of life issues?

6 [Slide]

7 There are several questionnaires which are
8 validated and recommended in our ANSI standards,
9 Javitt, Vitale, Schein and NEI refractive. If you
10 can make a specific recommendation about the
11 applicability of these questionnaires or
12 combination of them, we would greatly appreciate
13 it. This concludes our presentation.

14 DR. WEISS: Dr. Eydelman and Dr. Blustein,
15 your presentation was absolutely superb and I hope
16 the clarity of your questions can be met by the
17 panel's answer to your questions.

18 DR. EYDELMAN: Thank you.

19 DR. WEISS: Thank you very much. We are
20 now going to open the open public hearing session.
21 Before we do, there is a statement that the FDA
22 requires me to read. Both the Food and Drug
23 Administration and the public believe in a
24 transparent process for information gathering and
25 decision-making. To ensure such transparency at

1 the open public hearing session of the advisory
2 committee meeting, FDA believes that it is
3 important to understand the context of an
4 individual's presentation. For this reason, FDA
5 encourages you, the open public hearing speaker, at
6 the beginning of your written or oral statement to
7 advise the committee of any financial relationship
8 that you may have with a sponsor its product and,
9 if known, its direct competitors. For example,
10 this financial information may include the
11 sponsor's payment of your travel, lodging or other
12 expenses in connection with your attendance at the
13 meeting. Likewise, FDA encourages you at the
14 beginning of your statement to advise the committee
15 if you do not have such financial relationships.
16 If you choose not to address this issue of
17 financial relationships at the beginning of your
18 statement it will not preclude you from speaking.

19 We have two speakers today. I will ask
20 Dr. Adrian Glasser, Associate Professor at the
21 College of Optometry, University of Houston, to
22 come forward for his presentation. I will inform
23 members of the panel that there will be an
24 opportunity to ask questions, both to the FDA team
25 as well as the open public hearing presenters, at

1 the beginning of the panel deliberations.

2 Open Public Hearing

3 DR. GLASSER: Thank you. I would just
4 like to start by saying thank you very much for the
5 opportunity to present.

6 [Slide]

7 I am going to be talking on the topic of
8 pseudophakic accommodation measurements. As
9 mentioned, my name is Adrian Glasser. I am an
10 Associate Professor at the College of Optometry at
11 the University of Houston.

12 [Slide]

13 I am a scientist with research interest in
14 accommodation and presbyopia. I have research
15 funding and I serve as a consultant to several
16 companies with interests in accommodation
17 restoration concepts. I am here in my capacity as
18 an interested scientist and as a consultant to
19 industry.

20 My attendance at this meeting has been
21 sponsored by a company with interest in
22 accommodation restoration concepts. I am not
23 talking about any specific devices so I have no
24 proprietary interests in anything I will be
25 presenting in this talk.

1 [Slide]

2 The purpose of my presentation is to
3 attempt to open a healthy, constructive and
4 informed dialogue between the FDA, researchers,
5 clinicians and companies with interests in
6 accommodation restoration concepts on the issues
7 and challenges of pseudophakic accommodation
8 measurement.

9 [Slide]

10 The presentation that I will make is
11 primarily directed at accommodative IOLs rather
12 than multifocal IOLs. Accommodative intraocular
13 lenses are IOLs designed to provide uncorrected
14 vision over a continuous range of distances without
15 multifocality by producing an optical change in the
16 power of the eye through movement or through change
17 in shape of the optic. These are IOLs designed to
18 provide dynamic accommodation. Demonstrated proof
19 of efficacy is important for accommodative IOLs
20 and, perhaps even more so, if they are to be used
21 for the correction of presbyopia after clear lens
22 extraction.

23 [Slide]

24 Pseudophakic accommodation measurement is
25 important for patient informed consent, for patient

1 risk/benefit analysis, for clinical study design
2 and testing, for selection of clinical control
3 groups, for inclusion/exclusion criteria in
4 clinical trials, and in patient populations and for
5 product labeling following FDA approval.

6 [Slide]

7 I am going to ask more questions in this
8 presentation than I have answers for, and here are
9 some to start. What will the FDA consider as the
10 gold standard for pseudophakic accommodation
11 measurement? How will the FDA determine if the
12 benefits of an accommodative IOL outweigh the risks
13 of clear lens extraction? What kind of
14 accommodation testing will the FDA require for
15 accommodative IOL clinical study designs? Will
16 these be subjective tests, objective tests or a
17 combination of both? What tests or instrumentation
18 should researchers and clinical investigators
19 become familiar with for these clinical trials?
20 And, what kind of instruments will the FDA consider
21 as appropriate for objective accommodation
22 measurement, refraction to measure an optical
23 change in the eye versus, for example, A-scan
24 biometry to measure movements of an optic in the
25 eye?

1 [Slide]

2 I want to talk a little about subjective
3 testing of accommodation. Distance corrected near
4 visual acuity with subjective push-up test and
5 negative lens-induced defocus have long been, and
6 remain, clinical standards for accommodation
7 testing. These and other subjective tests are
8 easily implemented, are routinely used clinically.
9 They could readily be used in clinical trials and
10 they provide widely accepted indicators of
11 functional near vision, both for patients as well
12 as for clinicians. However, these tests are not
13 quantitative measures of accommodative amplitude
14 and they do not unequivocally demonstrate an
15 accommodative change in optical power of the eye.
16 What reliance will the FDA place on these and other
17 subjective tests for future clinical trials of
18 accommodative IOLs?

19 [Slide]

20 I want to talk a little about producing an
21 accommodative response. To measure accommodative
22 amplitude a full and maximum accommodative response
23 must be elicited from the subject or patient.
24 Accommodation can be stimulated with near or
25 proximal targets by inducing blur such as by

1 presenting minus lenses to induce defocus on a
2 distant letter chart, or with pilocarpine drops
3 directly applied to the eye. Some individuals
4 accommodate poorly in some conditions to pure blur
5 fuse for example.

6 If no accommodation is recorded, it does
7 not necessarily mean that the eye cannot
8 accommodate. It may simply mean the subject has
9 chosen not to accommodate. Pilocarpine drops on
10 the eye can be used to stimulate an involuntary
11 accommodative response. Will the FDA consider
12 pharmacologically stimulated accommodation for
13 determining efficacy of accommodative IOLs?

14 [Slide]

15 I would like to talk a little about
16 objective measurement of accommodation. Clinical
17 infrared autorefractors rely on analysis of
18 reflected light signals and often fail or are
19 inaccurate when light is reflected off high index
20 IOL materials.

21 Instruments often used to measure
22 accommodation objectively in research labs are no
23 longer commercially available. New developing
24 instruments are lacking validation, are not
25 routinely available now, and their availability in

1 the future may be uncertain.

2 Standard clinical autorefractors, while
3 tested and validated on phakic eyes, have not been
4 tested and validated in pseudophakic eyes and may,
5 in fact, not measure accurately or may not measure
6 at all in pseudophakic eyes. Lower accommodative
7 amplitudes expected of pseudophakic eyes will place
8 higher demands on the resolution of these
9 instruments.

10 [Slide]

11 Continuing with objective measurement of
12 accommodation, there is considerable uncertainty as
13 to the availability of instruments that are capable
14 of objective pseudophakic accommodation measure.

15 What objective instruments will the FDA
16 accept or mandate for future clinical trials of
17 accommodative IOLs? Have these instruments been
18 validation to accurately measure accommodation
19 either in pseudophakic or, in fact, in phakic eyes?
20 Will these instruments be able to reliably measure
21 pseudophakic eyes, and will these instruments be
22 generally available for placement at multiple
23 clinical sites?

24 [Slide]

25 I would like to talk a little about

1 comparison of performance with the standard or
2 monofocal IOL. Comparison with the standard
3 non-accommodative, non-multifocal IOL using
4 accepted subjective clinical tests, such as
5 distance corrected near visual acuity, can provide
6 an indication of whether an IOL provides functional
7 near vision beyond that which would be provided by
8 the standard IOL.

