

TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OPHTHALMIC DEVICES PANEL

Seventy-Seventh Meeting

Volume I

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Gaithersburg, Maryland
October 28, 1993

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Seventy-Seventh Meeting
Volume I

Thursday, October 28, 1993

Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
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Donald J. Doughman, M.D.
Olivia N. Serdarevic, M.D.
Michael G. Harris, O.D., J.D.

Nonvoting Member

F. Brent Green, M.P.H., Consumer Representative

Consultants:

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Clifford A. Scott, O.D.
Alan Sugar, M.D.
Scott M. MacRae, M.D.
R. Doyle Stulting, M.D., Ph.D.

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Nancy C. Brogdon

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P R O C E E D I N G S

1
2 DR. BROWN: Can I have your attention, please?

3 According to my watch it is about 8:30.

4 DR. WILKINSON: Good morning. I would like to
5 welcome each of you to the seventy-seventh meeting of the
6 Ophthalmic Devices Panel. I think Dr. Brown will lead us
7 off with several announcements.

8 DR. BROWN: Thank you, Dr. Wilkinson. Good
9 morning. I hope you enjoyed your trip out here. It is the
10 first time we have met away from downtown since I have been
11 involved with the Panel, and that goes back to about '78. I
12 hope you didn't have any trouble getting out here. It is a
13 nice trip out. It takes you a little longer but I think
14 that, all in all, you will appreciate the facilities.

15 We would like to get started with our business
16 today. I would like to welcome everyone, including our
17 Panel members and the audience, to our seventy-seventh
18 meeting of the Ophthalmic Devices Panel.

19 Before we get started, I would like to acknowledge
20 that Dr. C. Pat Wilkinson has been with us as Chairperson
21 for some time. Unfortunately, or maybe fortunately for him,
22 this is his last meeting as Chairperson, and I would like to
23 acknowledge our appreciation for your constant vigilance,
24 indulgence and all of those good things, and we really
25 appreciate your expertise. Thank you kindly.

1 In addition to that, we have some other Panel
2 members that are being -- I hate to use the word but
3 terminated. That sounds a little harsh. I didn't mean it
4 that way simply because we have really appreciated their
5 involvement which I would like to indicate by naming those
6 individuals: Dr. Michael Harris. We again appreciate your
7 involvement and we are going to insist that you become one
8 of our consultants. I hope you don't disagree with that.

9 DR. HARRIS: A pleasure.

10 DR. BROWN: Thank you. We have two individuals --
11 I see one here, Brent F. Green, who is our consumer rep.,
12 over on the end. He has been very diligent. He has
13 involved his area. He always has questions that he presents
14 to us and we do appreciate it and we are going to miss you.

15 The other individual is Martin Knopf, and I don't
16 see Marty here as yet. Marty is our industry rep. We will
17 acknowledge his presence when he comes in.

18 I would like to announce a change in our agenda.
19 The change is being made to delete the presentation and
20 discussion on the multifocal intraocular lens guidance
21 document. This decision to delete this item is based on the
22 fact that no changes to the guidance have been issued to the
23 industry.

24 At this time I would like to welcome any public
25 comments. If you will come forth to the table, please

1 identify yourself.

2 MR. HENTELEFF: Yes, my name is Tom Henteleff. I
3 understand nobody comes forward during these public aspects
4 but, anyway, I am taking that opportunity and I am doing
5 this on behalf of the Regulatory Affairs Section of the
6 Contact Lens Institute.

7 Later today, one of the subject matters that is on
8 the agenda is the status of reclassification of daily wear
9 contact lenses. The Contact Lens Institute and the
10 Regulatory Affairs Subcommittee obviously is very interested
11 in the reclassification of daily wear contact lenses, as
12 well as other aspects relating to contact lenses,
13 potentially including lens wear products also.

14 It appears, based upon the statutory language and
15 other factors, that the reclassification of daily wear
16 contact lenses is imminent. The Contact Lens Institute
17 thinks it is particularly important that guidance be made
18 available by the Agency as soon as possible to address what
19 they consider to be the regulatory safeguards necessary to
20 provide reasonable assurance of the safety and effectiveness
21 of contact lenses upon reclassification.

22 The importance of that, obviously, is that it is
23 important to the public to be assured that there is, indeed,
24 reassurance. But it is also essential to the industry to
25 know what FDA expects of the industry; what they are going

1 to have to do to satisfy the requirements under the new
2 regulatory scheme subsequent to reclassification.

3 So we just want to emphasize our opinion that it
4 is very essential from the perspective of industry to
5 coincide and, hopefully even before reclassification, but
6 certainly simultaneously with reclassification to know
7 exactly what FDA expects of industry under the post-
8 reclassification regulatory scheme. We would like to have
9 any information that can be publicly available when FDA
10 anticipates issuing such guidance, and whatever input the
11 Panel thinks is appropriate in that respect, obviously, is
12 appreciated. Thank you.

13 DR. BROWN: Thank you for statement. I don't want
14 to let the cat out of the bag but that is one of the issues
15 that will be discussed at our meeting.

16 Any additional comments from the floor? I would
17 like to count to ten. Please come forward.

18 (No response)

19 Thank yo very much. At this time I would like to
20 announce our tentative dates for Panel meetings next year:
21 February 24th and 25th, 1994. The time will be the same
22 more than likely, 8:30-5:00. Location has not yet been
23 determined. May 19th and 20th; the same applies, time and
24 date and location. October 20th and 21st; time and place,
25 the same.

1 At this time, I would like to deputize several of
2 our consultants in order that they may vote today. Pursuant
3 to the authority granted under the Medical Devices Advisory
4 Committee Charter, dated October 27, 1990, I appoint the
5 following people as voting members of the Ophthalmic Devices
6 Panel for the duration of this conference, today: Dr. Alan
7 Sugar, Dr. James Boucher, Dr. Doyle Stulting, Dr. Scott
8 MacRae and Dr. Skip Clifford Scott.

9 For the record, these people are special
10 government employees and are either a consultant to this
11 Panel or a consultant or voting member of another panel
12 under the Medical Devices Advisory Committee. They have
13 undergone the customary conflict of interest review. They
14 have reviewed the material to be considered at this meeting.

15 Before we start our deliberation, review and vote
16 on our PMA today, I would like to read a statement to the
17 Panel members. I would like to remind each one of you, and
18 I am referring to the Panel members, of your responsibility
19 concerning conflict of interest. If you, your spouse, minor
20 child, blood relative living in the same household, partner
21 or employer, if known, have financial interest in a firm
22 whose product is being reviewed or discussed today, you must
23 not participate. This includes any firm with which you are
24 negotiating or are employed or from which you receive
25 grants, contracts, payment in kind or other gifts. If you

1 have not been given a waiver to participate, you must not
2 discuss competing products of other firms, or discuss
3 generic or class action matters that affect the firm with
4 which you are associated. Please remember that any changes
5 or negotiations taking place must be reported to the Center.

6 At this time, I would like to introduce Ms. Nancy
7 C. Brogdon, Interim Director of the Division of Ophthalmic
8 Devices, who will give an overview of the remaining portion
9 of the agenda and other pertinent items that are deemed
10 important. She will also introduce Dr. Debra Lewis, Acting
11 Chief of the Diagnostic and Surgical Branch. Dr. Lewis will
12 introduce the medical officer who will present the PMA to be
13 reviewed, discussed and voted on. Mrs. Brogdon?

14 MS. BROGDON: Good morning. I have a few comments
15 and updates for the Panel on several issues we are working
16 on. Before I do that, I just wanted to go through the
17 agenda for the rest of today. After my comments, we will
18 review one PMA for a silicone oil. We expect that will take
19 most of the morning, and we will take a break in the middle
20 of that if it goes on too long. We will break an hour for
21 lunch.

22 After lunch we will give you an update on where we
23 are with the pre-amendment devices of eye valve implants,
24 what our plans are for those. Then we will ask you to
25 review a petition for reclassification of YAG lasers for

1 iridotomy. After that we will go into the intraocular lens
2 issues. There will be a final discussion of labeling for
3 IOLs, and there will be an update for you and, hopefully,
4 some discussion of the ISO guidances that are currently
5 being worked on. We hope then to take a coffee break and,
6 after that, we will review the contact lens-related issues.
7 There will be an update on the reclassification status, and
8 I hope Mr. Henteleff can stay for that. We will talk about
9 where we are with extended wear contact lenses, a monovision
10 policy and salines for RGP contact lenses. So that is the
11 schedule for today. As you know, we have a closed session
12 meeting tomorrow.

13 The updates that I wanted to let you know about
14 have to do with the handout that you received in your
15 packets this morning. It is the tabbed one that talks about
16 some of the management action plan initiatives that we are
17 working on in-house.

18 The Center is committed to becoming more efficient
19 in the way we handle documents. It is unlikely that we are
20 going to get huge numbers of resources any time soon and we
21 have to work as efficiently as possible.

22 One of the things that our Division and the other
23 four divisions in the Office are doing is a more expeditious
24 filing decision on all three types of applications we get.
25 We get IDEs, we get PMAs and we get the 510(k)s that you

1 hardly ever see. We are committed to making quick decisions
2 on whether the applications we receive are fileable or
3 whether they are so vastly deficient we shouldn't proceed in
4 our review. So we are trying to get letters out to the
5 sponsors quickly if we find a document unable to go further
6 in the system. So we are trying not to let greatly
7 deficient documents sit for a long while in the Center
8 before we get to them.

9 The second major policy is what we call expedited
10 review. This is a policy that would allow us to take a
11 really new technology that is viewed as being important and
12 bring those applications to the top of the stack, and to
13 take them before other documents that may be older but more
14 standard types of devices. So the expedited review policy
15 lays out the criteria that the device and the application
16 would have to meet. We hope that the Panel members will let
17 the Agency know if there are technologies under development
18 that you believe need to be expedited. If we see things
19 that we believe need to be expedited, we will write the
20 justifications for those. Also firms are able to nominate
21 devices for expedited review. And we hope the Panel will
22 give us input too.

23 What we don't want to see is pro forma requests to
24 expedite everything because it will be the same scientists
25 in-house who are reviewing the expedited review documents.

1 So the more of those we do, the longer it will take for us
2 to get to routine documents. So we have to be careful about
3 the ones we select. But we feel that this is an important
4 initiative for us to be able to take things that are really
5 important to patients ahead of other documents.

6 The third initiative we call triage for short.
7 What it means is that we are formalizing the extent of the
8 resources that we put to our different types of documents.
9 We are saying a Tier III type of document is a major new
10 device that we haven't seen before. It is either the first
11 or second of a kind. We are devoting a team of reviewers to
12 review of the document and it will most likely come before
13 the Panel.

14 A Tier II device is one that we have seen before.
15 We have our safety and effectiveness questions pretty well
16 worked out. It may involve a team review internally or it
17 may involve a single reviewer.

18 Tier I is probably the major change. This applies
19 mainly to some of the 510(k)s we receive and it means it
20 will be a single reviewer looking at those. They will be
21 reviewing for intended use; for adherence to applicable
22 electrical safety standards, and other guidances that we
23 have set out within the Division. The two main devices that
24 we are using this on right now are sunglasses and spectacle
25 frames.

1 So I would appreciated it if you would read the
2 descriptions that you have been given of the tiers. You
3 have also received a copy of our tier assignments for the
4 various ophthalmic devices. As you look through that list,
5 please let us know if any of those designations trouble you.
6 If you feel that we are minimizing the review of something
7 that we shouldn't or elevating something that we shouldn't,
8 please let us know.

9 I would also like to let the audience know that
10 the ophthalmic triage document is finally publicly available
11 and you can obtain that through DSMA, the Division of Small
12 Manufacturers Assistance. If you need a copy of it, you can
13 fax a request to DSMA at the following fax number: (301)
14 443-8818. You can request document number 892. That is the
15 ophthalmic triage. Make sure your fax request includes your
16 full mailing address and a phone number in case DSMA has
17 questions.

18 Another thing I would like to let the Panel know,
19 although it won't affect you directly, is that we are
20 reassigning some of the devices that we see in-house from
21 our Surgical Branch to other branches in the Division. This
22 is to redistribute the work load, and redistribute our
23 resources and make sure that we are able to devote enough
24 attention to the new technologies.

25 So in line with that, effective December 1, we are

1 switching the following three devices to the Intraocular
2 Implants Branch: Eye valve implants, keratoprotheses and
3 corneal implants, including epikeratophakeal lenticulas. So
4 these will be reviewed by the Intraocular Implants Branch.
5 However, we are trying to provide as much continuity of
6 review as we can. The branches will be talking to one
7 another and sharing reviewers. So we hope not to get into a
8 situation where we have lost the institutional memory about
9 these devices that are in the pipeline.

10 We feel we need to make these redistributions in-
11 house for resource reasons, and we will work with any firms
12 which have concerns about this. There are a few problematic
13 documents that have long histories and the Surgical Branch
14 will bring those to completion before they are switched. So
15 if there are concerns from the industry, please call us
16 individually and we will discuss your situation with you.

17 As Dr. Brown said, the next issue is a PMA. I
18 would like to introduce Dr. Debra Lewis. Dr. Lewis has
19 been, since May of this year, the Acting Chief of the
20 Diagnostic and Surgical Devices Branch. That Branch will
21 present a PMA for your review. Dr. Lewis?

22 DR. BROWN: Excuse me, Dr. Lewis, before we get
23 started, could I invite the sponsors to come forward so you
24 will be available for questions and, we hope, answers?
25 There should be a register on that table so you can identify

1 yourself by your signature. If not, I will provide one.

2 DR. LEWIS: While the group is getting set up, I
3 just want to mention what a pleasure it is to work with the
4 Diagnostic and Surgical Devices Branch. It has been
5 extremely interesting and important work and I have a very
6 hard-working staff.

7 I also want to let you know about some new staff
8 members who have joined us since the last meeting: Jan
9 Calloway, who is a microbiologist -- and if you are
10 available, go ahead and stand so people can have an
11 opportunity to see you; Dr. Everette Beers, who is a
12 toxicologist and engineer; and Quynh Hoang, who is a
13 biomedical engineer, joining us from cardiovascular.

14 DR. BROWN: Thank you, Debra. Could you proceed
15 at this time?

16 DR. LEWIS: Sure. This PMA is for a silicone oil
17 which is to be used for the treatment of complicated retinal
18 detachment. As we will see today, this application has
19 features which make its review very challenging.

20 As background information, this product was the
21 subject of an earlier PMA which was considered by this Panel
22 and found to need additional follow-up data. That earlier
23 PMA was subsequently withdrawn and is now under new
24 sponsorship, and this PMA should be considered as a new
25 submission. The sponsor has provided new data and analyses,

1 and has attempted to address the problems of the original
2 study design.

3 Please note that there is no currently approved
4 device for use in complicated retinal detachments, including
5 CMV retinitis detachments. After consideration of the
6 criteria for a PMA expedited review, it was determined that
7 this application met those criteria and it has been
8 identified for expedited review status.

9 At this time I also want to recognize Dr. Don
10 Galloway, from our Office of Science and Technology, for his
11 work as the team leader for this PMA and for coordinating
12 the technical reviews. I also want to thank the other
13 scientists from that office for their expert contributions
14 on this application.

15 It is critical that the Panel understand that we
16 are still working with the firm to resolve deficiencies in
17 the statistical, chemical, toxicological and microbiological
18 areas. These deficiencies must be adequately addressed
19 before any approval could be issued. The firm realizes this
20 and has continued to work with the Agency to resolve our
21 remaining concerns. We also note that labeling issues will
22 be an important consideration on this application.

23 The clinical reviewer for this PMA is Dr. Emma
24 Knight. I would like to turn the discussion over to Dr.
25 Knight now, who will present her review of this application.

1 (Slide)

2 DR. KNIGHT: Good morning. One of the things
3 that I have found since coming to the Center of Devices is
4 that I have looked quite extensively at clinical trial
5 designs and found this quote in one of my books that I
6 thought was rather relevant on a day-to-day basis, as well
7 as the presentation of this review. Unfortunately, I don't
8 have the option to sit down.

9 (Slide)

10 The PMA, as Debra mentioned, or this device,
11 rather, has come before the Panel once in October, 1990 and
12 then in April, 1991. The PMA at that time was tabled and
13 the concerns were accountability, accuracy of the data and
14 formatting of the data in the PMA. That was when it was
15 subsequently withdrawn and Chiron worked to address those
16 issues.

17 (Slide)

18 In considering this application, I think that it
19 is important to have a discussion on the history of retinal
20 surgery in general to establish the time lines that exist
21 for use of silicone oil.

22 Gonin developed the basic principles that are
23 still used today in retinal surgery, and that includes
24 closure of the tear, drainage of the fluid and coagulation
25 of the edges of the tear. He incised the retina, drained

1 the retina and closed the edges using direct diathermy.
2 This resulted in a success rate of 40 percent back in 1923.

3 In 1953 there was introduction of buckling
4 procedures by the placement of an explant sponge on the
5 sclera. This increased success rates to around 84 percent.

6 Some other advances, including the binocular
7 indirect ophthalmic scope, from 1947, and in the late '50s
8 and the early '60s the introduction of encircling bands.

9 Subsequent to that, improved materials in the mid
10 '60s and, of course, one of the most important things was
11 the development of photocoagulation techniques to replace
12 diathermy, which included late photocoagulation in 1959 and
13 cryosurgery in 1964. As a result of these advances, at the
14 end of the 1960s we were able to cure essentially 80-90
15 percent of all primary retinal detachments.

16 (Slide)

17 Kasner, in 1968, performed the first open
18 skiavitrectomy, and this let us know that the eye actually
19 could tolerate the removal of the vitreous body. However,
20 it also told us that we need to improve our operative
21 technique based on outcomes. It was largely in this
22 country, through efforts by Machemer as well as others, that
23 the operative technique developed in pars plana vitrectomy
24 became used.

25 Subsequent to that, during the early '80s, special

1 tools and instrumentations, membrane peeling, touching,
2 cutting and excising the retina became more and more common.
3 As a result of this advancement into what we call vitreous
4 surgery, by the end of the '70s, of that 10-20 percent that
5 remained uncured, we could then see success rates of 60-80
6 percent.

7 (Slide)

8 However, we found that in order to improve the
9 long-term outcomes for these patients we had to proceed with
10 further improvements. The ability to check re proliferation
11 has been addressed by radiation, cytotoxic agents and
12 steroids, and continues today to be subjects of many drugs
13 that have yet to show us that we can do that.

14 It was also shown that with more aggressive
15 surgical techniques we would need a tamponade for long-term
16 effects to support that. It was as early as 1883 that we
17 injected sodium chloride into the eye in order to replace
18 the vitreous. So this was not anything new.

19 It was basically Cibus, in the early '60s, who
20 advanced the use of silicone oil. He injected silicone oil
21 by syringe into the space between the preretinal membrane
22 and the retina to peel the membrane and press the retina
23 flat, at the same time producing tamponade of existing
24 holes. He did not, however, remove the vitreous.

25 Many people were enthused by his early reports.

1 But it proved that as more and more surgeons tried to do
2 this, the technique was extremely difficult and surgeon
3 dependent and overall the long-term results were
4 disappointing. Many complications occurred, including
5 severe tissue reactions and giant cell formation,
6 intraretinal oil was seen and, sadly, Cibus had an early
7 death. So that sort of checked some of the use of silicone
8 oil.

9 It was John Scott, from Cambridge, in the '70s who
10 continued to develop Cibus' methods and introduced a lot of
11 instrumentation techniques that helped some of the
12 advancement in this surgery. It was Zivojnovic, in
13 Rotterdam, in the early '80s who combined the vitreous
14 surgery and silicone oil tamponade, which he called the
15 logical consequence, that gave us what we have today for
16 extreme vitreous surgery.

17 Essentially, what we are talking about here is a
18 proliferative condition, and the number of cases per year
19 that we are talking about in these cases is probably around
20 800-900.

21 (Slide)

22 One of the people who took up the technique and
23 continued with it was Dr. Lucke, from Germany. It was,
24 indeed, the Lucke study which was presented as part of this
25 PMA and as primary support of this PMA to address the issues

1 of silicone oil.

2 It should be noted that this was a prospective
3 study. It initially started out with the early oils. It
4 proceeded, from 1984-1989, with the study of 299 patients
5 for whom modern day vitreous surgery was used and who were
6 noted as the late group, if you know this study, and this is
7 what was reported in this PMA.

8 It should be noted that the sponsor did do an
9 analysis of all 299 patients, all subjects, as well as 236
10 cohort group who had follow up for 6 months. There was no
11 statistical differences between those 2 analyses.

12 (Slide)

13 The indications in the Lucke study were primarily
14 proliferative vitreoretinopathy and proliferative diabetic
15 retinopathy. The other remaining indications -- for
16 posterior holes there were 17 patients; for giant tears, 13;
17 there were miscellaneous conditions in 9 patients; and 5
18 patients with perforating injury. It should be noted that
19 the underlying pathology in all of these conditions is a
20 proliferative component.

21 (Slide)

22 At baseline and enrollment, these patients had
23 already had prior detachment surgery which involved buckling
24 techniques in 45 percent. Prior vitrectomy had been
25 performed in 19 percent, and the use of gas was present and

1 failed in 9 percent. Overall, 72 percent of these patients
2 had failed what we would consider previous detachment
3 surgery.

4 Also important to note is the status of the other
5 eye in these patients. In 24 percent of these patients, it
6 was blind, and in another 6 percent it was felt that the
7 opposite eye needed surgery.

8 (Slide)

9 All patients had prior surgery. The difference
10 between the 170 and 236 is primarily taken up by prior laser
11 surgery being included in that "all patient" surgery.

12 (Slide)

13 If you look specifically at PVR, which is a topic
14 that we look at based upon the silicone oil study, what is
15 extremely significant is the number of surgeries that this
16 particular population had. You can see that it wasn't just
17 one; that there were multiple surgeries in many patients.

18 (Slide)

19 If you look at improved visual acuity status at 6
20 months, for all patients the overall rate is 70 percent. If
21 you look at it stratified by indication, those percentages
22 are given here. The lower percentages I think in the
23 perforating injuries is probably true, however the numbers
24 are too small to draw much conclusion. In 15 percent of
25 patients there was no change from preoperative visual

1 acuity. In 15 percent of patients postoperative acuity was
2 worse. Ambulatory vision, defined in this study as 20/1000
3 for purposes of this slide, was present in 72 percent of the
4 population.

5 It should be noted that within the PMA the sponsor
6 did evaluate visual acuity status based upon doubling of the
7 visual angle, ambulatory vision, whether preop. to postop.
8 vision was improved, stayed the same or was worse. So the
9 actual presentation of visual acuity is done in several ways
10 within the PMA.

11 (Slide)

12 This is a slide that we subsequently asked the
13 sponsor for. If you look at the visual acuity status
14 greater than or equal to 20/500, you will find that at 6
15 months that number is about 68 percent and at 12 months,
16 with a 78 percent follow-up rate, it was about 64 percent.
17 Beyond that time period on this graph the numbers fall off
18 and the curve is probably not reliable.

19 (Slide)

20 The retinal attachment status in these patients at
21 6 months was reported. There was a 70 percent attachment
22 rate at 6 months. I should note that there is a mistake on
23 this slide. Partially or fully detached should be 54/236
24 and that is 23 percent, which equals 100.

25 (Slide)

1 We also looked at the macular attachment status in
2 the cohort group. If you will notice the box there, it
3 addresses several different ways to look at macular
4 attachment. What we are interested in is case 1, where both
5 the retina and the macula are attached.

6 In looking at that, what you will see is that at 3
7 months, with full follow up, macula was attached in 75
8 percent of patients; at 6 months in 77 percent of patients;
9 at 12 months in 80 percent of patients; then at 18 months it
10 is in 78 percent of patients, however, follow-up rates fall
11 off to 58 percent.

12 (Slide)

13 We looked at hypotony at each follow-up visit by
14 macular status. What we saw is that at 3 months it was
15 about 5 percent and rolls to around 8-9 percent beyond that
16 time period.

17 (Slide)

18 That is shown in this slide based upon the thin
19 line, the middle line on the slide.

20 (Slide)

21 If we look at keratopathy at each follow-up visit
22 by macular status we can see that at 3 months it is about 12
23 percent; at 6 months 14 percent; and at 12 months about 16
24 percent. So this remains pretty consistent throughout the
25 follow-up periods.

1 (Slide)

2 I am sorry this slide is a little bit hard to
3 read. What it is addressing is removal of silicone oil.
4 This involves all patients, which is 299 patients that had
5 eyes implanted with silicone oil. Of those, 228 were
6 successes and subsequently 97 had silicone oil removed. Of
7 those 97 who had silicone oil removed, if you go down to the
8 second box from the bottom, it leaves 86 patients who had
9 silicone oil removed and remained attached. Those patients
10 who also had it removed, 7 of those patients had problems
11 and had silicone oil re-instilled, and 6 of those went on to
12 remain with silicone oil in the eye and remain attached.
13 One of them had it removed again, had no silicone oil in the
14 eye and remained attached.

15 (Slide)

16 Initially in the study it was planned to remove
17 silicone oil at 3-4 months. It is obvious that this did not
18 happen, and it should be remembered that some of that
19 decision is made on individual patients. If you remember
20 the number of surgeries these patients had, there was a
21 reluctance to go back and take the silicone oil out by both
22 surgeons and the patients to have another operation.

23 This does look at some time frames for removal of
24 silicone oil and gives us some reasonable assumption that
25 the oil can be removed and the retina can remain flat. What

1 we don't know about this is the reason for silicone oil
2 removal.

3 (Slide)

4 We looked at some of the patients who had visits
5 and visual acuities reported both before or concurrent with
6 oil removal and at their final visit. That was 62 patients
7 that we had information on. Of those 62, 77 percent had a
8 visual acuity of greater than or equal to 20/500.

9 (Slide)

10 I would like now to go to additional support for
11 the PMA that is presented by the sponsor, and this was the
12 sponsor's IDE investigator study. This also was a
13 prospective study, and was conducted from 1988-1991.

14 There were 155 patients in this study. There was
15 a provision in this protocol for previously failed retinal
16 surgery. Out of the 155 patients, 79 followed the protocol.
17 I believe it was the decision of the retinal surgeons to use
18 their best clinical judgment.

19 (Slide)

20 The indications in this study are a little bit
21 different from the Lucke study. The number of PVR patients
22 is higher. It was 42 percent in the Lucke study and the
23 number of the proliferative diabetic patients is slightly
24 lower. In the Lucke study it was 39 percent. There were no
25 CMV patients in the Lucke study. The tears and holes

1 comprised 13 percent there and perforating injury was 2
2 percent.

3 Of significance to remember is that the underlying
4 component is still proliferative disease. One of the things
5 that you will see later is that the PVR in these patients
6 tends to be a more complicated PVR than seen in the Lucke
7 study.

8 (Slide)

9 In these patients you had a mean follow up at 7.7
10 months for the final visit. What you see here are the
11 percentages of visual acuity status, whether improved, no
12 change or worse, and ambulatory vision was defined in this
13 study as greater than 5/200 and was 34.2 percent.

14 (Slide)

15 If you look at retinal attachment status, this was
16 reported for all patients and in approximately 64 percent
17 the retina was attached. If you look at macular attachment
18 status, what you will find is that about 75 percent of the
19 maculas were attached, indicating that there is some partial
20 retinal detachment which still leaves macular attachment.

21 (Slide)

22 One of the things that I tried to do with this
23 PMA, which I thought was going to be easy, was to take the
24 silicone oil study group, because of its importance in the
25 decisions, and to show that silicone oil does have uses, and

1 compare that to the study. Well, I found some problems in
2 doing that and it wasn't nearly as easy as I thought.

3 So I want to point some of those out and the
4 reasons why a direct comparison cannot necessarily be made,
5 although that doesn't mean that we can't necessarily derive
6 impressions from these studies.

7 If you look at the ambulatory visual acuity, in
8 the Lucke study at 6 months it was 80 percent. If you look
9 at 18 months, taking a worst case scenario, it would be 2
10 percent. If you take just patients who were followed that
11 long, which gives an N of 138, you have a 72 percent
12 incidence of ambulatory visual acuity.

13 In the U.S. study, which had a mean follow up of
14 7.7 months, again 34 percent was the incidence of ambulatory
15 visual acuity.

16 The 004 study is essentially individual
17 investigator IDEs where Chiron maintained some gathering of
18 data and I will let them explain that, but they basically
19 did do some monitoring of those studies with regards to
20 gathering data. The percentage of ambulatory visual acuity
21 there was about 40 percent.

22 In the silicone oil study group, at 18 months you
23 have a rate of 43 percent for C₃F₈ and 45 percent for a
24 different silicone oil. If you take again the silicone oil
25 study group, follow up at 18 months was only 56 percent for

1 the silicone oil. If you take a best case scenario, it
2 would be an ambulatory visual acuity of about 80 percent.
3 So these percentage rates do give you some impression that
4 things are similar.

5 If you look at retinal attachment rates, the
6 numbers are presented here and are basically rather
7 consistent, with the exception of the 002 study. As I said,
8 I suspect that some of that may be due to the stratification
9 in the PVR patients that appear at least to be worse.

10 (Slide)

11 The purpose of this slide is to look at 18-month
12 follow up with visual acuity status just in uncomplicated
13 PVR patients. If you look at the number of patients with
14 18-month follow up, it was 43 patients, which gives you a
15 visual acuity status greater than 20/500 in about 70 percent
16 of patients.

17 If you take a worst case scenario out of all PVR
18 uncomplicated patients, and the number is 64, then the
19 visual acuity status would be 46 percent greater than or
20 equal to 20/500. That would be the worst case.

21 If you look at the 25 patients who had grade C3
22 PVR or worse, which is a comparison to the silicone oil
23 study population, the percent of patients with an ambulatory
24 visual acuity is approximately 54 percent at 18 months.
25 This is consistent with the 50 percent seen for both

1 silicone oil and C₃F₈ in the silicone oil study group.

2 (Slide)

3 Macular attachment status at 18 months in these
4 patients in the Lucke study was approximately 72 percent.
5 If you take the worst case scenario, it is 48 percent.

6 (Slide)

7 I tried to look at complications between the
8 studies. The first thing that I realized was that you had
9 to look at the definition of keratopathy. In the 3 PMA
10 studies we looked for bulbous or band keratopathy and it was
11 approximately 8-9 percent in the Lucke study and in the
12 sponsor investigator study. In the Lucke study you did see
13 a higher rate in aphakic patients versus phakic patients.
14 The patients in the U.S. study were all aphakic or
15 pseudophakic. In the individual investigator sponsor's
16 study, it was approximately 15.2 percent.

17 If you look at the definition for the silicone oil
18 study group, you can see that the definition is markedly
19 different. So I don't think you can compare the rates
20 between those studies.

21 (Slide)

22 If you look at glaucoma incidence, the initial
23 letter for the studies, 001, 002 and 004, is at discharge.
24 You then have 6 months and 12 months. The incidence at any
25 given time within the study for the 001 study is given at

1 the bottom. Again, there were different definitions for
2 glaucoma in these populations, particularly when looking at
3 the silicone oil study group. So there is a caution in
4 making that comparison. But what is relevant is that the
5 incidence of glaucoma overall was in the range of 9-10
6 percent at 12 months, with the exception of the 004 study in
7 which it was actually lower.

8 (Slide)

9 I would like to turn my attention now to the CMV
10 retinitis patients who have retinal detachments. We had 12
11 patients in the original 002 study. I asked Chiron could
12 they please look in their data file and find me those
13 patients alone and give me some information on that. They
14 did. What we found were 205 patients who had treatment of
15 retinal detachments in CMV retinitis associated with AIDS.

16 (Slide)

17 It should be noted that CMV retinitis is present
18 in about 34 percent of patients with AIDS. This 34 percent
19 number I got from calling the CDC because the literature was
20 kind of all over the place. I thought it was about 20
21 percent. This number came from CDC. It is bilateral in 50
22 percent of patients.

23 (Slide)

24 The important thing to note here, and why we
25 looked at these patients separately, is that the underlying

1 pathophysiology is different from the proliferative
2 retinopathies. It involves infarction and intraretinal
3 hemorrhages. You get an exudative retinal separation and
4 ultimately you get necrosis of the retina. What you see is
5 chorioretinal atrophy, thinning and a Swiss cheese
6 appearance of the retina.

7 (Slide)

8 Ultimately, the outcome in these patients, even if
9 you fix the retinal detachment, has other factors involved.
10 Certainly, with the occurrence of hypotony, the presence of
11 optic neuritis is important and really this is,
12 nevertheless, a progression of the disease and unless the
13 disease itself is controlled with antiviral agents you will
14 continue to lose vision.

15 (Slide)

16 The demographics on these patients -- of the 205,
17 there were 155 who had sex reported and they were primarily
18 male. The average age of these patients was 40.2 years,
19 with a range of 23-89.

20 Very important in these patients, I think, is that
21 they are primarily phakic patients and remained phakic after
22 surgery, unlike the proliferative patients. The average
23 follow-up time for acuity vision measurement is 3.95 months,
24 with a range of 0-35 months, and we have that measurement
25 for 194/205 patients. The average time until death from the

1 time of surgery is 193 days.

2 So this is longer than some of the literature
3 reports, and whether it reflects an earlier intervention
4 time or better treatment of the disease -- I don't think you
5 can really be sure of either one of those.

6 (Slide)

7 Visual acuity in these patients is reported in the
8 literature in several ways. One of them is best achieved
9 visual acuity. In these patients, because of the
10 progressiveness of the disease, you do want to have some
11 idea that the surgery is doing some good. What you see is
12 that from preop. to best achieved visual acuity in 83
13 patients, or 40 percent of patients, there is improvement.

14 (Slide)

15 This is a scatter plot of preop. visual acuity on
16 the X axis and best achieved visual acuity on the Y axis.
17 What you can see in this plot is, if you look to best
18 achieved visual acuity, that there are a number of patients
19 who do have good vision.

20 (Slide)

21 If you look at final visual acuity in these
22 patients, what you see is that, yes, they do lose vision and
23 that only about 30 percent of them have improved visual
24 acuity, and overall 40 percent have the same or improved
25 visual acuity.

1 (Slide)

2 If you look at this scatter plot and compare it to
3 the last one, you can see a downward trend of visual acuity.

4 (Slide)

5 In the literature reports there was a suggestion
6 that perhaps the loss after surgery was bimodal at 1- and I
7 believe 4-month time period. So we looked at these patients
8 to see if we saw any of that trend and we did not.

9 The columns here represent those patients 0-1
10 months, patients greater than 1 month to 3 months, greater
11 than 3 months to 6 months and those patients greater than 6
12 months. What you can see is that patients who had
13 improvement or maintenance, or no change in visual acuity
14 from preoperatively to best achieved are running just over
15 50 percent in each group for follow up.

16 If you look at the change in final visual acuity,
17 you do see some drop down, probably in the 43 percent, 48
18 percent range. So there is loss of visual acuity based upon
19 the progression of the disease.

20 At this point I was going to summarize some things
21 but based upon Dr. Stulting's review and Dr. Wilkinson's
22 review, we did ask the sponsor to submit some additional
23 information, which they did, and which we got in a very
24 recent time. We did get it in order to present it to the
25 Panel. So I am going to bring up several points and if

1 there is anything further that the primary reviewers from
2 the Panel would like to bring up, please do so.

3 (Transparency)

4 I am sorry for the quality of these slides. We
5 made these up off the fax in order to get them in time for
6 the Panel meeting so they may be a little bit hard to read.
7 What I would like to point out in this slide is that these
8 are all PVR uncomplicated patients with at least 18 months
9 of follow up. There is a total of 43 patients in that
10 group. Of that 43, 34 were attached and the visual acuity
11 by macular attachment rate represents 88.2 percent.

12 So if you take a worst case scenario and take all
13 of the 55 patients who meet the criteria in the silicone oil
14 study, it would still be 50 percent, once again consistent
15 with the silicone oil study.

16 Also it should be noted that follow up of 43
17 patients is 78 percent, which matches the silicone oil study
18 group which had a 73 percent follow up for the silicone oil
19 group and an 81 percent follow up for the C₃F₈ group.

20 (Transparency)

21 We also looked at hypotony stratified by macular
22 status in these patients because it was felt to be
23 significant in the silicone oil study group at the rate of
24 about 30 percent for the C₃F₈ group and 16 percent in the
25 silicone oil group. What we see here is what appears to be

1 a lower rate. This is the group who developed hypotony and
2 it is running at about 4-5 percent in this group. So I
3 think this appears to be better; I don't think you can make
4 direct comparisons.

5 (Transparency)

6 This slide was supplied by Chiron and I would like
7 to thank Dr. Weiner for supplying it. Even though you can't
8 read it, it is a review of literature articles in the '70s.
9 What it shows is some of the procedures that were done on
10 these patients prior to the development or the use of
11 silicone oil or even gases. These are all complicated PVR
12 patients, most of them Grade D or worse.

13 What you see is that -- I know you can't read it
14 but what it says is that 69 patients were reported as
15 inoperable. If you look at this study, you have 29 cases
16 who were considered inoperable. Overall, if you look
17 through this slide, you will see the use of buckles which
18 gave a retinal attachment rate of about 31 percent. If you
19 add in vitrectomy and buckle -- these are small series so
20 the percentages aren't reliable but what is important is
21 that it is all in the 20-30 percent range and there was a
22 great number of these patients who were considered
23 inoperable. So until the use of silicone oil and tamponade,
24 there was a great number of these patients who did not
25 receive any treatment whatsoever.