9 Will the FDA accept subjective comparisons
10 of near visual performance with standard IOLs for
11 clinical trials of accommodative IOLs? If so, what
12 level of improvement over the performance of a
13 standard IOL should be demonstrated? How many
14 standard IOL control patients are required to
15 demonstrate efficacy of an accommodative IOL?

16 [Slide]

17 Finally, I will end by asking a few
18 general questions about what is required to
19 establish efficacy. For accommodative IOLs is it
20 more important to establish the existence of
21 accommodation or to establish the amplitude of
22 accommodation?

23 If distance corrected patients can read at
24 near after implantation of an accommodative IOL, is
25 this adequate to establish efficacy?

1 Many products are FDA approved without a
2 fully elucidated mechanism of action because they
3 work. Would this be adequate for accommodative
4 IOLs?

5 How long a follow-up will be required to
6 demonstrate longevity of efficacy of accommodative
7 IOLs? And, will testing standards for FDA approval
8 be different for accommodative IOLs versus for
9 multifocal IOLs? Thank you very much.

10 DR. WEISS: Thank you, Dr. Glasser. If
11 you would remain at the podium for a moment, are
12 there any questions from the panel while Dr.
13 Glasser is up at the podium? Dr. Bradley?

14 DR. BRADLEY: Thank you, Dr. Glasser for
15 that presentation. I think you raise a very long
16 and challenging list of questions for the FDA and
17 it really would take too long to go through all of
18 them, but just a general question, you ask whether
19 pharmacologically induced accommodation would act
20 as a substitute for, let's call it, voluntary
21 accommodation. In your experience, do you have any
22 reason to believe that it is an effective
23 substitute, or do you think there may be, for
24 example, a possibility that although one can induce
25 accommodation pharmacologically the patient could

1 not activate their accommodative mechanism
2 willfully? Is that a possibility? Or, should we
3 be happy with pharmacologically induced
4 accommodation?

5 DR. GLASSER: I wouldn't suggest that as a
6 substitute. I don't think that it should be the
7 sole means of identifying whether an accommodative
8 IOL can produce an accommodative change. I do
9 think that it is an important addition perhaps to
10 the armament of tools that can be used to assess
11 the accommodative ability of an IOL.

12 Let me just add to that by saying that it
13 is well-known from the literature that myopes, for
14 example, have lower stimulus response functions
15 than emmetropes. So, there may well be some
16 individuals in the patient populations who struggle
17 to elicit an accommodative response even if active
18 accommodation is truly there, and it might be
19 important to understand whether the lens inside the
20 eye is capable of accommodation. I think the
21 pharmacological approach provides a useful tool in
22 that regard.

23 DR. BRADLEY: Thank you.

24 DR. WEISS: Seeing no other questions from
25 the panel, thank you very much, Dr. Glasser, for

1 your presentation. We are going to then have Dr.
2 Lane.

3 DR. LANE: Thank you, Dr. Weiss and
4 members of the panel for inviting me to share some
5 comments with you today about intraocular lenses
6 for presbyopia.

7 [Slide]

8 I am in private practice in the Twin
9 Cities. I am a clinical professor at the
10 University of Minnesota in ophthalmology and among
11 a number of different hats that I wear, I am a
12 clinical monitor for Alcon Surgical, for which I am
13 a consultant, and I am here today representing them
14 and they have paid my expenses to be here.

15 [Slide]

16 As a means of introduction, I would like
17 to talk about presbyopia as not being a normal
18 state and, as I take out my reading glasses to try
19 and read some of my notes, that certainly becomes
20 very evident. It is a progressive, degenerative
21 loss of the ability to accommodate and it is really
22 no different than an eye with any other refractive
23 error in that there is no structural damage done
24 but, clearly, it is not a normal eye.

25 The impact on the quality of life is

1 driving an increasing patient demand for spectacle-
2 and contact lens-free vision. There are very high
3 expectations of the generally younger patient
4 population for this as is certainly evidenced by
5 the popularity of corneal refractive surgery.

6 [Slide]

7 As I look at things, there are really two
8 pathways in which I think the agency can proceed.
9 One is with the practice of medicine, that is to
10 say let the market forces play themselves out. The
11 second is to recommend formal clinical trials.

12 [Slide]

13 With regard to the practice of medicine,
14 the existing off-label practice medicine approach
15 of refractive lens exchange--which I am using
16 synonymously with clear lens extraction so it
17 depends whether you are coming from a cataract
18 point of view or you are coming from a refractive
19 surgeon point of view--is accepted in the
20 ophthalmic community and is continuing, and this is
21 continuing without the approved surgical options to
22 address safety and efficacy. As we have already
23 heard, there have been no studies that have been
24 done looking at this in any long-term prospective
25 fashion, and despite inadequate information for

1 surgeon and patient informed consent.

2 [Slide]

3 Therefore, what is probably reasonable and
4 prudent is a refractive lens exchange clinical
5 trial. The development of a reasonable, adequate
6 and well-controlled study focusing on safety and
7 efficacy assessment that will allow for the
8 appropriate informed consent is essential. Well,
9 "reasonable" is certainly a very nebulous term but
10 what we are really talking about here is being
11 practical. What we are talking about is using the
12 already established safety record of modern
13 cataract surgery, and what we are talking about is
14 encouraging the use of existing regulatory
15 framework and guidance, wherever possible, from the
16 already existing body of information that we have
17 about cataract extraction and about refractive
18 surgery. We believe the study should also address
19 the functional outcomes which are so important to
20 this group of patients and is really what is
21 driving the entire procedure.

22 [Slide]

23 The parameters to measure are very
24 well-known and I don't think we have to reinvent
25 the wheel here. Existing regulatory guidance

1 already provides the sound basis for many study
2 measurement parameters: distance, intermediate and
3 near visual acuity and binocular defocus; stability
4 of refraction; contrast sensitivity; pupil size,
5 visual disturbances and adverse events; intraocular
6 lens observations and position; and certainly
7 quality of life.

8 [Slide]

9 As we look through the data, and we have
10 also done a very thorough literature search similar
11 to what was presented by Dr. Eydelman, we need to
12 mitigate the perceived risks with known outcomes
13 for modern cataract surgery. This would include
14 things like endothelial cell loss. Certainly, the
15 similarity, however, of this refractive posterior
16 chamber lens procedure to modern cataract surgery
17 eliminates, we feel, any need for ongoing
18 endothelial cell count measurements. We have a
19 body of evidence in terms of modern clinical
20 cataract surgery done in a modern fashion.

21 But retinal detachment--again, the
22 numbers, depending on where you look, vary all over
23 the board. The numbers that we looked at are
24 similar to those that were presented by Dr.
25 Eydelman and show that anywhere from 0.0-0.9

1 percent incidence of retinal detachment with modern
2 phacoemulsification techniques in the post-1980
3 era. This was modern cataract literature that was
4 surveyed for retinal detachment risk factors.

5 [Slide]

6 The risk factors that we identified that
7 we believe should be proposed as potential
8 exclusion criteria are similar to those that were
9 discussed by Dr. Eydelman. We too found that age
10 is a risk factor, especially less than 40; that
11 high myopia is a risk factor, especially greater
12 than 8 diopters; that axial length is a risk
13 factor, especially greater than 25 mm; and that any
14 history of peripheral retinal disease is a risk
15 factor.

16 Certainly, there are surgically-related
17 risk factors. Posterior capsule integrity is
18 critical. There is loss of posterior capsule if
19 there is vitreous loss. If there is a YAG laser
20 capsulotomy the incidence, as has been seen,
21 increases. However, with the use of modern lens
22 removal techniques and new foldable intraocular
23 lenses, I think that many of these risks can be
24 minimized. Most of the studies Dr. Eydelman
25 presented were from the early 1990s with larger

1 incisions, with PMA lenses, with different edge
2 designs and with different surgical techniques.
3 This is going to be a population of people that, by
4 and large, will have larger pupils; will have
5 softer lenses; will have many of the decrease in
6 risk factors that we now see in the cataract
7 population of patients that we are having to deal
8 with. So, we should be able to perform safer
9 surgery.

10 [Slide]

11 The results of our retinal detachment
12 literature survey shows that the retinal detachment
13 rate in lens removal patients, when applying the
14 proposed exclusion criteria that were just
15 mentioned on the slide, was no different than that
16 occurring in the untreated population, which is
17 between 0.0 and 0.1 percent with up to 8 years of
18 follow-up.

19 [Slide]

20 With regard to control groups, and we
21 certainly understand that this is a concern that
22 has been voiced by the agency with regard to the
23 study, efficacy goals really should be reasonably
24 met without creating overly burdensome
25 requirements. We feel we must reasonably weight

1 the potential issues for the patients against the
2 value of the information to be gathered. Is it
3 reasonable? Is it fair? Is it practical for a
4 patient who comes in desiring refractive lens
5 exchange to be randomized to no treatment? I think
6 we must use the existing guidelines that we already
7 have in place for refractive procedures, for laser
8 procedures as we proceed and look at the choice of
9 control groups.

10 [Slide]

11 In summary, we have a number of proposals
12 that we would like the panel to consider. First,
13 we would like to minimize the study size and the
14 duration by employing the proposed exclusion
15 criteria derived from the retinal detachment
16 survey. Based on an incidence of retinal
17 detachment of 1/1,000 using this exclusion
18 criteria, a clinical study that would be powered to
19 detect a difference would need to be an exceedingly
20 large sample size.

21 We would recommend that we apply the study
22 subject's own preoperative data to provide the best
23 method of control. This provides roughly the same
24 statistical power as using a non-operated control.
25 It is consistent with current guidance documents

1 and, importantly, it addresses the patient
2 considerations discussed previously.

3 [Slide]

4 We would ask to utilize the preoperative
5 endothelial cell minimum as an exclusion criteria
6 based on the FDA phakic IOL requirement in the
7 guidance that has already been given in that
8 respect. Finally, we would ask to employ the
9 appropriate quality of life assessments, as an
10 example the RSVP survey.

11 [Slide]

12 In conclusion, I would like to take off my
13 Alcon hat here for a moment and put on my hat as a
14 teacher and as a practitioner and as a leader of a
15 number of ophthalmic organizations. I recognize
16 that there are a number of various interests at
17 play here. From the patient's standpoint, we want
18 to meet the demand of their increasing interest in
19 being totally spectacle and contact lens free.

20 We want to provide safe and effective
21 treatment that is based on real information and
22 true informed consent. As a surgeon, I want to
23 provide the opportunity to deliver a service
24 desired by our patients which we can feel confident
25 about with regard to safety and efficacy.

1 As the FDA, I think you need and want to
2 fill a vacuum that presently exists and to set a
3 threshold of safety which we can live by and
4 industry, while certainly not in this for only
5 altruistic reasons, does want to produce products
6 that are safe and effective to fulfill patient
7 needs.

8 Finally, one that is not listed is
9 societal. Refractive lens exchange allows the
10 potential for generations to come to reach Medicare
11 age with their lenses already removed, saving
12 government billions of dollars and, thus, becoming
13 the ultimate cataract preventative.

14 [Laughter]

15 All joking aside, I do see a real
16 opportunity here but unless reasonable and
17 practical considerations are employed, this
18 increasingly popular procedure will continue to be
19 performed outside the scope of the best interests
20 of the above parties. Thank you.

21 DR. WEISS: Thank you, Dr. Lane. Do we
22 have any questions from the panel? Dr. Grimmett?

23 DR. GRIMMETT: Dr. Lane, thank you for
24 your presentation. I have a question regarding
25 slide 7. I did a literature review over the last

1 year or so when we discussed phakic IOLs and
2 endothelial cell loss and the long-term endothelial
3 cell loss rates we have been basing off old data
4 from Bill Bourne regarding procedures that we
5 really no longer perform. You indicated on your
6 slide that we have known outcomes with modern
7 cataract surgery for endothelial cell loss rates
8 and I was wondering if you could direct me to the
9 literature reference or data regarding those known
10 outcomes.

11 DR. LANE: I am sorry, Mike, I misspoke.
12 As you well know, there are no known--basically I
13 am using the numbers that have been used, and have
14 been used by the agency to go forward with a number
15 of the other studies that have gone forward and
16 approval processes for new intraocular foldable
17 lenses, and so on, using those data. I guess from
18 a historical perspective, if you will, the basis of
19 the endothelial cell counts from studies that have
20 been performed most recently with more modern
21 intraocular lenses, foldable intraocular lenses,
22 that have achieved approval by the agency seems to
23 be sufficient to allow approval of those particular
24 lenses. So, really I guess what I am referring to
25 is data that has been presented from previous

1 applications, if you will, of foldable intraocular
2 lenses and the endothelial cell counts coming from
3 those and coming from oncoming studies that will be
4 looking at some new foldable lenses coming down the
5 line. So, from a literature standpoint in terms of
6 going back and looking at the literature and is
7 there something out there that you have missed, the
8 answer is no.

9 DR. WEISS: Dr. Mathers?

10 DR. MATHERS: Thank you for your
11 presentation. I have a similar question regarding
12 the rate of retinal detachment. It would seem that
13 your slide suggesting that the rate of retinal
14 detachment in a select group after cataract surgery
15 is no greater than those that do not have cataract
16 surgery. But we heard this morning of several very
17 large studies indicating that the retinal
18 detachment rate is considerably higher, and also is
19 highest in the youngest population for which we
20 seem to have the least amount of data. Could you
21 explain this discrepancy?

22 DR. LANE: I really don't see that there
23 is a discrepancy, Dr. Mathers, because the
24 literature that was discussed this morning included
25 the entire cohort. What we are doing is separating

1 out the high risk factors. We are separating out
2 the patients with high axial lengths. We are
3 separating out the patients with high degrees of
4 myopia. We are separating out patients with known
5 peripheral retinal disease. So, the numbers that
6 were given that are higher are based on the entire
7 cohort that would include those while this group
8 includes only those that have those exclusion
9 criteria.

10 DR. MATHERS: But do we have literature
11 that shows what the detachment rate in the younger
12 population with cataract surgery actually is?

13 DR. LANE: I don't know the answer to
14 that, and I certainly don't think we know--I don't
15 know the answer to that.

16 DR. WEISS: Just as a follow-up question
17 to that, if we are going to be suggesting that they
18 should be used in younger patients or used in
19 higher myopes, what would you suggest then be used
20 in those cases that we don't have the answer for
21 adverse event follow-up in terms of duration as
22 well as percentage?

23 DR. LANE: A very good question. I don't
24 obviously have the answer to that either, but I
25 think that in the same way in which Dr. Eydelman

1 suggested that the introduction of any presbyopic
2 lens be performed in a cataract population first,
3 the next logical step to me would be to perform it
4 in a group that included certain exclusion criteria
5 that we are talking about. If that trial proves to
6 be successful, as it would have to be if it was
7 going on to the next step, then the next step would
8 be to try some of the higher risk population and
9 perform adequate studies to be able to show that.

10 DR. WEISS: Just a follow-up question, if
11 you were putting this study together what would you
12 want in terms of range of refractive error? It
13 sounds like you would be suggesting that the
14 refractive errors that are most in demand to have
15 this done, namely the very high myopes, be
16 eliminated from an initial study and the younger
17 patients be eliminated from an initial study. Or,
18 am I misreading what you are saying?