1 (Transparency)

2 In light of that and some questions that Dr.
3 Stulting had asked, this was a stratification by diagnosis.
4 I did this for visual acuity, retinal status, macular status
5 and complication rates. The top table shows the Lucke study
6 and the bottom table shows the U.S. study. What you see,
7 first of all, is if you look at PVR alone is the number of
8 patients in the Lucke study is 52 patients, up here. If you
9 look in the U.S. study, what you see is that it is only 11
10 and that PVR with complications in this study is 73. So it
11 does give you an impression that the PVR within the U.S.
12 study was worse.

13 (Transparency)

14 The retinal attachment status rate is reported and
15 I think if you look at this, and particularly if you look at
16 the U.S. study and look at the retinal attachment rate here,
17 it is approximately 60 percent in the complicated PVR
18 patients. If you remember, these are patients who were not
19 helped by conventional retinal surgery or vitreous surgery
20 and includes that 20-40 percent who were left over whom we
21 could not treat.

22 (Transparency)

23 This slide is basically an incidence of
24 keratopathy. What you see is that it is 8.6 percent in the
25 Lucke study and 16.4 percent in the U.S. study. The Lucke

1 study did stratify for presence of keratopathy preop. and
2 presence of keratopathy postop. De novo establishment of
3 keratopathy was 6.6 percent if it was not present
4 preoperatively. The overall rate was 8.6 percent.

5 (Transparency)

6 If you look at cataract development, the incidence
7 of cataract development in the Lucke study was 52 percent
8 and in the U.S. study -- there were a lot of missing data
9 here so I am not sure what it was. Let's leave it at that.

10 One of the important things to note though is that
11 in doing some research I found that if you look at just
12 vitrectomy patients alone, the incidence of cataract at 6
13 months is about 40 percent in those patients, and that is
14 visually significant cataracts. If you take it out to 18
15 months the incidence of cataracts in patients who have
16 vitrectomy alone is as high as 70 percent. So this 52
17 percent may be due just to surgery alone.

18 (Transparency)

19 The incidence of glaucoma in the 2 studies -- I
20 think we looked at this before -- was basically 14.8 percent
21 in the Lucke study and in the U.S. study it was 6.4 percent.
22 But if you look, there is a significant amount of missing
23 data there.

24 (Transparency)

25 Well, can we think any advantages of using

1 silicone oil? First of all, postoperatively the positioning
2 of the eye is undoubtedly in some patients a difficult
3 problem. If you have to lie face down, if you have a
4 posterior hole, if it is an elderly patient -- many of these
5 patients just cannot do it and the success of the surgery
6 can depend on that.

7 The recovery and ambulation and ability to move
8 around is more rapid with silicone oil. If you look at the
9 silicone oil study group, there was a significant difference
10 at 1 month. This went away after the gas was resorbed in
11 the eye and was not significant later. So CMV retinitis
12 patients where the early ambulation and quality of life is
13 important, this is an important consideration for the use of
14 silicone oil. Also for monocular patients this may be very
15 important too.

16 One of the relevant pieces of information in the
17 silicone oil study was that in previously vitrectomized eyes
18 with PVR hypotony was a significant problem with C_3F_8 . It
19 occurred in as much as I think 33 percent of patients. That
20 is probably lower in silicone oil, based upon the results
21 that we saw here. So you may want to consider that in
22 previously vitrectomized eyes.

23 Primary use is indicated in some patients,
24 particularly the CMV retinitis patients where quality of
25 life and fast recovery is important.

1 Air travel has always been recognized as a problem
2 with the gases. Finally, what the retinal surgeons will say
3 is that there are selected cases where you know that you are
4 going to have to use silicone oil. If in doing the surgery
5 you have to make a large inferior retinotomy, that may be a
6 serious consideration as to whether you use gas or whether
7 you use silicone oil.

8 (Transparency)

9 These come from the silicone oil study also and
10 talk about initial vitrectomy. In eyes not undergoing
11 previous vitrectomy with C_3F_8 , there was some statistical
12 advantage. So for initial vitrectomy consideration should
13 be given for that.

14 The other reasons for using C_3F_8 include the need
15 for reoperation. While we do know the long-term
16 complication rates at this time, it cannot be left in for
17 ever. We do have a good idea of those long-term
18 complication rates.

19 (Transparency)

20 What were the limitations in the silicone oil
21 study group? One of the points made was that randomization
22 was made only after the retina was flattened. This makes an
23 assumption that the only treatment difference between the
24 groups was the agent used for the tamponade. It does not
25 take into consideration things like use of retinopexy or

1 whether it was cryo or what amount of retinopexy was used,
2 and that there was no other intraoperative procedure, for
3 instance the amount of manipulation of the retina done that
4 made a difference. I think for these complicated patients
5 that may be a significant factor.

6 (Transparency)

7 So I think that there are still some things we
8 don't know. We don't know how the type of retinopexy and
9 the amount of retinopexy really affects the two different
10 groups.

11 With regard to recurrent retinal detachment, we
12 look at it in two ways, whether it is due to a failure of
13 the surgical objective to begin with, and we like to think
14 that if that occurs, it occurs in usually the first few
15 weeks and certainly before 6 weeks. However, that is an
16 assumption that we can't be sure of. There may be a hole
17 there that we haven't taken care of and it just doesn't
18 manifest itself until after that time point. Again, until
19 we check reeproliferation, that is usually the cause of
20 recurrent retinal detachment.

21 The other issue is the use of scleral buckles,
22 particularly in the CMV retinitis patients, and whether they
23 are necessary. I don't think we have that answer from these
24 data. I think it was almost surgeon preference that was
25 shown there.

1 Finally, we do not know the optimal time for
2 removal of silicone oil. I think we will find that it is
3 likely that we can remove silicone oil and that when we do
4 there may be some slight increased risk at the time of
5 removal, but that if the surgery goes well, then these
6 patients do well afterwards.

7 I think that is it.

8 DR. WILKINSON: Thank you, Dr. Knight, for that
9 exhaustive review. It was very thorough. I would like to
10 also thank you personally for being so timely with these
11 review documents. I think both Dr. Stulting and I
12 appreciated being kept up to date.

13 Dr. Stulting and I were the primary reviewers. We
14 will have Doyle give us the high points of his review at
15 this time.

16 DR. STULTING: Thank you, Pat. This review is
17 being conducted under rather unusual circumstances.
18 Unapproved silicone oil and other devices for retinal
19 tamponade from more than one manufacturer have been in
20 common usage, without IDEs, in this country for almost a
21 decade without significant enforcement action by the FDA..

22 Retinal surgeons are familiar with techniques for
23 the use of silicone oil, with results and with
24 complications. Ophthalmologists in training learn how to
25 use silicone oil and other unapproved devices routinely at

1 highly respected academic institutions.

2 The NIH even supported a randomized study of an
3 unapproved silicone oil from another manufacturer, the
4 results of which were published more than a year ago. In
5 fact, many knowledgeable retinal surgeons would probably
6 consider a randomized, controlled, prospective study of
7 silicone oil for the treatment of certain kinds of retinal
8 detachment to be unethical at the present time.

9 The data presented in this PMA are severely flawed
10 by poor experimental design and poor accountability, as
11 discussed in several in-house reviews of this product and as
12 alluded to by Dr. Knight earlier. The supplier of the
13 product in question has presented data on its silicone oil
14 before the Panel in the past on two occasions. In spite of
15 a recommendation for disapproval and the Panel's clear
16 message that scientific data to support safety and
17 effectiveness are needed for approval, none has been
18 forthcoming. Instead, the device has continued to be used
19 in this country without comprehensive collection of outcome
20 data and without a single well-designed clinical trial. We
21 are again asked to make a recommendation for or against
22 approval of this silicone oil on the basis of efficacy data
23 that are far from convincing.

24 In this review I will not discuss in detail any
25 faults of the PMA. Instead, I would like to take a broader

1 approach and focus on the basic issues that we should
2 address in order to make our recommendation to the Agency.

3 First, is silicone oil safe? One of the
4 advantages of the prolonged common usage of this product is
5 the opportunity to observe complications if they exist. It
6 is pertinent, therefore, that there have been no reported
7 systemic adverse reactions attributable to the product. The
8 oil is apparently well tolerated, with minimal inflammation.

9 The well-known ocular complications of silicone
10 oil include cataract, corneal edema, band keratopathy and
11 glaucoma. Incidences are approximately 50 percent, 10
12 percent and 20 percent respectively. The exact incidence is
13 dependent upon the initial diagnosis, length of follow up,
14 duration of exposure to the oil, limb status, the presence
15 of oil on the anterior chamber and the presence of
16 emulsification. These complications may also be seen when
17 gases rather than oil are used for retinal tamponade. The
18 complications are treatable with cataract extraction,
19 chelation, corneal transplantation, topical medications,
20 oral medications and surgical procedures to reduce the
21 intraocular pressure. Although they are undesirable, these
22 complications may be acceptable if there is no other method
23 for reliably reattaching the retina.

24 Is the oil effective? In the Lucke study the
25 retinal reattachment rate was about 70 percent and

1 ambulatory vision was obtained in about 85 percent of eyes
2 at 1 year and about 70 percent at the final visit.

3 The critical issue, however, is not whether
4 retinas can be reattached with use of silicone oil but
5 whether success with this device is more probable with it
6 than it is without it. Unfortunately, the PMA does not
7 contain any data that directly address this point. None of
8 the studies include a control group and comparison with
9 previously published data which report, for example,
10 reattachment rates of 33-80 percent for gases. It is
11 futile, because of differences in case selection, endpoint
12 definition, length of follow up, etc.

13 Lucke and his group studied patients from three
14 practices with proliferative retinopathy, giant tears,
15 posterior holes, diabetic retinopathy and perforating
16 injuries who were operated upon between 1984 and 1989. The
17 results of this study have been reviewed in detail this
18 morning by Dr. Knight.

19 The results were compared to the silicone oil
20 study group results. After allowances were made for
21 different selection criteria and evaluation methods, results
22 seemed to be similar. It should be remembered, however,
23 that the silicone oil study group studied a product with
24 different physical characteristics from a different
25 manufacturer, and there was no detectable difference in

1 success rates for silicone oil and for fluoropropane gas.

2 Uncontrolled, open-label, prospective
3 investigations were conducted at 9 centers under the
4 sponsor's IDE 880198, referenced as study 002. Inclusion
5 criteria were the presence of retinal detachment associated
6 with proliferative vitreal retinopathy and a history of at
7 least 1 previous failed attempt at repair using vitrectomy
8 with gas. However, only half of the enrolled patients
9 actually met the inclusion criteria.

10 This surprisingly high incidence of protocol
11 violations in a study that was supposed to be monitored is
12 difficult to understand. Failure of investigators to comply
13 with the experimental protocol certainly raises questions
14 about the reliability of the data.

15 The reattachment rate in 002, including 76 eyes
16 that did not meet the criteria, was about 65 percent, with
17 only 29 percent of them followed for 1 year or more. The
18 data were not presented for various preoperative diagnoses
19 and the role of oil per se in the treatment of these
20 patients is extremely difficult to assess.

21 The results of treatment of an additional 230
22 patients at 10 additional sites operating under their own
23 IDEs were also included in the PMA. The reference is study
24 004. Of these, 52 eyes did not meet inclusion criteria
25 identical to those for 002; 37 percent of the eyes were

1 followed for at least 1 year and the reattachment rate was
2 about 65 percent. Again, the data are difficult to assess
3 because there was no control group.

4 An analysis of 205 eyes from 176 patients with
5 retinal detachment from AIDS-related CMV retinitis is also
6 included in the PMA. These patients were selected from
7 among the sponsor's and independent IDEs, as well as from 2
8 investigators who were provided oil on a compassionate
9 basis. Three investigational sites accounted for more than
10 90 percent of the cases. Average follow-up time was 4
11 months, with 59 percent of the subjects dying during the
12 period of observation. At the last visit the retina was
13 completely attached in 90 percent of eyes. This success
14 rate compares favorably to reports of success rates of about
15 70 percent with conventional therapy not utilizing oil.

16 There do not appear to be sufficient data from
17 Lucke or any other study to address the questions posed by
18 the Agency during the review process regarding the influence
19 of surgical techniques, instrumentation and timing of oil
20 removal on the outcome. The protocols were simply not
21 designed to answer these questions and they certainly should
22 not be over-interpreted.

23 My conclusions are as follows: The use of
24 silicone oil for retinal tamponade has become the standard
25 of care for certain types of retinal detachment based on

1 clinical impressions of surgeons who have used the device.
2 This has occurred in the absence of well-controlled efficacy
3 data and FDA-approved devices.

4 The available data do not allow one to determine
5 with certainty the relative efficacy of silicone oil
6 tamponade and other forms of therapy, including tamponade
7 with gases. The potential complications of silicone oil are
8 well documented, including glaucoma, band keratopathy,
9 corneal edema and cataract.

10 No systemic adverse reactions are likely or have
11 been reported. It is unrealistic at this point to expect
12 that prospective, controlled trials will be performed in the
13 U.S. in the face of existing data and the general
14 availability of the device. For certain indications, such
15 as active CMV retinitis detachment in AIDS patients, and in
16 the hands of experienced surgeons the advantages of silicone
17 oil probably outweigh the potential adverse reactions.

18 On the basis of all available data, I believe it
19 would be in the public interest to make silicone oil
20 available for the treatment of complicated retinal
21 detachment. If it is approved, labeling should certainly
22 reflect the known complications of the device and the
23 uncertainties of existing data.

24 The Agency, I believe, should take note of the
25 extremely difficult situation they and the Panel face in

1 evaluating this PMA. If the Agency intends to regulate
2 devices such as silicone oil, steps should be taken to
3 prevent their widespread, uncontrolled use outside of well-
4 designed experimental protocols. Thank you.

5 DR. WILKINSON: Thank you, Doyle. I am simply
6 going to read my summary. This PMA presents data which are
7 not optimal for reasons which have been noted by both Dr.
8 Knight and Dr. Stulting. Nevertheless, the PMA provides
9 meaningful evidence regarding realistic expectations for the
10 use of this device in the real world.

11 Severe retinal detachments which cannot be
12 effectively managed in any other way can be successfully
13 repaired using this type of device. However, the use of the
14 device is associated with well-recognized complications.
15 The precise numbers regarding positive and negative outcomes
16 are unknown. Relatively consistent -- in fact, very
17 consistent success and complication figures have been
18 recognized for years. Cataracts will probably occur in most
19 eyes in which the oil is left for several weeks but these
20 can be managed successfully. Keratopathy is common,
21 particularly in eyes in which the oil is present in the
22 anterior chamber. However, it appears to be no more common
23 in oil-filled eyes than in the gas-filled eyes, at least in
24 the silicone oil trial. The same can be said for glaucoma.
25 This is a problem that occurs in eyes in which both gas and

1 silicone oil have been utilized.

2 I believe that this PMA should be recommended for
3 approval. The use of the device should not be taken lightly
4 and the labeling should clearly reflect this.

5 In general, the device should be employed in
6 situations in which there are no alternatives which the
7 informed patient and his or her physician believe are
8 appropriate.

9 The results of the silicone oil study are
10 available and are well understood by all contemporary
11 vitreoretinal surgeons all over the world. They are all
12 aware of the pros and cons of these devices. There are
13 certainly reasons where oil seems to be somewhat better than
14 gas, and Dr. Knight alluded to these. There are basically
15 two major groups. There are certain, admittedly somewhat
16 unusual types of vitreoretinal pathology, and there are also
17 very specific factors related to the patients such as age,
18 health, ability to maintain a position, the necessity of
19 flying etc. These are the two main factors where one might
20 select oil. But I think any vitreoretinal surgeon would
21 admit that there are cases which can be effectively managed
22 only with silicone oil.

23 The question of precise indications for the
24 removal of silicone oil will remain unanswered at least in
25 the near future, and labeling should reflect the fact that

1 optimal data are simply not available and that each case
2 must be judged individually. Only general statements are
3 appropriate at the present time. Early removal probably
4 reduces the incidence of silicone-related complications,
5 particularly if the oil is in the anterior chamber. Retinal
6 detachment following oil removal appears to be less likely
7 if the retina is completely attached and the posterior
8 segment exhibits no signs of persistent vitreoretinal
9 traction forces. More specific information regarding oil
10 removal will require future research efforts.

11 I would like to open the forum now for additional
12 comments by our Panel members. Thoughts? Comments?
13 Criticisms?

14 (No response)

15 DR. BROWN: In setting up the time sequence, we
16 tried to judge how long a discussion would go on.
17 Fortunately, we are a little ahead of schedule. Before we
18 go into asking questions and expecting the proper answers
19 from the sponsor, why not take a coffee break for about 15
20 minutes? Come back, please, about 10:15. Thank you.

21 (Brief recess)

22 DR. BROWN: Could we be seated so we can get
23 started, please? I know you are anxious to finish your
24 conversation, drink your coffee etc., but the sponsor is
25 seated and anxious to go, and we want to respond to their

1 readiness. Dr. Wilkinson, could you continue, please?

2 DR. WILKINSON: We have several representatives
3 for the sponsor. Do we have questions for any individuals
4 from the Panel members or from the Agency staff?

5 MR. GREEN: Dr. Wilkinson, I have a couple of
6 potentially naive questions that I would like to ask as the
7 consumer representative, if I could. I just wanted to say
8 that as a consumer representative I have a couple of naive,
9 or maybe not so naive questions -- I am not sure which -- to
10 ask. The first is that I just want to raise a concern that
11 AIDS patients seemed to comprise a fair amount of the sample
12 size on some of the research done, yet, I am wondering who
13 the ideal patient for this oil really is. Is it AIDS
14 patients or not?

15 MS. PATTERSON: My name is Carol Patterson, and I
16 am regulatory director for Chiron Vision which is the
17 primary sponsor for this file.

18 I think from a general discussion of what I
19 believe to be the real indications for use for silicone oil
20 are best addressed by Dr. Palestine, Georgetown University,
21 who can give you a concise, brief description of those
22 cases. It is complicated. When you deal with diabetic
23 retinal detachments and when you deal with PDR and PVR, it
24 is not trivial. It actually takes a vitreoretinal surgeon
25 to truly comprehend those. But we will do our best to

1 summarize it.

2 DR. PALESTINE: This is Alan Palestine,
3 Washington, DC. I think there are several situations where
4 a vitreoretinal surgeon would like to have silicone oil
5 available as a tool to fix retinal detachment. One of them
6 is CMV retinitis in AIDS.

7 The reason for that comes from experience such as
8 mine. Between 1987 and 1990 I wasn't using silicone oil,
9 and in the patients that I treated with CMV retinal
10 detachment, my reattachment rate was 66 percent. That
11 experience was similar to other surgeons' around the country
12 and the standard of care gradually became to use silicone
13 oil, which made the reattachment rate 95 percent, or the
14 detachment rate only 5 percent. So the prognosis in those
15 patients really increased around the country in practices
16 where AIDS was a substantial percentage of a vitreoretinal
17 surgeon's practice. Silicone oil basically became a much
18 preferred procedure. The use of silicone oil in these
19 patients, as Dr. Knight pointed out, lets them be
20 rehabilitated more rapidly.