19 DR. LANE: No, you are not misreading what
20 I am saying. I think that, you know, based on the
21 literature search that we did looking at the
22 exclusion criteria that are present, that is the
23 group of patients that I think should be targeted.
24 While, yes, the high myopes would certainly benefit
25 potentially from this kind of technology and may be

1 the ones who would really sort of gather at your
2 doorstep to do this in greatest numbers, for the
3 time being certainly all of the literature suggests
4 that those patients are at higher risk. So, I
5 think, again, that may be a study that needs to be
6 done in a better fashion using more modern
7 techniques but I think we have to get there
8 probably in a step-wise fashion rather than trying
9 to do it.

10 I wouldn't necessarily agree that the
11 majority of patients who would want to have this
12 are necessarily the high myopes. There is a whole
13 group of presbyopic patients out there who would
14 want to have this for presbyopic reasons. While
15 that certainly is an important group, it is
16 certainly not the only group and may not even be
17 the largest group.

18 DR. WEISS: Dr. Stark, did you have a
19 question?

20 DR. STARK: You did show a reference on
21 slide 9, Solomon, indicating that the retinal
22 detachment risk was 0.1percent. It went by so
23 fast I didn't get it--

24 DR. LANE: That is in the untreated
25 population. That is very similar to the

1 information that Dr. Eydelman presented. It is
2 essentially a control group, if you will.

3 DR. STARK: Oh, okay. Good.

4 DR. WEISS: Seeing no other questions from
5 the panel, thank you very much, Dr. Lane, for your
6 presentation. Dr. Randall Olson has a letter that
7 Sally Thornton will be reading as part of the open
8 public hearing presenters.

9 MS. THORNTON: This is a letter from Dr.
10 Randall Olson, who is the John A. Moran
11 Presidential Professor and Chair of the Department
12 of Ophthalmology and Visual Scientists, and
13 Director of the John A. Moray Eye Center at the
14 University of Utah Health Science Center:

15 I would like to comment on the use of
16 intraocular lenses for correction of presbyopia
17 after clear lens extraction, a topic that is to e
18 discussed by the Ophthalmic Devices Panel of the
19 Medical Devices Advisory Committee on Friday, March
20 5, 2004. We have performed about 100 "clear"
21 lensectomy procedures in presbyopes over the past
22 two years. The term "clear" lensectomy is a
23 misnomer for us. In our patient population, it is
24 rare for a presbyopic patient not to have some
25 level of lens opacification, even though it may not

1 be significantly decreasing their Snellen visual
2 acuity. In a study, done by Waltz, Wallace in
3 Ophthalmic Practice, 2001, of over 200 refractive
4 lensectomy patients, the average age at surgery was
5 53 years, our average is even older. We feel that
6 we are doing these patients a disservice to perform
7 corneal surgery, such as LASIK, when cataract
8 surgery due to further lens opacification may be
9 just around the corner. The precision of the
10 refractive component of cataract surgery drops
11 precipitously for post corneal refractive patients,
12 and it is precisely this group that demands
13 refractive precision.

14 For the patient, clinical studies have
15 shown a high rate of patient satisfaction with
16 refractive lensectomy. They perceive being
17 "spectacle free" as an improvement in their quality
18 of life. With the present levels of refractive
19 precision, the acceptance rate is as good as, or
20 better than, LASIK.

21 The only concern for refractive lensectomy
22 that could conceivably be greater than cataract
23 complications is the possibility of an increased
24 rate of retinal detachment following surgery in
25 high myopes. The retinal detachment risk is not

1 germane for emmetropes or hyperopes. We have
2 published several studies in this area, Powell,
3 Olson Journal of Cataract and Refractive Surgery,
4 1995, Olsen and Olson in the Journal of Cataract
5 and Refractive Surgery, 1995, and Olsen and Olson
6 in the Journal of Cataract and Refractive Surgery,
7 2000, showing a decrease in the rate of retinal
8 detachment as surgical techniques and equipment
9 have improved. For high myopes, the risk probably
10 can be reduced by careful prescreening and the use
11 of a phaco technique that maintains the depth of
12 the anterior chamber during surgery. It should
13 also be noted that the lens is less dense and more
14 easily removed in refractive lensectomy patients
15 than cataract patients. This reduces surgical
16 complications for this group.

17 In spite of the issue of retinal
18 detachment in high myopes, which has been
19 investigated in multiple studies, a prospective
20 study of "clear" lensectomy does not seem
21 warranted, in that our cataract database is already
22 so large and so inclusive. In addition, to truly
23 study "clear" lensectomy in presbyopic patients
24 would be extremely difficult since few of these
25 patients have clear lenses.

1 Signed, Randall J. Olson, M.D. Thank you.

2 DR. WEISS: Thank you, Sally. That will
3 conclude the open public hearing session. We will
4 break for 15 minutes before beginning the panel
5 deliberations.

6 [Brief recess]

7 Panel Deliberations

8 DR. WEISS: We are now going to open the
9 panel deliberations session and I will ask, Dr.
10 Eydelman, if you could come to the podium and
11 perhaps we could use the questions as a guidance.
12 Actually, perhaps Dr. Blustein could come forward
13 as well so that if there are any questions for the
14 FDA from their panel presentation we could have the
15 panel ask those at this time. Do any of the panel
16 members have questions for FDA? Dr. Ho?

17 DR. HO: Malvina, just a question on the
18 FDA grid for PC IOLs, what is that data derived
19 from?

20 DR. EYDELMAN: One second and I will show
21 you, I am just going to put the slide up.

22 [Slide]

23 This was a composite of all the PMA data
24 that was performed. As you see, the total N was
25 5,906 eyes. This particular grid encompasses all

1 surgeries from '87 to '96.

2 DR. HO: So, it is a mixed bag with
3 respect to the way the cataracts were removed I
4 suspect.

5 DR. EYDELMAN: Correct. We actually
6 looked at this specific question two days ago
7 because we were considering it under ISO. We have
8 unofficially re-looked at what these numbers would
9 be if we just moved it forward.

10 MR. CALOGERO: At the last ISO meeting
11 this week we looked at updating the grid and we did
12 some early, preliminary work. Unfortunately, I
13 don't have the grid values. They changed somewhat
14 but what we did, we truncated off the oldest PMAs
15 and now, if you look at the data from 1994 out to
16 2003, there are minor changes in these rates but
17 the retinal detachment rate goes down somewhat.

18 DR. EYDELMAN: The only number that was
19 significantly different was the CME. It went from
20 3 percent to 1.5 percent. But since that was
21 unofficial, sort of our little draft, we didn't put
22 that up. This is the official FDA grid that the
23 companies have been comparing their IOLs to.

24 DR. HO: Thank you.

25 DR. WEISS: Dr. Grimmett?

1 DR. GRIMMETT: A question in follow-up,
2 Dr. Eydelman, did the hyphema rate go down?

3 DR. EYDELMAN: Slightly.

4 GRIMMETT: Slightly?

5 DR. EYDELMAN: Slightly. For the purposes
6 of ISO, we were looking if it would change at all
7 our sample size for determination and it didn't.

8 DR. GRIMMETT: That is surprising to me
9 because, at least in my clinical practice, it is
10 just not common to see hyphema after modern phaco
11 surgery. So, I am just surprised by that.

12 DR. EYDELMAN: I think it was 1.5. I
13 don't want to quote, I don't have the numbers but
14 it was over 1 percent. Again, cumulative is
15 defined as occurring any time between surgery to
16 one year. It is just additive.

17 DR. WEISS: Mr. McCarley?

18 MR. MCCARLEY: Yes, Rick McCarley. I have
19 three quick questions. Hopefully, they will have
20 quick answers. Are we limiting the discussion
21 today to multifocal lenses and accommodative IOLs
22 or are we also talking about standard monofocal
23 IOLs where you would use monovision, for instance?
24 In other words, any IOL that is placed in the eye
25 to correct the patient who can no longer

1 accommodate?

2 DR. EYDELMAN: The discussion was intended
3 to be limited to the correction where the subjects
4 have both distance and near VA for correction of
5 presbyopia.

6 MR. MCCARLEY: So, not for monofocal IOLs?

7 DR. EYDELMAN: Well, it could include
8 accommodative.

9 MR. MCCARLEY: That is not accommodative?

10 DR. EYDELMAN: Correct. It is for those
11 IOLs that simultaneously provide distance and near
12 VA corrections.

13 MR. MCCARLEY: Okay. The second question
14 is what is the FDA's current labeling for, for
15 instance, accommodative IOL or the multifocal IOL
16 related to the age range that they suggest? In
17 other words, my understanding is it used to be 60
18 years and older but that was changed later on to be
19 adults not less than 18 or not less than 21. Is
20 that correct?

21 DR. EYDELMAN: Currently all IOL sponsors
22 may require an indication for the adult population,
23 but that is for IOLs status post cataract
24 extraction, correct.

25 MR. MCCARLEY: My final question is the

1 FDA knows that this clear lens extraction has been
2 going on for a while and knows that it is
3 increasing in popularity. Has the FDA, in the
4 interest of public health, done anything to inform
5 doctors or patients now, working with maybe the AAO
6 or the SCRS, to let them know what we know now so
7 that they will be better informed for what we know
8 is going on? In fact, what do you have planned
9 between now and when any study might be completed?

10 DR. EYDELMAN: Well, as I mentioned, it
11 has only been done as off-label and, as such, it
12 has been quite an issue. Off-label means we do not
13 have an approved indication with safety and
14 efficacy data that we can share.

15 MR. MCCARLEY: So, you recognize there is
16 a potential public impact but the FDA doesn't feel
17 they can do anything right now to notify the
18 doctors or the patients?

19 DR. WEISS: Do you want to comment on
20 that, Ralph?

21 DR. ROSENTHAL: We are a regulatory agency
22 that regulates the medical device industry and it
23 is not our responsibility to inform the public
24 about issues regarding off-label use unless we feel
25 there is a significant public health issue.

1 MR. MCCARLEY: I thought that was how Dr.
2 Eydelman's presentation started off, that this is a
3 significant, major public health issue.

4 DR. EYDELMAN: No, my presentation started
5 off that if CLE for correction of presbyopia
6 becomes widely used it can have a significant
7 health impact. As an aside, I said that CLE has
8 been performed as off-label use, mostly for high
9 refractive errors. Those two are two distinct
10 ideas.

11 DR. WEISS: I think also some companies
12 would like to get this on-label so I don't believe
13 it is just being driven by FDA. Dr. Mathers?

14 DR. MATHERS: Is there any data indicating
15 that the movement of an accommodative IOL would
16 have any bearing on, say, position of the vitreous
17 space or affect retinal detachment, uveitis or
18 endothelial cell loss? In other words, there
19 appears to be no downside to an accommodative IOL
20 that changes its position but there might be
21 compared to another kind of straight IOL. Do you
22 have any data on that?

23 DR. EYDELMAN: No, we don't. We only have
24 one, as you know, IOL currently approved so we have
25 very limited information on that issue.

1 DR. WEISS: Any other questions from the
2 panel? Seeing no other questions, we can then
3 address the first question that the FDA is asking.

4 1 A), do you recommend a control
5 population for studies of clear lens extraction in
6 the correction of presbyopia, or do you believe
7 that the study subject's own preoperative data is
8 sufficient for comparison?

9 This is basically going to be a yes or no,
10 and I want to poll each of the panel members if
11 they want a control population or is the study
12 subject's own preoperative data sufficient? We
13 will start with Dr. Maguire. Would you like a
14 control population, Dr. Maguire, or is preoperative
15 data from the patient enough?

16 DR. MAGUIRE: I am going to pass right
17 now.

18 DR. WEISS: We have an abstention. Dr.
19 Stark?

20 DR. STARK: Well, I think it would be
21 difficult to randomize patients, if they wanted
22 this procedure, to no treatment or treatment. So,
23 I think we could get enough information on
24 complications if we had adequate long-term
25 follow-up. My primary concern would be the retinal

1 detachment rate even in young people who are not
2 myopic. So, I think we could get this from
3 historical control or age-matched populations. So,
4 I don't think a randomized, controlled study is
5 necessary in this.

6 DR. WEISS: I am just going to step back
7 for this question, for part A), it is not actually
8 the type of control population but whether or not
9 you want a control population. From what I
10 understand from what you are saying, you do want a
11 control population but not something so onerous
12 but, still, you would like a control population.
13 Is that correct?

14 DR. STARK: Yes.

15 DR. WEISS: Dr. Brown?

16 DR. BROWN: Yes, I do feel strongly about
17 that. I would like there to be a control
18 population, particularly if we include high myopes
19 in any of these studies.

20 DR. WEISS: So, you would like a control
21 population as well. Dr. McMahon?

22 DR. MCMAHON: A question--we are jumping
23 right into controls but are we talking from a
24 perspective of efficacy or safety, or both?

25 DR. EYDELMAN: We are talking with respect

1 to study design.

2 DR. BRUCKER: Can I raise a question?

3 DR. WEISS: Actually, what I would like to
4 do is not have a discussion now but sort of get a
5 feeling for where people are at. Then, once we get
6 involved in the type of control population we will
7 break it up into discussion.

8 DR. BRUCKER: Could I still ask the
9 question because it is applicable to what you are
10 asking.

11 DR. WEISS: Okay, Dr. Brucker.

12 DR. BRUCKER: Clear lens extraction is a
13 surgical procedure--

14 DR. WEISS: Yes.

15 DR. BRUCKER: That surgical procedure can
16 be done by any physician at any time, period.

17 DR. WEISS: A hundred percent correct.

18 DR. BRUCKER: The risks and complications
19 that we are talking about have to do with clear
20 lens extraction. It has nothing to do with the
21 insertion of an IOL. So, the question that you are
22 posing seems to be a question that can't be taken
23 out of that context. The insertion of an
24 intraocular lens is not assumed, from my
25 understanding, to be the cause of the complication.

1 Therefore, the use of a surgical procedure called
2 clear lens extraction should have nothing to do, in
3 my opinion, with whether you put in monovision,
4 presbyopic vision or anything else; it is clear
5 lens extraction. Perhaps we should have a little
6 bit of discussion about the issue of clear lens
7 extraction before you start talking about
8 intraocular lenses.

9 DR. WEISS: I think technically what you
10 are saying from a purist standpoint is correct,
11 however, when IOLs get evaluated they get evaluated
12 in terms of hyphema and retinal detachment rate
13 and, from what you are saying, they shouldn't be
14 evaluated in that way either because the IOL is not
15 causing the RD or the hyphema but, yet, it is
16 included in the surgical procedure and when the
17 patient is going in for that surgical procedure you
18 can't separate out for them that, oh well, this is
19 the part that caused it and this part didn't cause
20 it.

21 So, for the purpose of this discussion,
22 although your points are well taken and FDA can
23 correct me, I think it doesn't really apply. We
24 still have to put it all together because when a
25 patient is looking at it, who is 45 years old, who

1 is a minus 15, whether they are getting the RD 7
2 years down the line from the IOL or they are
3 getting it from the surgical procedure they are
4 still going to end up with an RD and that is the
5 information they need. Agency, would you agree?

6 DR. EYDELMAN: You are absolutely correct
7 because we are talking about approval of a
8 particular IOL for a specific indication and that
9 indication would incorporate a clear lens
10 extraction which would precede the implantation.
11 So, it is looked at as a package deal.

12 DR. BRUCKER: Yes, but you presented
13 Ripandelli's work and many of the eyes in
14 Ripandelli's work didn't have IOLs. They had clear
15 lens extraction and they had retinal detachments.
16 It is the retinal detachment coming from the clear
17 lens extraction that really is the subject of
18 discussion.

19 DR. WEISS: Dr. Brucker, as I said, I
20 think from a logical technology standpoint, you are
21 right but it doesn't apply to what the agency wants
22 at this point. Dr. Bressler?