21 The other thing that wasn't presented by Dr.
22 Knight in CMV patients is that the bilateral detachment rate
23 is about 50 percent. So if you detach one eye, the chances
24 of detaching the other eye are about 50 percent. Now, not
25 every patient gets bilateral surgery because they may come

1 to you blind or the CMV may destroy the other eye. But the
2 chance of bilateral blindness in these patients is
3 exceptionally high. Coupled with the relatively short life
4 span, the goal is to rehabilitate these patients as soon as
5 possible for the purpose of getting them back to some
6 quality of life with some vision as rapidly as possible. So
7 that is a very good reason why the vitreoretinal surgeon
8 might want silicone oil.

9 Another example is a patient with a very
10 complicated proliferative vitreoretinopathy where a large
11 amount of the retina has had to be removed because of
12 traction or something like that. Those patients are going
13 to have more trouble being fixed without silicone oil.

14 Another example might be somebody who is in their
15 70s, who just simply can't keep their head down to keep the
16 gas tamponading the retina, whereas with silicone oil they
17 don't need to keep that head position.

18 So the way I see it, and I am going to let Dr.
19 Blumenkranz make some comments as well about this, is that
20 silicone oil has a number of indications and it is a tool.
21 It is not something I would necessarily want to use in every
22 case but, like with all the other tools I am presented with
23 -- the scissors, the picks and the light sources and the
24 various laser probes in vitreoretinal surgery -- in some
25 cases there seems to be a higher expectation that that tool

1 used in this case, in the opinion of the experienced
2 surgeon, will produce a better result or, because of patient
3 selection is a preferable way to go. It is really very
4 dependent on how the surgeon is going to use the tools. Dr.
5 Blumenkranz may have some additional comments.

6 DR. BLUMENKRANZ: I think you have really covered
7 them, Dr. Palestine. You asked about the ideal patient, and
8 probably the ideal patient is the AIDS patient with a CMV
9 retinitis and retinal detachment. As you could see from the
10 data that were presented today, the life expectancy was
11 approximately 190 days. If you were to use alternative
12 modalities, such as a gas, even assuming that they were
13 equally effective in ultimately reattaching the retina and
14 producing equal vision, there is approximately a 90-day
15 period of time where a patient who has gas does not have
16 useful vision. If you look at that in the context of that
17 patient's predicted lifetime, it is approximately half the
18 remaining time. So that alone, I think, is a compelling
19 reason to use oil which allows essentially as much normal
20 vision as possible really within several days after surgery,
21 whereas a gas may take anywhere from two to three months to
22 permit retention of normal vision.

23 DR. WILKINSON: Other comments or questions? Yes,
24 Mike?

25 DR. HARRIS: I have a comment and a question to

1 discuss among the Panel, not necessarily with the sponsors.
2 Both of the primary reviewers have indicated that the study
3 and the data have significant flaws and we did not go into
4 the details, yet, the application of this particular product
5 is somewhat unique and seems to be somewhat compelling, and
6 I have a question for this particular application and for
7 others that may come along in the future. How are we, and
8 how did you when you made your recommendations weigh the
9 completeness of the PMMA against the compelling need for
10 this particular product?

11 DR. WILKINSON: Personally, I think the fact of
12 the matter is that a lot of things have happened in a
13 relatively short time in vitreoretinal surgery in the world,
14 and there are several reasons why the gases and silicone oil
15 have not been popular market items. I don't think they have
16 been profit items and I think that we, as ophthalmologists,
17 probably got ahead of the game in terms of using these
18 things on cases in which they clearly were indicated,
19 without any thought to having the sponsor or the producer of
20 the substances because in many cases the people who made
21 these substances wanted nothing to do with a PMA.

22 The fact of the matter is that these were
23 discoveries which profoundly changed the way we manage
24 cases, and the Agency became aware of this phenomenon in '84
25 and The Federal Register published the statement saying they

1 would look at literature reviews for the SF₆, specifically.
2 I really don't think, particularly with some substantive
3 changes that have occurred in the Agency, that the
4 industrial complex now is going to allow private individuals
5 to continue to make this mistake. I think there is just
6 kind of a time warp where a lot of things have literally
7 become the style of choice, the method of choice without a
8 doubt in certain cases and, yet, the appropriate research
9 just simply was never done, and I don't really think it will
10 come up in the future.

11 But I think from an ethical point of view it would
12 be -- literally, if the President of the United States had a
13 given type of detachment, he would receive these substances,
14 and that is just the way it is. It is unfortunate and I do
15 believe that the Agency has taken enough of a stance on not
16 allowing this to happen in the future that we, hopefully,
17 won't have to deal with it in the future. But I think this
18 is a special device and I think similar considerations were
19 probably made for the gases issue when we look at it
20 closely.

21 DR. STULTING: I agree with Pat. The problem here
22 is that a device has become standard of practice before the
23 regulatory process has had a chance to consider it. So we
24 are in an unusual position of making the decision on
25 something that is in common use and, indeed, would probably

1 be unethical to study in certain situations. So we have to
2 make our decision, it seems to me, in the broad
3 interpretation of our responsibilities to the best interests
4 of the American public. Based upon the data that are in the
5 PMA, in the literature and all the data that I am aware of,
6 I think that the device ought to be approved, and that is an
7 opinion based on consideration of all of those areas of
8 evidence.

9 DR. HARRIS: I certainly appreciate your opinion
10 and your expertise in the area. My concern is that we not
11 send a wrong message to other sponsors that they can
12 function in the same manner and provide less than complete
13 data to support their PMAs and that we would consider them
14 for approval in the future.

15 DR. STULTING: I agree with you completely but, at
16 least for this product, the sponsor that is currently
17 bringing it to us is one that has picked it up late in the
18 game. The real problem here is that use of the device was
19 permitted in the United States without appropriate
20 enforcement of existing regulations.

21 Here we have a device that theoretically should be
22 used only investigational and it was used outside of those
23 regulations, and that is the reason it has become the
24 standard of practice. If, from the initial use of the
25 device, we had collected adequate data in well-controlled

1 trials, we wouldn't be sitting here having this discussion.

2 And I agree with you 100 percent that the message
3 should go out loud and clear that we, as Panel members,
4 don't want to be put in this position ever again. If it
5 weren't for the fact that we would be behaving contrary to
6 the public interest, I think that we should have a blanket
7 policy of disapproving devices that come to us with
8 inadequate data. But in my opinion this is a special case,
9 and one in which the public interest should override our
10 discomfort with the quality of the data presented in the
11 PMA.

12 DR. WILKINSON: And it has been implied but not
13 stated literally that the NIH and at least a dozen IRBs
14 around the country allowed this device -- a similar device,
15 not an approved device but a similar device to be employed
16 in a prospective, randomized trial.

17 DR. BOUCHER: Obviously, this device has some
18 complications. It has limited use. One of the ways, of
19 course, when you approve a device like this is to let the
20 users know the complications and the risk involved and where
21 it is appropriately used is through labeling. I don't know
22 can labeling be written to assure the proper use of this
23 device, or is there potential for this device to be abused?

24 DR. BROWN: Dr. Knight, are you in a position to
25 make a statement on that?

1 DR. KNIGHT: I can make a statement on it; I don't
2 know if I am the best qualified here. I certainly think
3 that we can address most of these issues in the labeling. I
4 think that the indications are primarily the proliferative
5 states and that those are defined. If you make it clear
6 that this is the last option and that those are the patients
7 you want to use it in, I think you can make the labeling
8 clear enough.

9 MR. GREEN: Can I also just raise the issue that
10 it is not just labeling that is at least my concern, but it
11 is how consumer warnings are delivered. When a patient is
12 in a "desperate" situation, searching for a solution, and is
13 confronted by a physician of repute and what-not, it is very
14 difficult, I think, for the average patient to say, well,
15 yeah, there's warnings and there's hazards but, you know,
16 how seriously do they really apply to me? So I am not quite
17 sure what I am saying other than just simply voicing a
18 concern that the labeling be clear; it be written in an
19 understandable way. And I am not sure how labeling and
20 warnings are really delivered to the patient, and I don't
21 know how to get at that but I just want to voice the concern
22 and have the record show that it is of concern.

23 DR. SCOTT: I think that issue itself is addressed
24 by the normal patient-doctor relationship where there is
25 informed consent that has to be discussed and signed before

1 every procedure. As part of that, complications are put in
2 lay terms and the patient is given the opportunity to ask
3 how they apply to them individually.

4 DR. STULTING: To address ~~that~~ area of concern, I
5 think you have to understand that this is a device that is
6 not going to be used in a widespread nature. It is one that
7 is used in poor prognosis cases of retinal detachment with
8 complications frequently that have failed for other reasons.
9 There is really not very much incentive for financial gain
10 or other types of gain for physicians to employ it, and I
11 think that the likelihood of abuse or over-use of the device
12 is really minimal. So that too is part of the consideration
13 I think that at least I made before making a recommendation
14 to approve it.

15 DR. MACRAE: I would like to ask Dr. Blumenkranz
16 is there information about the removal of silicone oil in
17 terms of any guidance that you can provide for a
18 practitioner?

19 DR. BLUMENKRANZ: There is some information
20 available on the removal of silicone oil. In the Lucke
21 study a relatively small percentage of patients had the oil
22 removed. I think as the time lines increase, the percentage
23 of oil being removed increases. In the silicone oil study
24 group there were some data presented at the American Academy
25 of Ophthalmology a year ago that suggested that oil removal

1 was advisable in those patients who had responded favorably
2 to the intervention, in other words, a patient whose retina
3 is attached with oil in place may actually have some further
4 vision improvement and long-term stabilization by removal of
5 the oil at a later date.

6 I think current clinical practice suggests that in
7 patients who have had surgery and in whom the retina has
8 been reattached, if the oil is removed between 4-8 months or
9 4-12 months after surgery, that patient may have yet further
10 improvement. The caveat is that if patients have partial
11 detachment of the retina, in other words, somewhat less than
12 a completely successful operation, oil removal may be
13 hazardous. Similarly, in patients who have hypotony,
14 meaning a low intraocular pressure, those patients upon oil
15 removal may have further deterioration.

16 So it still remains I think to an extent in the
17 realm of the judgment of the clinician who is taking care of
18 the patient. But, as a general principle, I think it can be
19 stated that when a patient has responded favorably and is
20 doing well, oil removal is an advisable step at a later
21 date.

22 DR. BROWN: Could I ask the individuals seated and
23 the sponsor's table, each time you answer if you would
24 identify yourself for the record, please.

25 DR. BLUMENKRANZ: I am Mark Blumekranz. I am from

1 Stanford University.

2 DR. WEINER: Dr. Alan Weiner, Vice President of
3 R&D for Escalon Ophthalmics. We are the clinical monitor
4 for the study and the oil distributor.

5 DR. WILKINSON: Any further questions or comments
6 from the Panel or Agency members? Hearing none, can we have
7 a motion --

8 DR. BROWN: Before you start, may I interject
9 something? We got something hot off the press. You saw the
10 gentleman bringing it up. This has to do with conflict of
11 interest again. I want to make sure that the Panel members
12 understand their responsibility. It says here "Conflict of
13 Interest Statement for the Ophthalmic Devices Panel meeting,
14 October 28th and 29th, 1993:

15 The following announcement addresses conflict of
16 interest issues associated with this meeting, and is made a
17 part of the record to preclude even the appearance of
18 impropriety. To determine if any conflict exists, the
19 Agency reviewed the submitted agenda and all financial
20 interests reported by the Committee participants. The
21 conflict of interest statutes prohibit special government
22 employees from participating in matters that could affect
23 their or their employees' financial interests. However, the
24 Agency has determined that participation of certain
25 consultants whose financial interests are not so substantial

1 as to be deemed likely to affect the integrity of their
2 services and the participation of certain members, the need
3 for whose services out weigh the potential conflict of
4 interest involved.

5 In the best interest of the government, full
6 waivers have been granted to the following participants for
7 their interest in firms that could potentially be affected
8 by the Committee's deliberations: Drs. C. Pat Wilkinson,
9 James A. Boucher and Walter Stark. These doctors have
10 interests in companies that market contact lenses of
11 intraocular lenses. Many of the issues to be discussed at
12 today's meeting were part of the Panel's recent conference
13 call or homework assignments and the doctors mentioned above
14 have received waivers to participate in discussions of these
15 issues.

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

19 We would like also to note for the record that the
20 Agency took into consideration other matters regarding Drs.
21 Olivia Serdarevic, Clifford Scott, Michael Harris, Alan
22 Sugar and R. Doyle Stulting. These doctors reported
23 interests in firms on matters not related to what is being
24 discussed today. Since these matters are not directly
25 related to specific matters before the Panel, the Agency has

1 determined that these doctors may participate fully in
2 discussions before the Panel.

3 In the event that the discussions involve any
4 other products or firms not already on the agenda for which
5 an FDA participant has a financial interest, the
6 participants should exclude themselves from such involvement
7 and their exclusion will be noted for the record. With
8 respect to all other participants, we ask in the interest of
9 fairness that all persons making statements or presentations
10 disclose any current or previous financial involvement with
11 any firm whose products they may wish to comment upon.

12 In addition to that, as you noticed, Dr. Alan
13 Sugar physically removed himself from the Panel
14 participation on this particular device."

15 That is the end of the statement.

16 DR. WILKINSON: Thank you, Dan. The last chance
17 for comments or questions?

18 (No response)

19 Okay, may I hear a motion regarding this PMA?

20 DR. STULTING: I move that PMA P910071 be
21 recommended for approval, with labeling to reflect comments
22 that were heard during the discussion this morning.

23 DR. WILKINSON: Is there a second, please?

24 (The motion was duly seconded)

25 DR. WILKINSON: It has been moved and seconded

1 that this PMA be recommended for approval. Discussion?

2 DR. DOUGHMAN: Actually, I have a comment. I
3 think I should remove myself from voting since I am
4 presently negotiating with Escalon for some of their
5 products to use in experimental work that I am doing.

6 DR. BROWN: Thank you. Could you also remove
7 yourself physically, please?

8 (Laughter. Dr. Doughman leaves the Panel table)

9 DR. WILKINSON: Other discussion? All those in
10 favor of the motion, signify by saying aye.

11 (Chorus of ayes)

12 Opposed?

13 (No response)

14 Thank you.

15 DR. BROWN: In addition, for the record, this is
16 the report and recommendations of the Ophthalmic Devices
17 Panel for premarket approval application P910071. The name
18 of the device, the applicant's address, the name, the date
19 of the meeting is October 28, 1993. The data and
20 information upon which the Panel based its recommendation
21 are contained in the PMA, the applicant's summary and
22 reviews conducted by the staff of the Division of Ophthalmic
23 Devices and those conducted by the Panel members and the
24 draft CDRH summary of safety and effectiveness data. The
25 results of the preclinical and clinical studies presented in

1 the PMA constitute valid scientific evidence which the Panel
2 members as experts used to evaluate the safety and
3 effectiveness of the device.

4 The members concluded that this information
5 provided reasonable assurance that the applicant's device is
6 safe and effective under conditions of intended use as
7 described in the draft labeling. The rationale supporting
8 the Panel's recommendation is that the device has been
9 demonstrated to be effective under conditions of clinical
10 use in a significant portion of patients. The visual acuity
11 of a significant percentage of patients was preserved or
12 improved as a result of the use of the device.

13 Furthermore, there is evidence to adequately
14 demonstrate the safety of the device and the absence of
15 unreasonable risk for illness or injury associated with the
16 use of the device when used under conditions of intended use
17 and in accordance with final draft labeling. The long-term
18 complications are known and are treatable. Given the
19 otherwise poor prognosis of these patients, the benefits
20 outweigh the risks.

21 The Panel has concluded that the attached list of
22 conditions must be met or agreed to by the applicant as
23 conditions of approval.

24 The second page lists the conditions of approval,
25 and I will ask Dr. Stulting to list those additional

1 conditions.

2 The last page requires that the Panel members
3 voting on this sign and indicate whether they voted for
4 approval or disapproval. Then the Chairperson will
5 authenticate the signatures.

6 While that is being done, I want to thank the
7 sponsors for coming up and answering the questions. At this
8 time, I think you can go back to your seats or any other
9 place you so desire.

10 MS. PATTERSON: In turn, the sponsor would like to
11 thank the Panel and the FDA for the review of this PMA.

12 DR. BROWN: Ms. Brogdon has something to say.

13 MS. BROGDON: I would just like to remind the
14 Panel and the firm that, as Dr. Lewis mentioned earlier,
15 there are still some chemistry and toxicology issues that
16 the Agency will continue to work with the firm on. So there
17 maybe more time delay than you would predict from your
18 recommendation on which the Agency would be able to take
19 action. So we will continue with these issues.

20 MS. PATTERSON: The sponsor acknowledges that and
21 we are working on that with the internal reviewers.

22 DR. BROWN: Expeditiously!

23 MS. PATTERSON: Expeditiously!

24 DR. BROWN: Thank you.

25 DR. LEWIS: I do appreciate that and I just want

1 to keep in mind too that one of the topics we talked about
2 was time of removal and removal guidance. One of the
3 options that we may be considering is a post-approval study
4 to answer that question. That is something that we would
5 have as an option to address that, if necessary.

6 MS. PATTERSON: We are willing to discuss that.
7 Thank you.

8 DR. MACRAE: I am not even sure that it is
9 appropriate to mention this, but I really think you really
10 need some clinical input. This is an exceptionally
11 difficult issue.

12 DR. LEWIS: It is.

13 DR. WILKINSON: And there are data from the
14 silicone oil trial and you know the percent that redetach
15 and it is roughly 20 percent. It is an exceptionally
16 difficult decision and I think making any mandate whatsoever
17 that does not involve the physician taking care of that
18 patient would be a real bad idea. So I hope you will seek
19 real input about this issue.

20 DR. MACRAE: I would second that. This is a
21 technology area that has advanced so rapidly that by the
22 time that the Agency would put recommendations out, within a
23 year or two those recommendations would probably be obsolete
24 with regard to the technology. So I would caution the
25 Agency in terms of trying to over-define how the device is

1 managed.

2 DR. LEWIS: I do appreciate your comments on that.
3 We want to have this communication continue so that the
4 actions that we take are the most appropriate actions.

5 MS. PATTERSON: We would like to acknowledge also
6 that we agree. I think it is critical that when the
7 labeling progresses, we believe as authors of that labeling,
8 to the point where we have something that is clear and
9 concise that it be reviewed by a core group of four to six
10 expert vitreoretinal surgeons for critique. I think that is
11 important. It is an important point and we commit to doing
12 that.

13 DR. MACRAE: I see as one of the rules of the
14 review process to define areas of danger for the patient,
15 and that should definitely be included. But those areas
16 that are vague and unclear in terms of outcome, you may not
17 want to define that simply to give practitioners the room to
18 find those outcome answers at a later date.

19 MS. PATTERSON: I agree. We have talked about
20 this and have discussed at length. We believe that we can
21 expand the labeling to the extent of the discussion of the
22 subpopulations and the populations in these studies so the
23 surgeon can have access to the information we do have in
24 order to make a good judgment on his individual cases.

25 DR. LEWIS: And just to add one last thing to

1 that, we do recognize this has been identified for expedited
2 review status. So we will keep that in mind as we continue
3 those communications.

4 DR. WILKINSON: Well, I think we are done. These
5 are post-vote comments.

6 DR. BROWN: You always have to adjust to
7 circumstances and I have adjusted. We are running way ahead
8 of schedule. That is good as far as I am concerned. It
9 means the preparation was done adequately and we have
10 accomplished what we set out to do. According to the
11 schedule that I made, we should be at 12:30 and it is about
12 10:55. So what I would do then is to again thank the
13 sponsor.

14 MS. PATTERSON: Thank you, Dan.

15 DR. BROWN: Debora, since you are there at the
16 table, I think what we will do is to assume it is 1:30 and
17 if you look at your schedules you know what the next thing
18 is.

19 DR. LEWIS: So, Dan, then you would like me to go
20 ahead and move to the --

21 DR. BROWN: Yes. Could you just wait until we
22 have settled down here?

23 DR. LEWIS: Sure.

24 DR. BROWN: Debra, do you want to continue now?

25 DR. LEWIS: Sure, I can continue now. I have

1 asked Dr. Beers to join us. As I have mentioned, he is new
2 to our staff. He came to FDA about four months ago from the
3 United States Army. For the previous eleven years he had
4 been involved in neurophysiology and neurotoxicology
5 research for the Army. Dr. Beers holds a joint Ph.D. in
6 neurophysiology and biomedical engineering, and he is a
7 Board certified toxicologist.

8 Today he is going to be talking about one of our
9 projects that we will be working on in the Division over the
10 next year or so, and I would like to ask him to tell you a
11 little bit about the eye valve implants.

12 DR. BEERS: Thank you, Dr. Lewis. Good morning.
13 It is, indeed, a pleasure to be with you today and I am
14 quite honored to be able to address you this morning.

15 I am going to talk with you for a few minutes
16 about eye valve implants, also known as glaucoma shunts. I
17 am going to tell you a little bit about the background of
18 these devices and outline for you the possible positions
19 which the FDA may take in regard to resolving their pre-
20 amendment Class III status.

21 My reason for taking this opportunity to present
22 this information is that we want you to be aware of the
23 near-term decisions which we may take and which will
24 significantly affect the eye valve implant community.

25 Eye valve implants are defined in the Code of

1 Federal Regulations 21 CFR 886.3920. This reads, "an eye
2 valve implant is a one-way, pressure-sensitive, valve-like
3 device intended to be implanted to normalize intraocular
4 pressure. The device may be used in the treatment of
5 glaucoma."

6 Eye valve implants are pre-amendment devices, as I
7 mentioned. This means that at least one such device was in
8 commercial distribution prior to May 28, 1976. On February
9 27, 1978, the Ophthalmic Devices Panel recommended that
10 these devices be regulated as Class III devices. The
11 classification of these devices is mentioned further in the
12 Federal Register of September 2, 1987, entitled "Ophthalmic
13 Devices, Final Rule."

14 The next time we see something about these eye
15 valve implants is in the Federal Register of January 6,
16 1989, entitled "Proposed Rules." Here, eye valve implants
17 were identified as one of some 31 Class III device of high
18 priority for issuance of regulations under Section 515(b) of
19 the Food, Drug and Cosmetics Act. This is the section of
20 the Federal Food, Drug and Cosmetics Act, as amended, which
21 deals with premarket approval, or PMAs. This issuance of
22 regulations under 515(b) means that we would call for PMAs
23 for all eye valve implants.

24 I think it is worth noting at this point that
25 since 1984, eight eye valve implants have been cleared for

1 marketing via the 510(k) mechanism. That is currently the
2 way we are doing it now. There is a bit of difference among
3 these eye valve implants in that they don't exactly match
4 that definition that I gave you of one-way, pressure-
5 sensitive valve-like, in that not all are one-way, and not
6 all of them are valves, and not all are really pressure-
7 sensitive in the engineering sense of that phrase.

8 Additionally, a more appropriate name for this
9 device may be glaucoma shunt, which I think is what many
10 people actually call it, or perhaps anterior chamber aqueous
11 shunt. Although the intent of these devices, as stated in
12 the CFR that I read you, is to normalize intraocular
13 pressure, perhaps a better way to state the use of these
14 devices would be to say that they are intended to delay
15 visual function loss by lowering intraocular pressure in a
16 defined population.

17 Another thing to mention here is that according to
18 the Food, Drug and Cosmetics Act, Section 515(i), the FDA
19 must act by December, 1995 to authoritatively classify these
20 pre-amendment devices as either Class I, Class II, or Class
21 III. So in 1989 eye valve implants were identified as
22 something that we should seriously consider calling PMAs.
23 Again, we have until December, 1995 to decide how we are
24 going to regulate these devices.

25 Let me tell you now about some of the decisions

1 which we could possibly make regarding these devices.

2 First, well, we could call for PMAs. That would
3 be under Section 515(b). Now, if this were to happen, the
4 manufacturers of the eye valve implants would have 90 days
5 following promulgation of a final regulation to submit to
6 the FDA the safety and effectiveness information requested
7 by this final regulation. This safety and effectiveness
8 information may ask for things such as summary data,
9 clinical data, adverse information, engineering,
10 manufacturing, chemistry, micro., tox. tests. Then 180 days
11 after a PMA was filed, it would have to be approved by the
12 FDA or the device would have to be withdrawn from the
13 market, unless FDA determined that the continued
14 availability of the device was necessary for the protection
15 of the public health.

16 Secondly, we could recommend that the eye valve
17 implant be reclassified into Class II. Since this device is
18 an implant, as, of course, its name implies, evidence must
19 be presented that classification in Class III is not
20 necessary to provide reasonable assurance of the safety and
21 effectiveness of the device. Now, reclassification into
22 Class II also would require the establishment of appropriate
23 special controls for the device. Special controls could
24 include performance standards, guidelines and
25 recommendations and other things. The devices would then be

1 cleared for marketing through the 510(k) mechanism.

2 The final alternative would be to proceed with the
3 provisions of Section 515(i) that I mentioned earlier.

4 Basically, under this Section we would issue an order to
5 require industry submission of summary information and
6 citations concerning safety and efficacy of the device,
7 including adverse safety and effectiveness information.
8 Once having procured this information, we would then
9 complete the rulemaking to reclassify the device into Class
10 I or Class II, or require that the device remain in Class
11 III.

12 Now I would like to talk about some of the factors
13 which might affect our decision. While we acknowledge that
14 in previous years better clinical trials should have been
15 requested for this device, there is some question now about
16 whether or not a call for PMAs at this time would be likely
17 to yield further clinical information, either unknown or
18 unavailable to the ophthalmic community.

19 Dr. Emma Knight, next to me here, our
20 ophthalmologist, has been assiduously reviewing all
21 available clinical data, open literature publications, MDRs,
22 etc., to determine whether or not additional information
23 obtained via controlled clinical trials of already marketed
24 eye valves would add significantly to our knowledge base
25 concerning these devices. Additionally, non-clinical

1 information is being assessed by the Center's scientists.

2 In addition to the information about safety and
3 effectiveness of the device, we need sufficient information
4 to adequately define the intended population, and we need to
5 define appropriate clinical endpoints.

6 Finally, we recommend reclassifying this device
7 into Class II, what special controls should we impose?

8 Well, I have shared with you our thinking about
9 the eye valve implant and the possible regulatory routes we
10 may take, and I have outlined for you some of the problems
11 we face in deciding which rulemaking we should follow. This
12 concludes my comments. Thank you very much.

13 DR. LEWIS: I want to thank Dr. Beers for
14 introducing some of the issues that we are going to be
15 facing, actually that the Implant Branch will be facing in
16 the next year, and it is a high priority for the Office to
17 make these decisions and these decisions will have a large
18 impact on the valve community.

19 DR. WILKINSON: Would you like comments from the
20 Panel?

21 DR. LEWIS: Sure. I think that is fine. We
22 anticipate some additional discussion tomorrow as well. If
23 you would rather do that now or then, it doesn't matter.

24 DR. MACRAE: I am curious as to how many glaucoma
25 shunt valves are placed per year nationally. Do we have

1 those data?

2 DR. BEERS: I will defer that to Dr. Knight.

3 DR. KNIGHT: We don't have good data on any of
4 these. Most of these devices were cleared on 10-30
5 patients, treated for follow up for 6 weeks, and the initial
6 decision to put them into Class III was made in 1978. I
7 suspect the population is under 60,000, and that is based
8 upon some marketing information and some calculations in
9 discussions I have had with Dr. Gastolin (phonetic), from
10 the Advanced Clinical Trials Group, and his discussions with
11 Dr. Winkler (phonetic). So it is about a 60,000-80,000
12 population.

13 DR. MACRAE: In terms of the total number of
14 implants that have been placed?

15 DR. KNIGHT: Yes, that is the total number of
16 implants. Some of these may be reimplanted, that kind of
17 thing, but it is a rather small population, no doubt.

18 DR. MACRAE: And we don't know how many are being
19 put in per year now in the U.S?

20 DR. KNIGHT: No. At this point those are the only
21 data we have. One of the things that we would ask for would
22 be that kind of marketing data from the firms. Those are
23 the best numbers that we have available. It basically does
24 qualify as an orphan population, an orphan designation being
25 less than 200,000.

1 But probably the tough question is that there are
2 eight of these valves. In looking at the different designs
3 of devices, it is almost like a lot of tinkering going on
4 and not a lot of difference between them. There seem to be
5 new ones coming out. I am not sure why. And in the recent
6 few years the use of mitomycin C and 5FU, which are
7 unapproved drug products for ophthalmic use, has raised
8 questions as to whether or not that would be a better route
9 to go. There is presently a prospective, randomized trial
10 of Molteno valves versus 5FU I believe, though it might be
11 mitomycin. I believe it is Dr. Rubin who is doing it and
12 enrollment was, the last I heard, 50, 65 patients. It is
13 about 2 years out. So we are not getting big enrollments
14 here. So it may be some time before we answer that.

15 But as I said, I think that whole issue is clouded
16 by the fact that those are unapproved drug products. I
17 think 5FU has probably been replaced at this point by
18 mitomycin C, although there are people using both of those.

19 If we required trials, my question would be what
20 kind of trial would you like to see? I don't see any point
21 in doing a trial against two devices. The missing piece of
22 information here is the natural history of the disease. We
23 are making attempts, and I think we may get some of that
24 information from countries, probably not U.S. countries, but
25 in terms of the natural history of the disease there may be

1 information out there and we are looking for it. Certainly
2 not in the eye implant data. But I just got, probably in
3 the last three weeks, some leads on where those data might
4 be. So we will see if we can find those data and, if we
5 can, it would better help make the decision.

6 At this point, it is timing of implantation and it
7 is kind of like retinal surgeons who know when to use
8 silicone oil and the glaucoma surgeons know when to use
9 this. So it is the same answer and that is the problem with
10 reclassification.

11 At this point, we have data from 1978 until, you
12 know, 15 years later. We have a lot of data out there on
13 what these things do over time frames. We probably have
14 follow up in neovascular glaucoma out to five years and in
15 other indications it might be a little bit less and less
16 well defined. But I think the primary question is other
17 alternatives and the natural history of the disease.

18 DR. MACRAE: Are the companies actually giving you
19 five-year data?

20 DR. KNIGHT: No. No, this is basically from
21 literature. One of the things we can do is ask them for
22 those data.

23 DR. MACRAE: So you are currently having them do a
24 PMA but they are very small PMAs?

25 DR. KNIGHT: No. No, they are 510(k)s and at this

1 time, they are not -- they have been made aware of the fact
2 that we could call for PMAs and if you don't have the data,
3 then we can take you off the market. So I do know that some
4 companies have actively continued to collect data and some
5 have not.

6 MS. BROGDON: An alternative plan at this point is
7 to call for information from the sponsors with these devices
8 on the market. Then we would have a better basis for a
9 decision on whether to call for PMAs or to reclassify. We
10 would involve the Panel in that decision. If you have
11 feedback today, we would certainly like to hear it but this
12 issue will come before you anyway.

13 DR. DOUGHMAN: It seems like we are back to
14 silicone oil with unapproved devices and some of the
15 prophecies of Doyle and others on the Panel. But I am
16 certainly not comfortable even giving feedback without a
17 glaucoma specialist on this Panel as a consultant because
18 they are in the same position as the retina people are, and
19 they have very good reasons clinically and otherwise to use
20 these devices and these drugs. So I hope when you ask this
21 question you will have some expertise that I don't think we
22 have right now on the Panel.

23 MS. BROGDON: We are recruiting for some new Panel
24 members. As you know, several people are rotating off as
25 valued members and we certainly want some glaucoma

1 expertise. So thank you for that.

2 DR. BROWN: I was going to make the statement that
3 we are in the process of selecting now and that is one of
4 our considerations.

5 DR. LEWIS: I also received a comment while we
6 were discussing, someone wanting to be certain that people
7 understand that if we do call for PMAs under the 515(b)
8 proposal that the industry has an opportunity to request
9 reclassification. That is just for clarification purposes.
10 Someone wanted that to be known.

11 Our purpose today was simply to inform everyone of
12 this important issue that we are going to be working on. I
13 recognize the importance of getting glaucoma expertise to
14 help evaluate the situation and we will have opportunities
15 in the future to discuss it further.

16 DR. BROWN: Thank you, Debra. Since we are
17 talking about the petition for reclassification, I think
18 that is the next item to be discussed.

19 DR. LEWIS: Are you just going to move right along
20 to that?

21 DR. BROWN: Yes.

22 DR. LEWIS: All right.

23 DR. BROWN: Morris, could you come forward,
24 please?

25 DR. LEWIS: Dan, do you want me to start or do you

1 want me to hold off until people get settled?

2 DR. BROWN: Go ahead.

3 (Transparency)

4 DR. LEWIS: Today, I am going to be asking for the
5 Panel's recommendation on a reclassification petition for
6 the ophthalmic neodymium YAG lasers for iridotomy. The
7 petition requests that FDA reclassify these lasers for
8 iridotomy indication from Class III to Class II.

9 As you know, Class III medical devices require a
10 premarket approval application which must contain a full
11 assessment of the safety and effectiveness data for the
12 device in its intended use. Class II devices are evaluated
13 by the 510(k) process, with the Agency decision being based
14 upon substantial equivalence of the device to a currently
15 marketed device. Special controls may be required for these
16 devices to ensure that adequate information is available
17 upon which to make such a determination.

18 You are aware that this laser has already been
19 reclassified into Class II for the posterior capsulotomy
20 indication and today we are only considering the iridotomy
21 indication.

22 This reclassification petition contains the
23 required administrative petition information. We are now
24 asking the Panel for a recommendation as to whether you
25 believe sufficient information is currently known about the

1 ophthalmic YAG laser to establish that Class III status is
2 no longer needed for this iridotomy indication with this
3 device, and that Class II special controls are appropriate
4 for the device when used in conformance with the labeling.

5 In order to recommend approval of this petition,
6 you must indicate that there is sufficient information
7 currently in the public domain to enable the Agency to
8 develop such special controls.

9 If your recommendation is for approval, we will
10 need a summary of reasons for reclassification, a summary of
11 the data upon which the reclassification is based, and the
12 identification of the risks to health, if any, presented by
13 the device for its intended use.

14 The clinical reviewer for this petition is Dr.
15 Emma Knight and I will ask Dr. Knight to present her
16 clinical review at this time.

17 (Transparency)

18 DR. KNIGHT: Thank you, Debra. This is the
19 reclassification petition. It was brought to us from the
20 Intelligence Surgical Laser group. One of the problems here
21 is the fact that the YAG was reclassified just for posterior
22 capsulotomy. That means that if somebody now wants to come
23 in with a 510(k), if they want the indication of peripheral
24 iridotomy they still have to submit a PMA for that
25 particular indication. So it is a bit of a cleanup in order

1 to also get rid of some administrative details here.

2 (Transparency)

3 This is the present classification for the
4 neodymium YAG laser, and it specifically states that it is
5 for posterior capsulotomy. It consists of a mode lock, a Q-
6 switch solid state laser intended for posterior capsulotomy
7 which generates short pulse, low energy, high power of
8 coherent optical radiation. When the laser output is
9 combined with focusing optics, the high radiance at the
10 target causes tissue disruption via optical breakdown. A
11 visible aiming system is utilized to target the invisible
12 neodymium YAG laser radiation on or in close proximity to
13 the target tissue. Classification is Class II and this
14 Federal Register notice was final on October 4, 1988.

15 (Transparency)

16 This petition came from the Agency for
17 reclassification for posterior capsulotomy on May 22, 1986.
18 The only consideration at that time was given to posterior
19 capsulotomy.

20 (Transparency)

21 This describes the presently approved PMAs for the
22 peripheral iridotomy indication. The names that you see
23 here were the designated names at the time of the PMA
24 approval and anybody who knows who owns these at this point
25 in time is probably on Wall Street, as Dr. Waxler found out

1 as he tried to track down permission to use the summaries of
2 safety and effectiveness.

3 We did get those for the AML laser, and for the
4 Coherent laser and for the Nydak laser. So we do have
5 permission to use those. It took a while but we finally
6 found out who owned those.

7 (Transparency)

8 What was presented to you in your mail-outs was,
9 first of all, the American Academy of Ophthalmology
10 guideline for laser peripheral iridotomy for pupillary block
11 glaucoma. This was approved by the Board of Directors of
12 the Academy on June 26, 1988. It essentially outlines the
13 history of surgical iridectomy and the use of argon and
14 neodymium YAG for the indication of peripheral iridotomy. I
15 think that to repeat what it says here would be rather
16 redundant. It is pretty self-explanatory, and I am not sure
17 that I could answer any questions that you have about it
18 considering that the people who wrote it are the experts.

19 (Transparency)

20 One of the issues that I would like to bring up is
21 treatment parameters. If anybody has a comment on this,
22 probably it would be relevant. Some of these issues are
23 directly from the approved PMAs.

24 Energy settings recommended in the PMAs were to
25 begin at 5 mJ, increasing in small increments until the

1 anterior lens capsule is visible beneath the iris opening.

2 There was a recommendation that if results were
3 not obtained at a level of 10 mJ/pulse, reconsideration
4 should be given to choice of the procedure.

5 I think we have realized now that a contact lens
6 does improve the procedure. There is less corneal damage
7 and a better ability to focus the beam. It also provides
8 magnification, maintains eyelid separation and reduces
9 ocular movement.

10 I think we have refined the site of treatment. We
11 try to put it in the periphery, superiorly beneath the
12 superior lid; nasally to avoid inadvertent macular damage;
13 and in the area of a crypt away from vessels and away from
14 an IOL or an IOL haptic.