23 DR. BRESSLER: I think you do need a
24 control, and it will be more interesting discussing
25 what that will be on the second round.

1 DR. WEISS: Dr. Smith?

2 DR. SMITH: I agree, you need a control
3 both for safety and efficacy.

4 DR. WEISS: Dr. Ho?

5 DR. HO: The clinician scientist in me
6 wants an active control, however, I recognize the
7 difficulty of executing a trial in which someone is
8 seeking a refractive procedure and would be
9 randomized--

10 DR. WEISS: Just to reiterate, we don't
11 have to commit--

12 DR. HO: I would be okay with historical
13 age and refractive-matched controls.

14 DR. WEISS: All I want from anyone right
15 at this moment is do you want a control or you
16 don't want a control. I am going to keep it nice
17 and simple. It won't stay simple for long so enjoy
18 it while you have it. Dr. Mathers?

19 DR. MATHERS: By patients on control, are
20 you supposing that you do the surgery in one eye
21 and not on the other?

22 DR. WEISS: Well, any type of control you
23 want. It is just question 1 (A, do you want a
24 control or you don't want a control? You are going
25 to tell us afterwards what sort of control you

1 want.

2 DR. MATHERS: I want a control.

3 DR. WEISS: You want a control. Dr.

4 Grimmett?

5 DR. GRIMMETT: Yes.

6 DR. WEISS: Dr. Grimmett wants a control.

7 Dr. McMahon?

8 DR. MCMAHON: Yes.

9 DR. WEISS: Dr. Bradley?

10 DR. BRADLEY: I am not sure.

11 DR. WEISS: Another abstention. Dr.

12 Ferris?

13 DR. FERRIS: We have to have some sort of

14 comparison group so the answer of who wants some

15 sort of comparison group is simple, so I want a

16 comparison group.

17 DR. WEISS: Thank you. Dr. Brucker just

18 nodded in the affirmative. Mr. McCarley, you can

19 voice your opinion, of course.

20 MR. MCCARLEY: I was just thinking of the

21 same patient control.

22 DR. WEISS: Okay, and Dr. Maguire, did you

23 want to voice an opinion at this point?

24 DR. MAGUIRE: Well, yes, because we

25 haven't really established what we are talking

1 about so I don't want to say no.

2 [Laughter]

3 DR. WEISS: I take that as a continuation
4 of an abstention. I am hearing somewhat of a
5 consensus on 1 A), that most of the panel would
6 like to have a control population. So, now we get
7 into 1 B), which is on the screen, what type of
8 control population would you like. We have the
9 historical and the active, or if you can come up
10 with anything else. I don't believe the FDA was
11 emphasizing doing a randomized study. I don't
12 really think anyone is talking about that, but if
13 that is what you want to do you can certainly
14 suggest it. In the list of controls under
15 historical under 1 B) there are subjects--well, you
16 can read them yourself. There are four different
17 types of historical controls. There is one type of
18 active control, and then if there is anything else
19 that you would like. Dr. Rosenthal?

20 DR. ROSENTHAL: The active control would
21 be a group of patients who had no surgery. So, in
22 fact--

23 DR. WEISS: It could be randomized.

24 DR. ROSENTHAL: --you could randomize or
25 you could just collect a group of patients.

1 DR. WEISS: Then the randomization is
2 actually another level of specificity. You could
3 have an active control of another group of, let's
4 say, age- and gender- matched subjects, and how you
5 wanted to include them in the study, actually, the
6 FDA has not even asked us. So, they haven't even
7 asked us for that level of detail.

8 Let's start with Dr. Maguire, if you
9 wanted to voice your opinion on this.

10 DR. MAGUIRE: Yes, I think active control
11 subjects with no previous ocular surgery and not
12 planning on having any either for presbyopia would
13 be reasonable.

14 DR. STARK: Agreed.

15 DR. MAGUIRE: Because we have no
16 information on retinal detachment surgery in young
17 people, or certainly not adequate information, and
18 we would like to have more information on
19 endothelial cell loss based on Dr. Lane's answer to
20 Dr. Grimmett's question, so absolutely.

21 DR. WEISS: So, you would like an active
22 control of subjects with no previous ocular
23 surgery. Dr. Stark agreed with that. Dr. Brown?

24 DR. BROWN: Yes, an active case control
25 study that is matched on criteria that we would set

1 out in terms of refractive error and age, yes.

2 DR. WEISS: So, you would also like an
3 active control. Dr. Bressler?

4 DR. BRESSLER: I would like to discuss for
5 a minute a couple of considerations for why a
6 randomized control might be beneficial for getting
7 the answer and then we can get back to would those
8 people actually enroll.

9 We may see some visual acuity loss in a
10 few of these people that have this. In the few
11 studies that were done, granted in the high myopes
12 with clear lens extraction they did have one or two
13 people that are 40 losing a line of vision by six
14 months, for example, in their best corrected visual
15 acuity. Now, that could be to the detriment of
16 this if you didn't have a control group because you
17 would say, well, they started at 20/16 and they
18 dropped to 20/25, or something. However, it could
19 be that your control group developed some cataract
20 along the way. We are going to have 50 year-olds
21 with presbyopic symptoms, or whatever, and they may
22 drop to 20/25 just as often. So, you never would
23 have known that you weren't harming their vision,
24 for example, more than if you left it alone if you
25 didn't have a control group for that.

1 In addition, if you are going to look at
2 quality of life outcomes, for example, whatever
3 answers or change in the quality of life you get in
4 someone over time, you just won't know if that is
5 just due to the person having the surgery done and
6 being happy with their life or if it is due to
7 other factors that you would only get from a
8 control group.

9 So, I am all for an active control and I
10 think it needs to be considered as actually a
11 randomized trial to be able to answer the important
12 safety issue, which will be visual acuity besides
13 the retinal detachment, which is much rarer and you
14 may not be able to detect those changes, and any
15 quality of life studies that might be considered
16 down the line.

17 DR. WEISS: I would ask you if this could
18 not be a randomized study because it was deemed
19 that it would be too burdensome or the study
20 wouldn't be able to accrue the patients because of
21 that criteria, would you still want an active
22 control? Would that still be something that you
23 would want?

24 DR. BRESSLER: If you couldn't have it,
25 then yes, but you might not be able to answer these

1 questions if you see that the visual acuity has
2 declined. So, I just don't want to have the
3 industry paint themselves into a corner. That is
4 the whole advantage of doing this ahead of time.

5 DR. WEISS: Dr. Eydelman?

6 DR. EYDELMAN: Along the lines of what Dr.
7 Bressler just mentioned, the panel certainly can
8 consider whether they wanted two different controls
9 for safety and efficacy outcomes. If that is the
10 case, that just puts a little further question into
11 question 1 B).

12 DR. BRESSLER: I am not separating it
13 because safety assessment depends on what the
14 efficacy is as well. You are willing to take big
15 safety risks for one sort of efficacy and less
16 safety risks for another.

17 DR. EYDELMAN: Right, but determination of
18 safety and efficacy with an active control is going
19 to require greatly different sample sizes. Just
20 keep that in mind.

21 DR. WEISS: Dr. Smith?

22 DR. SMITH: I would prefer to have an
23 active control while recognizing these concerns
24 that several have voiced regarding the feasibility
25 of doing such a study, and I am open to discussing

1 ways to do that other than randomization but I do
2 believe in active controls. It is critical to
3 obtaining safety data in this age group for which
4 we do not have good data.

5 DR. WEISS: Just to remind panel members,
6 we welcome dissent. We don't need unanimity on
7 this. This is really to guide the agency as far as
8 the panel's sentiments so we don't have to have a
9 continual roll here if you want to go in another
10 direction. Dr. Ho?

11 DR. HO: As I was saying before, as a
12 scientist I think that I would love to have an
13 active control. I think it would be very difficult
14 to execute that study. I think Neil's concern and
15 point is a good one, however, the duration of the
16 study will likely not be long enough so that maybe
17 those 1/40 patients that drop a line might not drop
18 a line in the first few years.