15 The endpoint as described in the PMAs is basically
16 visualization of the anterior capsule of the lens. The
17 follow up should be reevaluated basically early in the first
18 1-4 hours is how it is written and done in the PMAs, over
19 that first 4-hour period. That is to identify those
20 patients who may have marked elevation of intraocular
21 pressure.

22 (Transparency)

23 This is taken from the petition itself and it does
24 show comparison of the treatment parameters that were used
25 in performing neodymium YAG iridotomies. There is some

1 nomenclature change here. It started out as surgical
2 iridectomy. It was called peripheral iridectomy and finally
3 changed to peripheral iridotomy.

4 But one of the things that I think is clear here
5 is that the pulse power may be less than 5 mJ. It depends
6 not just upon the milliJules/pulse but also the number of
7 pulses that are used. What was interesting to note was that
8 in the AMO YAG PMA, and it was stated within the PMA that
9 the total energy used, particularly milliJule and pulse
10 parameters, may have been higher just because the
11 investigators were not as experienced as if you look at the
12 last line there, which is Robbins and Pollicks (names
13 phonetic) article and reveals the prospective, randomized
14 study of argon versus neodymium YAG. So early on, anyway,
15 the experience with the YAG did play a part in total energy
16 numbers.

17 (Transparency)

18 This is the indication that was in the sponsor's
19 reclassification petition, and it is eyes at risk, acute,
20 subacute, intermittent or chronic pupillary block glaucoma.
21 I think most of the studies looked at pupillary block
22 glaucoma and chronic pupillary block glaucoma. Certainly,
23 the laser has over the years taken on treatment of second
24 eyes in patients who have an acute angle closure attack and
25 in patients who have intermittent attacks.

1 (Transparency)

2 The contraindications for use of laser is if you
3 cannot see the iris well enough; the absence of pupillary
4 block glaucoma and the relatively incidence, I think at this
5 time, in the presence of a glass IOL.

6 (Transparency)

7 Poor candidates, or at least consideration for
8 carefulness with the neodymium YAG includes uveitis patients
9 and then, of course, neovascularization. To avoid areas of
10 neovascularization in heavily vascularized irises it may be
11 -- and I say may be wise to pretreat with argon. There are
12 two studies that were presented within the review that you
13 got that disagree as to whether that is effective or not. I
14 think its overall use is probably not necessary, and those
15 were early papers, however, there may be reasons to consider
16 it if you have a lot of neovascularization. Corneal aqueous
17 haze, again, obscuring view; patients with bleeding
18 tendencies you might want to consider as poor candidates.
19 Patients who have nystagmus or blepharospasm or an inability
20 to cooperate, as with any other laser slit-lamp procedure.

21 (Transparency)

22 The risks of this particular procedure include --
23 first of all, these are not in appropriate order --
24 transient bleeding is probably the greatest risk with
25 neodymium YAG. It occurs anywhere from 30-50 percent of

1 patients. It is, for the most part, considered to not be
2 clinically significant and is easily controlled with
3 pressure on the eye.

4 The second most common complication would be
5 significant transient elevation of IOP. In argon lasers
6 that was reported in various studies to be between 20-30
7 percent, if not higher. In the neodymium YAG studies it did
8 occur. I believe the percentage was between 15-30 percent
9 across studies and across PMAs.

10 Significant transient elevation is usually defined
11 as greater than 10 mm or greater than 20 mm in some of the
12 literature articles, but I think 10 mm certainly is high.
13 If you have a patient with glaucoma, I think I would
14 consider even a 5 mm rise could potentially be damaging.

15 Damage to the lens is usually transient and focal,
16 and has not been shown to cause any significant progression.

17 Clinically significant hyphema is usually rare.
18 Both argon and neodymium YAG show localized corneal damage
19 but it is not clinically significant.

20 There is transient anterior chamber cell flare
21 with both modalities. It usually clears faster, by day
22 three, with neodymium YAG but can be present in up to one to
23 two weeks later with the argon laser.

24 Iridotomy closure is much less common with the
25 neodymium YAG laser than with the argon laser. In as many

1 as 33 percent, in Robbins paper, iridotomy closure of the
2 YAG occurred within the first 3 weeks and required
3 retreatment. In the neodymium YAG studies, immediately
4 postop. patency was seen in 98 percent; at 6 months it was
5 about 91 percent; and at a year it was at 88 percent. Apart
6 from that, the iridotomy closure in the YAG patients was not
7 necessarily associated with increased IOP. So the question
8 was whether it was a small hole that appeared to be closed
9 versus the argon laser which usually shows closure due to
10 iris proliferation.

11 The ability to adequately control glaucoma and
12 number of glaucoma medications etc. was independent of laser
13 use. Persistent elevation of IOP, once again, was dependent
14 more upon the preexisting level of glaucoma. Rupture of
15 anterior hyaloid face, retinal and choroidal damage and
16 persistent CME are all potential problems that could occur,
17 although they are very rare.

18 (Transparency)

19 These are rare complications that have been
20 reported in the literature, malignant glaucoma especially,
21 lens-induced endophthalmitis, retinal detachment is less
22 than 0.3 percent. Acute glaucoma in the presence of a
23 patent iridotomy has been reported. Lens rupture, monocular
24 blurring -- this was usually attributed to the placement of
25 the iridotomy. Acute pseudophakic pupillary block glaucoma

1 has been reported and zonular rupture has been reported.

2 (Transparency)

3 The advantages of neodymium YAG versus argon laser
4 are basically that it takes a shorter time to do the
5 procedure. You use much less energy. It is independent of
6 iris color and there is less iritis. The most obvious
7 advantage is a patent iridotomy for longer time periods
8 which decreases the risk of recurrent angle closure.

9 Disadvantages include the 30-50 percent rate of
10 anterior chamber bleeding. This is usually easily
11 controlled clinically and should only be recognized in the
12 face of precipitating factors.

13 (Transparency)

14 Finally, taken from the AAO Guideline is this
15 statement on the impact on the quality of care: The
16 increased safety of laser iridotomy versus surgical
17 iridectomy has allowed the same indications to be applied
18 more consistently and earlier in the disease, thereby
19 improving the quality of care of these patients.

20 There was a review that looked at cases to see
21 whether more iridotomies were being done and, in fact, yes,
22 they were but it was felt that this was because you were not
23 subjecting the patient to the risk of the intraocular
24 surgical procedure. It was not seen to impact negatively on
25 care and, in fact, was felt to improve the time course where

1 we were able to treat these patients.

2 I think that is all I have to offer. I think the
3 application was rather complete in terms of what it
4 contained and I don't think I can add much to that. Thank
5 you.

6 DR. WILKINSON: Thank you. We have two reviewers
7 of this petition. Dr. Serdarevic, would you like to give us
8 the highlights of your review, please?

9 DR. SERDAREVIC: Well, I won't review what the
10 petitioner is requesting since Dr. Knight has very
11 excellently reviewed all that.

12 I would like to proceed to the fact that I
13 recommend reclassification of the neodymium YAG laser used
14 for iridotomy indications from Class III to Class II since
15 sufficient information currently is known about this
16 procedure. It is a procedure that is widely used by most
17 ophthalmologists in this country, and has been felt by most
18 ophthalmologists in this country to be advantageous to
19 patients.

20 I also feel that Class II special controls can
21 provide reasonable assurance of safety and effectiveness for
22 the device when used in conformance with prescribed
23 conditions for use.

24 All the data in the three previously approved PMAs
25 and the peer-reviewed articles from 1984 to 1992 that were

1 included in the petition, as well as the guidelines
2 published by the American Academy of Ophthalmology document
3 the safety and effectiveness of the neodymium YAG laser when
4 used according to treatment guidelines in properly selected
5 patients for iridotomy.

6 There are no represented data or information known
7 by the petitioner that are unfavorable to the petitioner's
8 position. The petitioner has described which patients are
9 at risk for the procedure and what risks are now known
10 resulting from the procedure. As Dr. Knight has explained,
11 patients with preexisting conditions, such as active
12 uveitis, neovascularization and bleeding tendencies would be
13 at higher risk for adverse effects, such as iris bleeding.

14 Patients with preexisting conditions that preclude
15 an adequate view of the iris or that do not allow adequate
16 fixation would not be suitable candidates for the procedure,
17 and the following adverse effects on health that may result
18 from use of this device include increased intraocular
19 pressure, secondary glaucoma, pupillary block, damage to the
20 natural or intraocular lens, iris bleeding, inflammatory
21 reactions, cystoid macular edema, retinal detachment and
22 corneal damage. However, the risks of these adverse effects
23 have been documented to be low and acceptable when
24 prescribed directions for use and postoperative care are
25 followed.

1 I would also like to add that regarding the
2 labeling, as Dr. Knight has alluded to, we now have
3 additional information since the time of the previous PMA
4 approvals, and I would like to say that at this point
5 perhaps the indication should not be as specific regarding
6 the exact energy levels, and that information should be
7 taken into consideration regarding the newer applications
8 with the contact lenses etc.

9 DR. WILKINSON: Thank you. Dr. Sugar?

10 DR. SUGAR: Most of my comments have already been
11 covered by Dr. Serdarevic and Dr. Knight. Let me just say
12 that the use of substantial equivalence to support pre-
13 market approval of new neodymium YAG lasers for iridotomy
14 appears to be appropriate provided that the laser parameters
15 are essentially the same as those of the approved lasers, or
16 changes in those parameters are adequately supported by
17 appropriate data. This includes such features as corner
18 angles, spot sizes and power.

19 The limitation of 10 mJ as maximum laser power
20 appears to be appropriate, although the Agency may have
21 further information that would alter this recommendation.

22 The quality of the optical delivery system of the
23 laser is very important, and in particular the quality and
24 precision of the focusing system is critical and must be
25 reliably obtained and documented in the Class II

1 application.

2 For the reasons discussed, I recommend that this
3 petition for reclassification of neodymium YAG laser for
4 iridotomy from Class III to Class II be approved.

5 DR. WILKINSON: Thank you. Other comments or
6 questions from Panel members?

7 MR. GREEN: Yes, Dr. Wilkinson. Dr. Knight had
8 commented that one of the reasons this shouldn't be used is
9 the inability of the patient to cooperate. I was wondering
10 if you would say a little more about that. Is it an
11 inability to cooperate with the procedure itself, or with
12 post-procedure issues, or what?

13 DR. KNIGHT: Primarily what I am talking about are
14 patients who usually are unable to sit at a slit lamp. It
15 is a minimum amount of time, much less than argon laser, but
16 there are patients who cannot do that. Actually, there are
17 some, I believe, portable YAGs. I don't know whether or not
18 that has alleviated any of those patients. But it more
19 relates to patients who are unable to put their head in a
20 slit lamp.

21 The issue of nystagmus is for a patient who would
22 not be able to cooperate in terms of focusing and that may
23 require some question as to its use there. But I think
24 those patients are well defined and easily recognized.

25 DR. WILKINSON: Additional comments? Do we want a

1 motion?

2 DR. BROWN: Yes. I was going to add for the
3 record the report and recommendations of the Ophthalmic
4 Device Panel. This is a reclassification petition. The
5 date, October 28, 1993. The data and information upon which
6 the Panel based its recommendation are contained in the
7 reclassification petition, the reviews conducted by the
8 staff of the Division of Ophthalmic Devices and those
9 conducted by the Panel members. The results of preclinical
10 and clinical studies presented in the reclassification
11 petition constitute valid scientific evidence which the
12 Panel members as experts used to evaluate the safety and
13 effectiveness.

14 The members concluded that this information
15 provides reasonable assurance that the reclassification
16 petition, the results of which are safe and effective under
17 conditions of intended use as described. The rationale
18 supporting the Panel's recommendation is that the
19 reclassification petition has been demonstrated effective
20 when used in its intended use.

21 Furthermore, there is evidence to adequately
22 demonstrate that the safety and effectiveness of the
23 reclassification petition relating to the device assures
24 that there is no injury associated with its use, and that
25 the benefits outweigh the risks.

1 The Panel has concluded that the attached list of
2 conditions must be met or agreed upon by the petitioners.

3 On the last page are the signatures of those
4 voting, substantiated by the Chairman.

5 DR. WILKINSON: May I have a statement from you,
6 Olivia, regarding acceptance of it?

7 DR. SERDAREVIC: I would like to move that we
8 approve the petition for reclassification of the neodymium
9 YAG laser used for iridotomy indication from Class III to
10 Class II, and that labeling specifications for that purpose
11 are that we take into consideration new developments and new
12 research since the appearance of the previous PMAs for
13 neodymium YAGs.

14 DR. WILKINSON: Second?

15 DR. SUGAR: Second.

16 DR. WILKINSON: It has been moved and seconded
17 that this petition for reclassification be carried out. Is
18 there any discussion? If not, those in favor signify by
19 saying aye.

20 (Chorus of ayes)

21 Opposed?

22 (No response)

23 Thank you.

24 DR. BROWN: In that case, could you sign right
25 there and indicate the conditions of approval, please?

1 Unless there are some additional questions
2 pertaining to discussion this morning, I would say that it
3 is not 12:30 but about 11:45. Could we take a one-hour
4 break, please, for lunch? The hotel has provided a table
5 outside with sandwiches and some other things. There is a
6 cafeteria down to the left, and I think that is about it. I
7 would like to see you back here within an hour, about 12:45,
8 please.

9 (Whereupon, at 11:45 a.m., the Panel adjourned for
10 lunch, to reconvene at 12:55 p.m.)

1 AFTERNOON SESSION

2 DR. WILKINSON: We are going to begin the second
3 portion of the seventy-seventh meeting of the Ophthalmic
4 Devices Panel. I will turn this over to Dr. Brown.

5 DR. BROWN: Thank you, Dr. Wilkinson. Looking at
6 your agenda, it is 2:30 according to the agenda. However, I
7 have 12:55. So something is wrong. But, anyway, Nancy,
8 would you like to make a comment before we start?

9 MS. BROGDON: I would just say we are now at the
10 IOL-treated portion of the agenda, and the Branch Chief for
11 the Intraocular Implant Branch is Donna Rogers and she will
12 introduce the discussion items.

13 MS. ROGERS: The first discussion item that we are
14 going to go over is the IOL labeling update. Most of you
15 recall that we discussed several times with the Panel ways
16 to update IOL labeling and to otherwise streamline it.

17 At the May meeting, we went through a discussion
18 of particular questions that FDA had concerning the IOL
19 labeling and several Panel members indicated that they had
20 further comments. So I just wanted to give you the
21 opportunity to pass those along now so that we can,
22 hopefully, get something out to industry and move this
23 project along.

24 DR. WILKINSON: Can any of the Panel members
25 remember the comments that they had poised to present? Some

1 of them may have been submitted in writing. I don't know.

2 DR. MACRAE: I think I wrote two letters about IOL
3 labeling. Basically to summarize what I heard practitioners
4 ask for are, basically, "A" constants on the outside of the
5 labeling, as well as a diagram of the actual lens implant so
6 they could identify the characteristics of that lens
7 implant.

8 Essentially, all the major descriptive terms in
9 terms of the lens, the configuration of the lens as well as
10 the right- or left-handedness of the lens, particularly that
11 if it is a left-handed lens it should be clearly labeled,
12 with maybe a special designation that the industry could
13 come up with just to show that it is a left-handed lens so
14 that it isn't mistaken as a right-handed lens and put in
15 backwards.

16 But, essentially, all that labeling detail, as
17 well as a reasonable visual picture of it so that the
18 practitioner can identify the characteristics of the lens
19 should be on the outside of the box so that when the
20 practitioner is called upon to put a lens in that they don't
21 necessarily put in on a daily bases but because their lens
22 is out of stock, the practitioner can look at the box and
23 basically identify everything that they need to identify in
24 order to make a decision as to whether that is an
25 appropriate lens to use. Once they do, then they know

1 exactly what the characteristics of that lens are, that is,
2 whether it is a 6 mm lens, or 7 mm, or 5 X 6 mm lens, and
3 all that information is on the outside of the box. In my
4 opinion, that is one of the most important things we can do
5 in terms of facilitating practitioners being able to use
6 these appropriately.

7 DR. WILKINSON: Additional comments?

8 DR. DOUGHMAN: I want to emphasize the importance
9 of having the "A" constants on the outside where we can read
10 them because this is something that is missing on at least
11 half the implants I end up using.

12 DR. STULTING: I would recommend not only putting
13 it on it but figuring out some way of calculating it and
14 getting the appropriate information. I don't believe I have
15 ever seen the method of calculation or the data upon which
16 "A" constants have been based, certainly not in the PMAs,
17 and I have never really been aware of exactly how those
18 things were derived. It is not uncommon for an intraocular
19 lens to come to market and be approved, and then have a
20 representative come around a couple of months later and say,
21 "oh, by the way, the "A" constants are probably off by 1 or
22 so."

23 I think as we refine intraocular lens implants and
24 are not worried so much about a 10 percent incidence of
25 corneal edema and are more worried about whether people are

1 within half a diopter of ametropia, that we now need to
2 refine the procedure for getting the things approved and to
3 market, and one of the refinements would be not only to
4 display the "A" constant but also to have some reasonable
5 and accurate means for calculating what it ought to be in
6 the first place. That would be done by implanting the lens
7 in a group of patients and back-calculating, knowing what
8 the postoperative refraction is, to figure out what the "A"
9 constant should have been.

10 DR. DOUGHMAN: There may be also some value in a
11 warning about either the very short eye or the very long
12 eye, about what formulas you are using to calculate the lens
13 power because sometimes we are going in and having to either
14 replace these lenses because they are either too strong or
15 not strong enough just because of that. I am not sure how
16 that could be done on the label but I think it has to be
17 done some way so the surgeon is aware of a short eye ending
18 up with too strong a lens.

19 DR. WILKINSON: I guess that sums it up, Donna.

20 MS. ROGERS: Okay.

21 DR. WILKINSON: You did get the written
22 submissions, correct?

23 MS. ROGERS: No. Actually, since the last meeting
24 I haven't gotten any written comments from people who had
25 indicated they wanted to send written comments. So that was

1 the reason why we put this on the agenda. I did get a
2 couple of letters before the meeting and Dr. MacRae, I
3 recall, had sent some written comments, and Dr. Stark. I
4 recall Dr. Stulting indicating he wanted to make some
5 additional comments. And there was another Panel member too
6 I think.

7 DR. STULTING: I am not sure when it was but I did
8 submit some things. There are some examples. There are
9 some archaic things that are now in the standardized
10 labeling like, for example, this is indicated for
11 implantation in patients 60 years of age or older, that need
12 to come out. If you didn't get the written ones, maybe we
13 can submit them again.

14 MS. ROGERS: Okay. You know, I know we have
15 discussed this a number of times in different Panel
16 meetings. So some of your comments may have come up at
17 other Panel meetings, but it was just sort of left hanging
18 at the May meeting. What we had sent out to everybody,
19 there still seemed to be some problems with that. So I
20 think if any other comments occur to you, we are always
21 looking for written comments.

22 But I think we can probably move on then to the
23 next IOL item, which was the ISO/CEN international standards
24 for intraocular lenses. Don Calogero has been a member of
25 the American delegation to the standard and has put a lot of

1 effort into not only ensuring some consistency with FDA's
2 requirements, but also considering changes where they might
3 be appropriate and really pushing for these changes to have
4 some scientific validity.

5 He is going to make the presentation today and we
6 are also very fortunate to have with us an ophthalmologist
7 who is the Swedish delegate to the standard, and she may
8 also be asked to be part of the discussion today so you can
9 understand another member's viewpoint.

10 Also at the end of the discussion I would like to
11 open up the floor to the audience and allow industry to make
12 any comments at this time regarding the proposed standard.
13 This standard will be discussed for a final vote -- I think
14 those are the correct words -- at a meeting in November. So
15 it is important that we hear any serious objections to what
16 is going on with the international standard because we would
17 like to harmonize, to the extent possible, FDA's
18 requirements with the international standard. So I will
19 turn the floor over to Don.

20 MR. CALOGERO: I would like to point out that
21 there is a handout in the back of the room, which is
22 essentially the latest draft of the ISO/CEN clinical
23 investigation standard for IOLs. If anyone wants a copy, if
24 they don't have a copy, they can get it now and I will wait
25 a moment.

1 DR. BROWN: Could someone make sure that the Panel
2 members have it?

3 MR. CALOGERO: The Panel members have some
4 sections of that document. I have the complete document
5 here. It may be easier to work from the complete document.
6 I can pass these out.

7 DR. BROWN: Would you, please?

8 MR. CALOGERO: As Donna mentioned, FDA has been
9 working as part of the U.S. delegation in terms of
10 developing the ISO/CEN standard for IOLs. ISO is the
11 international standard organization; CEN is the European
12 standards organization.

13 The actual ISO/CEN standard for IOLs is a
14 collection of several separate standards, and those
15 standards are intraocular lenses terminology; intraocular
16 lenses optical requirements and their test methods; IOLs'
17 mechanical requirements; IOLs' labeling information; IOLs'
18 biocompatibility; IOLs' sterilization, which has since been
19 deleted; and IOL shelf life and IOL clinical investigations.

20 What I am going to spend most of today talking
21 about is the clinical investigations section. But what I
22 intend to do is just briefly discuss what I see as some of
23 the key points in the other IOL standards which would
24 potentially have an impact on IOLs in the United States.

25 The first IOL terminology standard is simply a

1 document which defines the terms that are contained in the
2 other standards.

3 The IOL optical requirements and test methods
4 standard is much more significant. This standard defines
5 the methods that are used to perform the required optical
6 testing and contains optical acceptance levels and
7 tolerances.

8 In this particular document the requirement for
9 IOL image quality is 60 percent resolution efficiency in
10 air, and this is equivalent to the U.S. requirement. In
11 most cases it is identical. But it goes on to say that in
12 cases where this test is not appropriate, which would be the
13 case with high power IOLs -- hydrogels, low refractive index
14 materials -- the requirement for image quality is 45 percent
15 modulation or contrast at 100 cycles/mm in the eye model,
16 and the geometry for the eye model is described in the
17 document. It turns out that this is a very critical value
18 because in the IOL clinical standard that particular
19 document doesn't limit the IOL power range that a sponsor
20 can have for his product, as FDA currently does with the 4-
21 32 diopters.

22 So internationally and in the European market, the
23 range that a company can make available will essentially be
24 limited by this particular optical requirement. Theoretical
25 work performed in our laboratory by Dr. Grossman indicates

1 that even the best optic shape factor, which is the
2 biconvex, will not be made available in powers needed for
3 hyperopic patients with this optic quality requirement. Of
4 course, as you change the shape factor to meniscus and other
5 shape factors the actual maximum power that would be
6 available would be substantially less than could potentially
7 be required in hyperopes. In the United States we have had
8 waiver requests for hyperopic patients up to maybe 46
9 diopters. Even the biconvex geometry might basically just
10 get into the low 40 diopters and nothing above, and, of
11 course, meniscus would be in the 30 diopters.

12 This point will be discussed at the next ISO/CEN
13 meeting which is going to take place in Chicago next month.
14 So I wanted to mention that fact.

15 Another significant aspect of this document deals
16 with the power tolerances for IOLs. In this particular
17 document -- it kind of relates back to what you were saying
18 here about the "A" constants and the need today to attempt
19 to achieve ametropia. For powers less than 15 diopters the
20 tolerance in ISO/CEN is 0.3 diopters. Between 15-25
21 diopters, the tolerance is plus/minus 0.4 diopters; 25-30 is
22 0.5 diopters; and greater than 30 diopters IOL power, the
23 tolerance is plus/minus 1 diopter.

24 Now, this compares with the current requirement
25 that is in the AINSI IOL standard, which is that the

1 tolerance for powers less than 25 diopters is plus/minus 0.5
2 diopter, and the tolerance for powers greater than 25
3 diopters is plus/minus 0.75 diopter. Now, these particular
4 tolerances were derived from ring studies that were
5 performed and represent the actual power tolerances that
6 companies today can meet while striving to achieve the
7 internal manufacturing tolerance of 0.25 diopters.

8 I want to point out that companies shouldn't used
9 the tolerances that are in these standards as justification
10 to increase the manufacturing power tolerances because that
11 would only result in larger actual tolerances when compared
12 to a reference test method.

13 Lastly, one last item that I am going to recommend
14 be added to the ISO/CEN optical standard is something that
15 deals with criteria for absorption characteristics of UV
16 absorbing lenses. Currently there is no standard
17 requirement in ISO/CEN, whereas AINSI has a requirement in
18 that the transmittance at 370 nm must be less than 10
19 percent for a 3 mm aperture with the thinnest lens
20 available.

21 That concludes this discussion. At any point when
22 I conclude a particular standard, if anyone has questions,
23 you can just bring them up at that point. Yes?

24 DR. DOUGHMAN: You talk about a difference between
25 the internal standard companies will achieve or try to

1 achieve of a quarter of a diopter versus the external
2 standard which can be up to 0.75 diopters, depending upon
3 the power.

4 MR. CALOGERO: Right.

5 DR. DOUGHMAN: Is there some way of monitoring
6 that? Is there some agency that monitors that internal
7 versus external control?

8 MR. CALOGERO: No. FDA has a requirement at the
9 IDE and the PMA phase that companies attempt to achieve the
10 plus/minus core diopter tolerance, and that is in all the
11 manufacturing SOPs. The problem essentially is that power
12 determination is really a subjective measurement. We are
13 using a human observer to attempt to achieve best focus at
14 the highest frequency. When you look at the actual ability
15 of all of the sponsors in aggregate by comparing their
16 performance against a standardized referenced method, you
17 find that overall, industry as a whole is only able to
18 achieve this tolerance which is described in the standards.
19 So at this point I really don't know of any way to make that
20 tolerance stricter when looked at from a perspective of,
21 say, an NDS standardized method.

22 Let me ask a question going back to the optical
23 standard. Currently FDA has a power range upper limit of 34
24 diopters. We are currently thinking of opening up that
25 range. In terms of the hyperopes, we get maybe just a

1 handful of requests for waivers above that power. We get
2 much more on the lower end for the myopes. Does anyone have
3 anything in terms of feedback to us in terms of what
4 percentage of the IOL subjects requiring a lens would
5 actually require a lens greater than plus 34 diopters? Is
6 it a hundredth of one percent? Are there any data published
7 anywhere to give us an indication? I guess no one knows.

8 DR. MACRAE: You can get those data based on eye
9 length. I think that those data would be available. You
10 might contact Jack Holiday about that.

11 MR. CALOGERO: Oh, okay. Fine. Thank you.

12 The next IOL standard which is in this group of
13 standards is IOL mechanical requirement standard. This
14 basically describes the mechanical test methods that are
15 necessary to perform the mechanical testing required by the
16 IOL clinical standard, which everyone has before them, for
17 IOL modification determinations.

18 It also includes the dimensional tolerances for
19 IOLs. The tolerances in this standard are slightly tighter
20 than those found in AINSI. A ring test is currently being
21 performed to validated the mechanical test methods in this
22 particular standard. That is everything about the
23 mechanical.

24 The IOL labeling standard sets the minimum
25 labeling requirements for IOLs in terms of information

1 required on the package insert, the lens tray and the outer
2 box. The two interesting things that I found in looking at
3 that document were that the actual lens drawing is going to
4 be required for the outer box for the IOL, and the "A"
5 constant is listed as optional for the box. So that is the
6 current international standard in terms of labeling.

7 The IOL biocompatibility standard closely follows
8 FDA requirements but adds the requirement for three levels
9 of genotoxicity tests, rather than one, to determine the
10 effects of DNA, gene mutations and chromosomal aberrations.

11 As I said, the IOL sterilization standard was
12 initially worked on by the group, but it was dropped because
13 the actual horizontal standard for sterilization covered
14 IOLs.

15 A major change was made to that horizontal
16 standard in terms of the ETO residue levels that are allowed
17 for IOLs. In terms of harmonizing with the requirements in
18 the rest of the world, especially in Japan, the document
19 initially had the requirement of 0.5 mcg of total ETO being
20 the allowable limit for the lens. This 0.5 mcg corresponds
21 with 20 or 25 mg for the IOL to about 25 ppm, but it is 25
22 ppm with a total exhaustive method, whereas in the United
23 States we don't use the exhaustive method; we use a head
24 space method which generally removes about 50 percent of the
25 total.

1 The problem with leaving the level with 0.5 mcg
2 ETO was that the current sterilization cycles that companies
3 have are not able to achieve that level of ETO residues in
4 most cases. So, as a result, companies would be forced to
5 change their sterilization cycle, potentially lessening the
6 sterility assurance associated with the product.

7 There was a discussion last month in Minnesota on
8 this document and it was decided that that requirement
9 should be changed from 0.5 mcg to 1.25 mcg for ETO total,
10 with maximum daily release of 0.5 mcg. So now this 1.25
11 basically very closely corresponds to the current levels
12 that FDA had in place in the last, say, decade.

13 The last standard before we get to the clinical
14 investigations standard is the shelf-life standard. This is
15 the furthest IOL standard from completion. In its current
16 form it sets out very extensive shelf-life testing
17 requirements that differ by the type of material used for
18 the IOL body and loop material. In their current form, they
19 are more extensive than FDA requirements. That is basically
20 all I can say about that.

21 The last standard, and the one that interests us
22 here, is the IOL clinical investigation standard. What I
23 have done is I have listed out eight or ten major topics
24 where there are major differences between what is in the ISO
25 clinical standard and the current FDA requirements.

1 As Donna mentioned, perhaps the final meeting of
2 ISO/CEN clinical group is going to be in November, before
3 the Academy meeting. FDA and the U.S. delegation wanted
4 feedback and input from the Panel because if there are any
5 major concerns with certain portions of the document, this
6 would perhaps be our last opportunity to influence the
7 outcome of the document.

8 The first major topic is a modification to the
9 tier system that FDA currently uses for modifications to the
10 parent lens. In this particular document it doesn't refer
11 to it as the tier system because the word "tier" doesn't
12 translate very well into other languages. So it is called a
13 level modification rather than a tier modification.

14 What this particular document does is that it goes
15 beyond the types of modifications that are allowed in terms
16 of allowing a boundary range concept for modification of a
17 parent model. In the current FDA requirements a modified
18 lens is compared to a single parent, and there is various
19 testing to determine the relationship between the parent and
20 the modified lens. Based on that relationship, which is
21 fairly well defined in FDA documents, a company determines
22 what clinical investigation, if any, is required for this
23 particular modified lens.

24 The ISO/CEN document takes that concept and goes a
25 step beyond it. What ISO/CEN does is, in addition to

1 allowing the one-to-one relationship between parent and
2 modified lens, it allows a company to determine a range of
3 characteristics based on the mechanical characteristics that
4 are associated with their population of lenses that have met
5 the standard, or we can think in terms of PMA approved
6 lenses. So they would construct sort of boundary ranges
7 associated with the PMA approved models, and based on the
8 relationship of the modified lens to the boundaries they
9 determine the level of clinical investigation, if any,
10 associated with the modified lens. So it is a new concept
11 that is being introduced here.

12 Does anyone have any comments on this?

13 DR. MACRAE: Can you give us a concrete example?

14 MR. CALOGERO: Well, a concrete example would be a
15 company would take clinical studies -- a company would
16 define, say, the mechanical characteristics of their
17 population of PMA approved lenses. Suppose this company
18 only had two PMA approved lenses, a modified J and a C-loop
19 design, posterior chamber lenses, what they would do is they
20 would define mechanical characteristics of these two lenses
21 and then they would construct a boundary range associated
22 with the characteristics of these two models. Now when they
23 modified a lens, even if the lens had a very different
24 geometry, haptic geometry, than the C-loop or the modified
25 J, if it was some place in between, with the current FDA

1 requirements that would require a clinical study most
2 probably. In the case of this new document, since they have
3 constructed a boundary around these two models, most
4 probably when they define the mechanical characteristics of
5 the modified lens, if something is not very different like
6 the caliber of the material being very different, there
7 could conceivably be a large overlap in terms of the
8 mechanical characteristics of the modified lens with the
9 boundary range.

10 As a result, it may not require clinical
11 investigation, whereas currently in the United States the
12 sponsor would have to compare his modified lens to one of
13 the two parents, and if they differed substantially in terms
14 of contact angle with the tissue of these lenses -- if they
15 differed substantially in terms of compressed contact angle,
16 then most probably it would require a clinical
17 investigation. So that is sort of a concrete example of the
18 difference between FDA and ISO/CEN.

19 DR. MACRAE: So the boundary -- is it a physical
20 boundary you are talking about in terms of size --?

21 MR. CALOGERO: It is a boundary of parameters. If
22 you look in the document that was handed out, just for
23 example on page 47 in the document, you find that what the
24 company has done in this particular example is that they
25 have graphed out the contact angle associated with

1 particular models and the tissue at 10 mm overall
2 constrained diameter as a function of force in the MKS
3 system. This has set up a boundary condition. And this is
4 one of a group of boundaries that is defined for each parent
5 model. What a company would do is to compare their modified
6 lens to the group of boundaries that was constructed from
7 the parent models. If they have sufficient overlap between
8 the modified and the boundaries, then from that they
9 determine the level of clinical investigation, if any. Is
10 that clear to everyone?

11 DR. STULTING: I have a question. How do the
12 boundaries get defined in the first place? Are they some
13 statistical modification of the existing data? Is that
14 correct?

15 MR. CALOGERO: Well, the actual mechanical test
16 methods are defined in the mechanical standards which the
17 Japanese are working on in conjunction with the FDA
18 requirements. The actual properties or characteristics of
19 the models that are defined are spelled out specifically in
20 this document.

21 MS. ROGERS: The companies would still test
22 certain models and obtain clinical data on certain models.
23 Those models would have certain mechanical characteristics
24 associated with them. From those bench mechanical
25 characteristics there would be not a statistical but a

1 standard deviation, you know, associated with the model that
2 had been clinically studied, its values, and that is how the
3 boundaries are determined. Anything that is established in
4 a boundary would have had some clinical testing associated
5 with it.

6 DR. STULTING: Maybe I am misunderstanding but I
7 guess the thing that is bothering me a little bit is if you
8 take a parameter like compression force for an anterior
9 chamber lens, we know, or at least we think we know that
10 more rigid lenses are associated with complications --

11 MR. CALOGERO: I am sorry, this is for posterior
12 chamber lenses.

13 DR. STULTING: Well, it doesn't matter. Let's
14 suppose that you use any parameter that you have some
15 inkling has some problem associated with it. Let's suppose
16 that we believe that high compression forces in posterior
17 chamber lenses cause problems. It squashes out the bag or
18 something like that. I assume that you are going to apply
19 the same boundary computations for one that has high
20 deformability as to one that has low deformability?
21 Correct? So that if you have a model that just barely works
22 because it is just barely within whatever biological
23 parameters there are, you can potentially allow something to
24 be approved that is really outside of the biological
25 parameters just because of the way it is calculated.

1 MR. CALOGERO: Actually, I thought about that and
2 I was concerned if you are simply using a mathematical
3 equation, a standard deviation, you could potentially come
4 upon a situation where mathematically it fit in terms of
5 these boundaries but clinically you were in a situation
6 where you had a lens which was either too rigid or
7 essentially exposed the tissue, too much stress, or would be
8 too flexible and potentially could cause dislocation. What
9 I did is I set up -- where is it? Oh here, on page 15 of
10 the document. This was a concern that the convener had also
11 brought up, the fact that if we use just a simple
12 mathematical relationship to attempt to define these
13 modifications to parent characteristics we could run into a
14 clinical problem.

15 So I constructed a series of five equations that
16 define the relationship between modified IOLs and parent
17 IOLs. Essentially, the largest deviation that is allowed is
18 within the range that we have commonly seen in terms of
19 characteristics of posterior chamber lenses. Then as you
20 get outside either more rigid or more flexible from the
21 range we have seen associated with PMA approved models, the
22 actual relationship between the modified lens and the parent
23 lens becomes much, much more restrictive and it reaches a
24 point where it has to be identical, of course, as you drop
25 off and the lens becomes so flexible or it becomes too

1 rigid.

2 So we have, in fact, attempted to incorporate that
3 into this document. Obviously, you are not going to be able
4 to work through the equations at this point.

5 (Laughter)

6 Okay, so anything else on this particular issue of
7 boundary concept?

8 (No response)

9 Okay, we probably should move on to the second
10 area. The second area deals with the sample size for
11 clinical investigations. Currently in the United States is
12 a cohort sample size for an original model of 500. That was
13 very different from the clinical study requirements around
14 the world, I discovered. In France the clinical studies are
15 100 subjects. In Japan the clinical studies are 60 subjects
16 at only 2 investigational sites.

17 What we did in our particular group is we looked
18 at the actual statistics of the various sample sizes in
19 terms of what you can detect with each particular
20 complication and we developed power curves. It was
21 determined that in terms of actually what you are able to
22 detect in the clinical study, we don't give up very much by
23 going from a 500 sample size to a 300 sample size. Once you
24 fell below 300 subjects, the actual power of the study
25 dropped substantially.

1 So our position at the meeting was that we wanted
2 at the minimum 300 sample size. At this point we have
3 agreement with the other countries involved that their
4 requirements and the requirements in this document would be
5 the 300 sample size.

6 If you look in the information that was sent out
7 to you -- here it is; it is under number 2 in this packet of
8 information that was sent out to everyone. There is an
9 initial letter in there and then there is a table. This
10 table details out complication rates that are detectable
11 with a study with 80 percent power, and it is a one-sided
12 study. What we did is we looked at the complication rates
13 which would be detectable as being statistically different
14 from whatever level we had in the grid. We looked at
15 various sample sizes which ran from 500 subjects to 100
16 subjects and we have looked at a range of complication rates
17 from 0.1 percent up to 2 percent.