19 DR. WEISS: Would you be able to get a
20 little closer to the mike?

21 DR. HO: Sure. Therefore, I would be open
22 to a historical control but it would have to be an
23 age-matched and refractive error-matched control.

24 DR. WEISS: Would that be difficult to do,
25 Dr. Eydelman? I just saw a change in your

1 expression, not for the positive.

2 DR. EYDELMAN: Well, that would imply that
3 each sponsor, depending on the inclusion/exclusion
4 criteria, would have to go through the literature
5 and try to see if they can pull--most of the
6 articles don't have raw data so you would have to
7 try to identify articles that have exactly the same
8 age criteria as you wish to enroll. It gets a
9 little tricky. We have done it for glaucoma
10 devices and the sponsors found it quite difficult.

11 DR. WEISS: Dr. Bressler?

12 DR. BRESSLER: I just wanted to add to
13 Allen's comment that in the small series we had
14 from Dick and colleagues, that was only a six-month
15 follow-up and they had 3/50--and I know these are
16 broad confidence intervals but that was six percent
17 losing one line. So, you might get those answers
18 even with just a year follow-up or safety beyond
19 two years.

20 DR. WEISS: Dr. Ho?

21 DR. HO: That was also a group that was
22 highly myopic that might be more susceptible than
23 the general group you are speaking to here who
24 would like to have presbyopic surgery.

25 DR. WEISS: So, Dr. Ho, you still would

1 prefer to have a historical?

2 DR. HO: If that data can be derived, yes,
3 because I think consideration of an active
4 control--although burdensome and I would love it
5 but I think it would be difficult to execute that
6 trial.

7 DR. WEISS: Would I be able to ask you to
8 sort of isolate one of the four listed here as far
9 as what type of historical control? No, I would
10 not be able to? Okay, well, I can ask. Dr.
11 Mathers?

12 DR. MATHERS: I don't think it would be
13 that difficult to have an active control because
14 you are not really doing too much for these people
15 if they haven't had surgery. You are just
16 following them and you are doing some tests on
17 them. But I think that you would have to stratify
18 them to answer some of the questions. You would
19 have to stratify them by axial length, refractive
20 error, endothelial count and age. If you did that,
21 you could answer these questions and I do think it
22 is extremely important to answer these questions.
23 We are talking about really major health issues
24 here that affect millions, if not billions, of
25 people and, clearly, the private community or the

1 academic community have all completely failed to
2 look at this fundamental issue and maybe we have an
3 opportunity to help them. We haven't answered
4 these questions yet. Obviously, the literature
5 shows we have not.

6 DR. WEISS: Dr. Grimmett?

7 DR. GRIMMETT: For effectiveness issues I
8 would be in favor of an active control. Certainly
9 for quality of life issues it would be very nice to
10 compare patients who have not had surgery with time
11 to see how their quality of life compares to those
12 who have had the surgery.

13 Dr. Eydelman read my mind as far as
14 separating safety and effectiveness. I could go
15 with a historical control for safety issues,
16 perhaps patients who have had cataract surgery with
17 IOLs.

18 DR. WEISS: I have just been informed
19 that, unlike many panel meetings, my opinion is
20 actually wanted on this one even though I am
21 chairing this. So, I think I would like an active
22 control as well because of the frustration I think
23 for a sponsor as well as the panel often when the
24 PMA is presented and we don't have the information
25 to assess--let's say, the risk or whatever--and the

1 best way to do that is to compare it to an active
2 control. Although randomization would be
3 wonderful, I think it would be too onerous on the
4 sponsors so I wouldn't be supporting that. Dr.
5 McMahon?

6 DR. MCMAHON: I have a few comments on
7 this issue. I agree with Dr. Bressler that a
8 randomized trial with an active randomized control
9 group would be ideal, but I also agree with you
10 that it would be a bit onerous to maintain an
11 active control group for a period of three or four
12 years. Keep in mind, this is equivalent to a
13 refractive surgery population and keeping track of
14 the patients is hard enough, let alone controls who
15 might also be interested in this procedure. If you
16 are going to hold them off for several years I
17 think it would be very difficult to manage this.

18 With regard to active controls, I think
19 there are other mechanisms that can be played and I
20 think it can be done in a variety of interesting
21 ways. For the less common but more devastating
22 complications like retinal detachment I can see a
23 design where you have a prospective case control
24 kind of circumstance where you have a lot of active
25 controls who are not interested in the procedure

1 and a lesser number of actually operated patients.

2 But for things like efficacy you are going
3 to want more of a matched controlled set of
4 patients in that circumstance. So, I think an
5 active control group is the thing to do. I think
6 randomization is likely not to be manageable but
7 there are other options I think that can be looked
8 at.

9 DR. WEISS: Dr. Bradley?

10 DR. BRADLEY: Yes, I have several
11 comments. I think taking Dr. Brucker's comment
12 earlier to heart in that potentially the greatest
13 risk here is the surgical procedure not the lens
14 being inserted into the eye, one might not imagine
15 dramatically different risks associated with
16 different lenses. So, we may, therefore, be able
17 to employ historical literature controls for risk,
18 particularly in the age group that has already
19 undergone this particular surgery, which is
20 obviously the 50-plus age group and they have
21 obviously been having surgery for cataracts. So,
22 this may be effectively evaluated using historical
23 controls in the older group. That is certainly not
24 the case if the lenses are going to be inserted in
25 younger eyes. I think in that case an active

1 control for risk is required.

2 Regarding controls for efficacy, clearly,
3 if we are going to be reviewing novel multifocal or
4 novel accommodative IOLs, I think efficacy will
5 require an active control. So, again, I am sort of
6 dividing it between safety and efficacy. I think
7 efficacy will require active controls even in the
8 older group but safety may not.

9 DR. WEISS: Dr. Ferris?

10 DR. FERRIS: Some people may be shocked to
11 hear me say this. In fact, I am shocking myself to
12 say this, but I agree with Malvina that we need to
13 look at this separately for safety and efficacy and
14 I am saying that in part not, as Allen says,
15 because of what is scientifically best but what is
16 reasonable to do. From my perspective the
17 appropriate control group, particularly for these
18 younger people that are considering to have this
19 done for presbyopia, is the unoperated group. The
20 choice is wearing glasses and the risk of wearing
21 glasses is pretty low.

22 So, the underlying rates that have been
23 presented today for retinal detachment and
24 endothelial cell loss are probably the appropriate
25 rates to look at. They are so low that if you

1 tried to figure out the sample size that would be
2 necessary to have reasonable confidence intervals
3 around those rates, it is sort of an impossible
4 study. So, from one perspective I would think that
5 you would take the point of view that for safety
6 the rate is almost zero or very low. So, what you
7 want to know is what is the rate if you do this
8 procedure and I would bundle the whole procedure as
9 you were mentioning, the surgery plus the lens,
10 plus everything. So, from the safety side I think
11 that is the way that I would do it so I am saying I
12 guess historical controls.

13 Efficacy is a different issue I think
14 because now you can have an appropriate sample size
15 and, as Neil pointed out, whatever it was, 6
16 percent loss or 3 percent one line loss is what you
17 would find if you just repeated the visual acuity
18 the same day. There is a certain 5-letter change
19 in our experience. So, usually I say results are
20 always improved by omitting the control group. In
21 this case they are worsened by omitting the control
22 group. So, i would think from the company's point
23 of view they probably want an active control group
24 and that control group may be several things. One,
25 as mentioned here, their preexisting state, which I

1 think is a very important control group and,
2 secondly, maybe a comparable group, particularly if
3 you are going to look at changes over time and
4 quality of life. I also agree that doing a
5 randomization trial is virtually impossible. On
6 the other hand, uncontrolled confounding is going
7 to be an impossible issue to deal with when you
8 don't have a randomization comparison. So, it is
9 sort of skewed either way.

10 DR. WEISS: I think both Dr. Bradley and
11 yourself bring up a very good point. Just to sort
12 of elucidate it a little bit further, if you are
13 going to be doing a historical control for safety,
14 could you just clarify which one of those groups
15 you would both be using?

16 DR. FERRIS: From my view, it is the
17 untreated group, and the only caveat there is this
18 untreated group is potentially treated. As was
19 pointed out in discussions, eventually a large
20 proportion of these people are going to have
21 cataract surgery in their lifetime. The other
22 thing that we will bring up later but what I think
23 is very important is it is not the four-year risk
24 of retinal detachment, it is the 25-year risk of
25 retinal detachment.

1 DR. WEISS: So, you would like a
2 historical control of subjects with no previous
3 ocular surgery for safety but for efficacy have an
4 active control. Dr. Bradley?

5 DR. BRADLEY: I think my views on the
6 safety control group would be, again, the untreated
7 group.

8 DR. WEISS: Basically you are in agreement
9 with Dr. Ferris.

10 DR. BRADLEY: Yes, the one qualifier is
11 that there is a presumption that the literature
12 provides adequate data to support a historical
13 control, and my reading of the literature and the
14 presentations today lead me to believe that within
15 the cataract age group we have adequate data to
16 have historical literature-based controls but we
17 don't in the younger age group.

18 Again, the question is where is the
19 cut-off and I think that is perhaps for the FDA to
20 determine. Where does the literature adequately
21 provide this control?

22 DR. WEISS: Dr. Eydelman?

23 DR. EYDELMAN: If you are choosing to talk
24 about appropriate historical control being subjects
25 with no previous ocular surgery, then we have

1 adequate data in the literature for all ages.

2 DR. WEISS: Dr. Ferris?

3 DR. FERRIS: Well, just one other comment.
4 The one place where perhaps an active control group
5 would be useful for evaluating complications might
6 be in the high myopes. A side issue related to
7 what was discussed earlier is that I actually think
8 it might be a mistake not to include that group
9 because whatever happens with this study, that
10 group is going to be at excess risk of having this
11 done because they have excess benefit of having
12 this done.

13 DR. WEISS: So, basically a historical
14 control of subjects in, let's say, your routine
15 cataract if we are talking about doing a minus 3
16 presbyope where you don't really expect there to be
17 much difference from people without previous ocular
18 surgery, but if you are doing the high risk
19 patients, let's say the minus 20 myope, in that
20 case you might want an active control. If you were
21 doing a minus 20 myope, then neither of you would
22 like a historical control at that point and would
23 have an active control.

24 DR. FERRIS: It is actually in the
25 company's benefit. This is one of those places,

1 again, where you would like to have the control
2 rate because it is going to make your treated rate
3 look better because the control rate is actually
4 going to be significant. Otherwise, I am assuming
5 the control rate is close to zero.

6 DR. WEISS: It gets a little sticky from
7 the agency's standpoint--and correct me if I am
8 wrong--if we are speaking about a historical
9 control of subjects, except if we get involved in
10 certain refractive categories in which case now we
11 want to go on active control. Is there any
12 guidance you can give us on that? I guess we will
13 get involved in that when we get to question number
14 two. Dr. Brucker?

15 DR. BRUCKER: I think that we are making
16 this very complicated and unnecessary.

17 DR. WEISS: Welcome to the panel, Dr.
18 Brucker!

19 DR. BRUCKER: I have been here and I will
20 tell you we are making it complicated and it need
21 not be. It seems to me that, unlike some of the
22 comments around the table, these are patients who
23 will go elsewhere for refractive surgery. That is
24 not the case. These are patients who are perhaps
25 45-55 years of age and, like myself, they are

1 starting to have to use glasses. It is a pain in
2 the neck and it doesn't matter if they are minus 14
3 or plano like I am. The fact of the matter is that
4 these are patients that could use glasses. There
5 is no reason that this isn't a randomization trial.
6 It will make things simpler for the sponsor. It
7 will make things simpler for the patient. It will
8 make things simpler for the FDA. It makes things
9 simpler for everybody to get a group of patients
10 randomized and some will wear glasses. Okay, they
11 have done it. It is only for three more years.
12 And, some are going to have surgery. I don't see
13 what the big deal is. The end result is you are
14 going to have an idea. These patients are not
15 going to have scleral depressed peripheral
16 examinations. You are not going to know if they
17 have lattice. You are not going to know what is
18 going on in the back of their eyes. All you need
19 to do is take a look again at Ripandelli's paper.
20 Sixty percent of those patients wound up having
21 pre-treatment. It doesn't matter if they are
22 pre-treated or not. It doesn't matter what their
23 peripheral examinations are. Randomize the
24 patients. Spread it out whether they are high
25 myopes, plano emmetropes or hyperopes. Give them

1 all a chance to be in the study. Make the sample
2 size large enough. Follow them for three years and
3 you will have all of your answers and there weren't
4 be any complications or problems--let's not say
5 complications.

6 DR. WEISS: Mr. McCarley?

7 MR. MCCARLEY: I think a historical
8 cataract group would be fine unless the National
9 Eye Institute would be willing to fund and run a
10 study because it is actually the procedure we are
11 looking at, regardless of the intraocular lens.

12 DR. WEISS: I have a feeling that is not
13 forthcoming. Now we are going to go back; now that
14 we have heard everyone's opinions, some of our
15 opinions may have changed. Dr. Bressler?

16 DR. BRESSLER: I just wanted to clarify,
17 are we talking about active controls for safety or
18 efficacy? We haven't gotten to the question of
19 what is the safety that we are looking at. So, I
20 know we are in a circle and jumping in. I never
21 foresaw in suggesting active controls that you want
22 to power a study to see if there is a difference in
23 the retinal detachment rate. I mean, that is low
24 in the non-high myope population and that would
25 take 40,000 or more and it wouldn't be meaningful

1 that you reduced it from 0.01 to 0.05 or something
2 like that in percentage.

3 So, for certain safety outcomes you may
4 have to deal with historical controls and there is
5 adequate information for some of those. But for
6 other safety outcomes, for example changes in
7 visual acuity, you may be able to do it with
8 randomized controls so you don't have all the
9 confounding bias. As Rick pointed out, it is true
10 that we had 3/50 in our limited information here
11 that lost one line by six months and that could be
12 noise; it may not be noise. It may be the
13 beginning of two-line loss or three-line loss. It
14 was mainly in the hyperopes, not in the myopes in
15 that small study. That is 50 people versus--you
16 know, there are 60 million over the age of 65 that
17 are obviously going to be presbyopic.

18 So, I think it is incumbent upon the
19 safety, not the retinal detachment safety but some
20 of the others, to be aware of what these are; get
21 rid of the confounding bias and, although it may be
22 hard and take a little further discussion to get a
23 group who is willing to put this off for a few
24 years until we know what the outcome is, there are
25 enough presbyopes out there--it is not a rare

1 disease--that it may be possible. So, I just
2 wanted to add that clarification that I think I
3 agree with what most of the panel said but I am
4 still believing we would need for some of the
5 safety outcomes these controls.

6 DR. WEISS: I am going to have one comment
7 from Dr. Maguire and then I am going to ask if the
8 agency needs anything more from us on this
9 question, just because we have eight of these to
10 get through. Dr. Maguire?

11 DR. MAGUIRE: I have a question for the
12 agency. Does FDA separate groups for presbyopic
13 correction if it is reasonable to expect that one
14 of those groups is more likely to have problems
15 with safety and efficacy, specifically the high
16 myope group? That would be a reason to separate
17 them out. Is that correct?

18 DR. EYDELMAN: In any refractive
19 indication we usually break it up into the ranges
20 of refractive error. For example, for LASIK we
21 broke it up to 7 and above 7, and emmetropia would
22 probably be analyzed separately. So, yes, the data
23 would come in and then we would ask for internal
24 stratification of the data according to refractive
25 indication.