18 For example, we have found with a complication
19 rate of 0.1 percent at a sample size of 500, the actual
20 clinical data that you would have to have from your study
21 would have to have a complication rate of 0.6 percent or
22 greater to be statistically different from the level that is
23 allowed in the grid or the table with acceptable values in
24 this document.

25 If you look at the 300 sample size, you are now at

1 0.8. So you have actually gone from 0.6 percent to 0.8
2 percent. If you look at the higher complication rate, if
3 you look at a level in the grid of 2 percent and a 500
4 sample size, you are talking about a difference at 2.8 as
5 being statistically different from the grid level, where
6 with 300 subjects it is 3.0 being detected as statistically
7 different from the grid levels.

8 So based on this analysis, and also we have
9 generated power curves, and also below the visual acuity
10 from 500 to 300, drops from 85 percent to 84 percent and
11 best case from 92 to 91. So essentially you are losing 1
12 percent.

13 So based on this analysis, the U.S. delegation
14 agreed to this 300 sample size. So as a member of the U.S.
15 delegation and also as an FDA representative, I am bringing
16 this before the Panel for the Panel's input into a reduction
17 in sample size from 500 to 300 subjects.

18 DR. SUGAR: If you decrease the power to detect
19 complications, then you increase the burden on post-
20 marketing surveillance to pick up these complications. Do
21 we have an adequate system to do that? We are limiting in
22 terms of number and also I think somewhere it is form 5
23 instead of form 6, a shorter 9-month instead of a 12-month
24 follow-up period.

25 MR. CALOGERO: Right.

1 DR. SUGAR: Do we have adequate means to detect
2 complications, like for closed loop lenses where they were
3 picked up -- would not have been picked up in the system and
4 were picked up what would be considered fairly late.

5 MR. CALOGERO: You are talking about closed loop
6 anterior --

7 DR. SUGAR: Closed loop anterior chamber, that
8 kind of thing where there was actually a high rate of
9 complications but within the time period and within the
10 standards they passed those guidelines and required post-
11 market surveillance. But it was done rather informally and,
12 therefore, picked up late.

13 MR. CALOGERO: Right. That is kind of a little
14 bit different concept and we did think about that. To get
15 ahead of myself a little bit, in terms of the anterior
16 chamber lenses, in this particular document there was a
17 three-year follow up required for anterior chamber lenses to
18 attempt to pick up late onset complications.

19 DR. SUGAR: That is just an example of anterior
20 chamber lenses. The point is that if we are giving up our
21 power to detect safety concerns, are we covering ourselves
22 or covering our patients for the risk that is increased by
23 that?

24 MS. ROGERS: Well, what you are asking is really
25 does FDA have systems to sort of monitor post-approval

1 rates. There are systems set up. There is the complication
2 reporting system where ophthalmologists can report
3 complications. There is also a post-market surveillance
4 system set up within FDA that IOLs has not really been a
5 part of. This is a fairly new system and IOLs haven't been
6 added to these post-market surveillance studies.

7 So the answer to your question, you know, in my
8 mind is no because the systems right now are not very well
9 controlled. The reporting of complications is not well
10 controlled, you know, like a study like you are talking
11 about. But I think we have to backtrack a little bit
12 because the drops that we are talking about here, the
13 question we are asking is, is this still reasonably
14 considered a safe and effective product. When you look at
15 some of these numbers, and we are doing a 500-patient study
16 and seeing a complication rate of 1 percent, if you look at
17 this table, you know, the statistics work out that you are
18 only really assured that the population as a whole would be
19 at 2.3 percent. Okay? So when we are going down to 300, we
20 are talking about dropping that down to an assurance of 2.7.

21 So I don't know if this is exactly what you are
22 getting at but it is not -- your question might be a little
23 larger and we might not have that in place right now for
24 current studies.

25 MS. BROGDON: There is one thing I could add. We

1 are still able to require conditions that the sponsor has to
2 agree to as we approve PMAs. If the situation warranted to
3 require a continued study for some complication or some new
4 sub-study after approval, we may still do that, and you can
5 still recommend that.

6 DR. SUGAR: But that requires anticipating the
7 complications --

8 MS. BROGDON: Yes.

9 DR. SUGAR: -- to set up that requirement --

10 MS. BROGDON: That is right. That is why I said
11 if the situation warrants.

12 DR. SUGAR: -- when, in fact, we are relying on
13 MEDWATCH as a means of detecting complications. At least
14 from past history as an ophthalmologist dealing with
15 devices, I don't think it is going to be very effective
16 unless there is a very high risk of complications.

17 DR. MACRAE: Along the same lines, did you do
18 these calculations with 90 percent power as well?

19 MR. CALOGERO: I don't believe we did. Typically,
20 our statisticians used 80 percent power for IOL studies, and
21 that is what they did.

22 DR. MACRAE: At the clinical trials meeting that
23 we had earlier in the month, they talked about 0.8 and 0.9
24 as their power and I am still unclear as to what FDA is
25 going to do in terms of that standard. There was a lot of

1 talk about 0.9 as a standard power but I know traditionally
2 we have used 0.8.

3 MR. CALOGERO: Right. I wasn't at that meeting
4 and I really don't have any insights in terms of if the
5 Agency is moving, say, to using 90 percent. As I say,
6 typically we have used 80 percent power for IOL studies. As
7 such, the calculations here are for that power.

8 MS. BROGDON: It is something that we may have to
9 discuss further. I don't know that we can do that before
10 the ISO meeting. We do need to decide where that clinical
11 trials workshop applies (inaudible).

12 DR. MACRAE: You know, I think that when you are
13 looking at public health strategy, this is an important area
14 to be more rigorous than, let's say, the silicone study that
15 came before us before where there is so much variability.
16 This is an opportunity to do some real strong science
17 because the implants that you are going to be using are
18 going to be used in millions of patients. So I would
19 encourage the Agency to push for the types of studies that
20 would give us definitive data. It is very clear
21 scientifically, and basically echo Alan's words about the
22 difficulty after something is approved with which we can
23 identify problems. This is our one opportunity to have a
24 good impact on public health.

25 MS. ROGERS: Well, I guess I would want to get

1 back to looking at, with all the studies we have approved,
2 if you use the 80 percent power what we were really unsure
3 of at the time that we made our decisions. When we made
4 these comparisons, like visual acuity, the grid says 88
5 percent of the population should have 20/40 or better. With
6 the 500 patient study, we only really knew for sure that 85
7 percent of the population as a whole would be able to meet
8 that requirement. And what I am kind of getting at now is
9 dropping that down to 84 percent, are we really losing much
10 in our clinical studies?

11 MR. CALOGERO: Is the amount of difference between
12 what you can detect with 500 subjects and 300 subjects
13 clinically significant, from the Panel members' perspective,
14 with this loss of 1 percent in visual acuity? Is this loss
15 of 0.2 percent, say, in complication rates at a level of 0.1
16 clinically very significant so that FDA, through the U.S.
17 delegation should very hard attempt to push for a higher
18 sample size for this document, if possible?

19 DR. STULTING: What design changes would it be
20 applicable to? Just posterior chamber lenses?

21 MR. CALOGERO: No. Okay, the scope of this
22 document will be for all monofocal posterior chamber and
23 anterior chamber lenses for the treatment of aphakia.

24 DR. STULTING: Well, it seems to me that there are
25 some design modifications that I would be fairly comfortable

1 with being tested on a cohort of 300, and there are some
2 design modifications that I would not be comfortable with
3 being tested on a cohort of 300. It has to do with the
4 existence of knowledge about related design changes that are
5 already out there on the market.

6 For example, if you want to test a new posterior
7 chamber implant with some haptic configuration that is not
8 currently marketed by the company and is out of the range
9 here for a parent model, then I might be comfortable with a
10 300 cohort just because there are a lot of lenses out there
11 that resemble it very closely and we have already seen.

12 On the other hand, if a company wants to test a
13 silicone implant of a design that is not in existence right
14 now, then perhaps a 300-patient cohort would not be at a
15 level of comfort.

16 So I think that my view of acceptability of the
17 reduction in the cohort would depend very much upon the type
18 of design we are looking at. I think for an anterior
19 chamber lens, knowing past experience with those, that might
20 be too small to be appropriate. Similarly, for posterior
21 chamber implants of different materials and radically
22 different designs.

23 MS. ROGERS: Are there particular complications
24 that you are looking at that you feel the rates that you
25 could be assured of with the 300-patient study would be

1 problematic? I guess we are trying to get you back to what
2 we really can do today with these studies. So are there
3 certain complications that the drop would be unacceptable?

4 DR. STULTING: I believe that we have reviewed in
5 public session PMAs for posterior chamber implants where
6 certain complication rates were at the margins of
7 statistical significance for a 500-patient cohort. And I
8 would imagine that if we dropped it below 500 patients, it
9 might have fallen out of the range of statistical
10 significance and escaped our attention.

11 DR. MACRAE: Along the same lines, basically, I
12 think for the 2 percent complication rate I don't think
13 there is a major problem. Most of the difficulties arise
14 with complication rates in the 0.5 percent range and the
15 major complications that I am concerned about are lens
16 explanation and inflammatory reaction. So if we see a study
17 with one or two inflammatory episodes and the investigators
18 basically write it off as just a case of uveitis or
19 something, and we only pick up two cases or one case of
20 that, that could slip right through the process but,
21 meanwhile, that may be occurring --

22 MR. CALOGERO: Okay, it may slip through the
23 process but I think you were going to say that that might be
24 occurring at a much higher rate and I don't think that would
25 be true.

1 DR. MACRAE: What I was going to say is that may
2 be occurring within the population if we are using a large
3 number of those implants. If we are using 10,000 of those
4 implants, then there is a significant number of people who
5 will be affected by that.

6 MR. CALOGERO: Sure, 0.1 percent of a million is a
7 substantial number. I think the critical thing with these
8 clinical studies is that in the past we have been accepting
9 them with a certain level of assurance and, certainly, if
10 you have a design with a complication rate that is just
11 straddling that level and we lower it to a sample size from
12 500 to 300, you are going to miss that complication. But
13 the complication in the general population is only going to
14 be slightly higher than it would have been with the larger
15 sample size. The differences between the 500 and the 300 in
16 terms of detectability, from my perspective, are very small.

17 DR. STULTING: Well, I don't really think that is
18 a complete picture of what is going on here. The other
19 things that you have to factor into the statistical
20 treatment that you didn't is the fact that we are working at
21 an 80 percent power level and that we are working with more
22 than one PMA. You constructed looking at it the other way
23 so that you miss, with a probability of 20 percent,
24 complications that occur at a rate that is at this level or
25 below. If you then factor in the possibility that we look

1 at, say, 5 or 10 of these a year, what you are going to find
2 is that the probability of something going through with a
3 complication rate of 5, 6 or 7 percent is significant when
4 you calculate that probability based not only on the power
5 level but the fact that you are getting multiple
6 submissions. So there is another step in the calculation, I
7 believe, that you really haven't taken into account in the
8 tables, and that is the number of these things which we
9 actually look at. Would you agree with that?

10 MR. CALOGERO: Okay. So you are talking about the
11 compound effect of multiple studies from hundreds of
12 sponsors.

13 DR. STULTING: I mean it is more than just saying
14 your detection rate drops from 88 to 85 percent. There are
15 more things that go into it than that.

16 MR. CALOGERO: Okay. I think we will go back to
17 our statisticians and do different analyses, maybe altering
18 the power to 90 percent, looking at the effects of multiple
19 studies.

20 I have to take something back to this meeting in
21 November, and my thinking is that it may not be possible to
22 get the 500 sample size through this group of countries.
23 Would an acceptable compromise position be that there was
24 wording in the document that if the company had an IOL model
25 that was manufactured out of a new material in terms of not

1 simply that company, but a new material in terms of what
2 currently exists by going through the literature and such --
3 in terms of a new material and in terms of a radically new
4 design that has really never been studied a million times by
5 other companies, in those particular cases the company
6 should seriously consider a larger sample size than the 300
7 but at least a 500 sample size? Would something like that
8 be acceptable if we key in on essentially the unknowns, the
9 new materials, radically unknown designs?

10 DR. STULTING: That would be my recommendation.
11 The key there, obviously, is being smart enough to figure
12 out what really is radically new. But I am much more
13 concerned about having a larger sample size on a specific
14 design rather than burdening manufacturers with a 500-
15 patient cohort on every lens that is made from now until the
16 end of time.

17 MR. CALOGERO: Okay, fine. I will work on some
18 wording for that and we will present that at ISO next month.

19 DR. STULTING: For example, I think it is quite
20 out of line to have the same investigational requirements
21 for a planar posterior chamber lens and an anterior chamber
22 lens with just about any kind of design.

23 MR. CALOGERO: That certainly makes sense. Are
24 you talking about sample size or are you talking about
25 duration of the study?

1 DR. STULTING: Probably both. I mean we need to
2 learn from past mistakes and I think we may not be doing
3 that if we say that in the future you can come through with
4 an anterior chamber lens and study 300 patients for a year.

5 MR. CALOGERO: Okay, the way this document is
6 currently written, the requirement for anterior chamber
7 lenses is for 300 subjects followed for 3 years prior to
8 receiving the certification and going into general
9 distribution. So they do have 3-year clinical
10 investigations in this study but they do retain the 300
11 sample size. Do you feel that is sufficient, or should we
12 push also for a larger sample size for anterior chamber
13 lenses?

14 DR. STULTING: Well, maybe the way to answer that
15 question is to go back to the data that are in existence on
16 anterior chamber lenses that have been studied and approved
17 in the past, and ask whether that kind of a study would have
18 detected the problems that we now know about. I don't know
19 whether it would or not. But it seems to me the data exist
20 within the FDA on these lenses that have been approved with
21 post-market surveillance, and you can go back and at least
22 get some idea whether you are doing an appropriate thing by
23 looking at existing data.

24 MR. CALOGERO: Okay, fine. We can go back and
25 look at that. Of course, that will be on one-year data that

1 we have but we will have additional two-year follow up on
2 some of the models.

3 MS. BROGDON: Dr. Stulting, when you are talking
4 about lenses that failed, are you speaking of the closed
5 loop anterior chamber lenses?

6 DR. STULTING: Well, some closed and some open. I
7 am not sure I said "had failed." I think it is common
8 knowledge that certain anterior chamber implant designs are
9 associated with an unacceptably high risk of complications
10 by today's standards and you have data on that. Those are
11 lenses that were approved apparently on data in the PMA.
12 The question is will a 300 cohort at 3 years reveal those
13 problems.

14 MR. CALOGERO: If there are high complication
15 rates and the duration of the study is three years, wouldn't
16 it be fairly easy even with a sample size of 300 to pick up
17 these complications?

18 DR. STULTING: I don't know.

19 DR. MACRAE: Weren't the original closed loop
20 studies 18 months?

21 MS. BROGDON: No, they were probably one-year
22 studies. I assume we are speaking of the ones that we know,
23 the open public hearing on the StableFlex and 91Z
24 (phonetic). Those were initially set up, I believe, as one-
25 year studies but ended up with three-year data almost.

1 DR. MACRAE: And yet the three-year data really
2 weren't conclusive in terms of picking up and recommending
3 approval.

4 MS. BROGDON: I think we have more three-year
5 data. There are three-year data on more of those subjects
6 that are more convincing than they were a few years ago.

7 DR. MACRAE: Because at that point in time, as I
8 recall, we didn't really have sufficient data, that we
9 needed the outside influence of David and a number of other
10 people to help us.

11 MS. BROGDON: Yes, I think we have the data. I
12 was just checking to make sure those are the lenses you were
13 referring to.

14 DR. MACRAE: I just want to clarify one point. In
15 the definition section you have a definition of AC IOL
16 except rigid design.

17 MR. CALOGERO: Oh, yes. I am sorry. I am going
18 to make a recommendation at the next meeting that rigid
19 anterior chamber lenses also fall under the three-year
20 follow-up requirement. Currently in this document they are
21 only followed for one year, and maybe that was an oversight
22 on my part.

23 DR. MACRAE: The rigid design, that includes a
24 lens like the Choice lens, let's say, but also would it
25 include a lens like Multiflex or a three-point fixation? Is

1 that considered rigid?

2 MR. CALOGERO: No. That would be considered, I
3 would imagine, semi-rigid. The definition of rigid is
4 requiring, I believe, more than 50 g of force to compress
5 the lens 0.5 mm.

6 DR. MACRAE: So the semi-flexible lenses, do they
7 come under the purview of three-year follow up?

8 MR. CALOGERO: Right, all AC lenses would be
9 followed for three years.

10 DR. MACRAE: Could I just make one comment about
11 the 300 patients?

12 MR. CALOGERO: Yes?

13 DR. MACRAE: In one section they talk about the
14 number of investigators, and they say that one investigator
15 may not see more than 25 percent of the patients or do more
16 than 25 percent of the patients.

17 MR. CALOGERO: Yes, that is the next topic.

18 DR. MACRAE: Okay. Why don't I just go ahead and
19 raise my point now?

20 MR. CALOGERO: All right.

21 DR. MACRAE: In other words, you could have -- not
22 that this is going to happen but I, as a Panel member, would
23 not like to see an investigator come in with 3 investigators
24 doing 75 percent of the study. In other words, each
25 investigator in this 300-patient study would do 75 patients

1 basically. I just don't think that is a good precedent. We
2 should somehow encourage the manufacturers to have multiple
3 investigational sites and also to have a fairly equal
4 distribution.

5 MR. CALOGERO: Okay, this was an attempt to
6 prevent the companies from having investigators with too few
7 subjects, an investigator that has only one or two subjects.
8 I see what you are saying. You would also like a minimum
9 number of investigators. Is there any guidance --?

10 DR. MACRAE: I am not saying that. What I am
11 saying is that I don't want an investigation to come in with
12 3 of the investigators doing 75 percent of the
13 investigation, which is basically the way that things could
14 be if each one took 25 percent of the cohort. So I would
15 like it broken up a little bit more.

16 One alternative would be to recommend that the
17 investigator could not do any more than 15 percent of the
18 cohort. That way you would have a more representative
19 sampling from all the investigators.

20 MR. CALOGERO: Okay, I see what you are saying.
21 Essentially you would have six or seven investigators.

22 DR. MACRAE: Right.

23 MS. ROGERS: I think we would have to work out
24 some of the numbers. There are kind of two issues. One,
25 you have to have the investigators doing enough subjects so

1 that you don't have a study where each guy is doing two or
2 three. The other issues is that we have to keep the
3 percentage such that it is not limited to a very minimum
4 investigators and two or three people are doing the bulk of
5 the study. So you are recommending maybe 15 percent as
6 being more reasonable than 25 percent, yet still giving each
7 investigator a reasonable -- you see, there is a balance
8 here.

9 DR. MACRAE: Right. One of the problems we are
10 running into is that instead of dealing with 500 patients
11 now, we are dealing with 300. Usually in a 500-patient
12 study we deal with about 10, maybe even 15 investigators.

13 MS. ROGERS: But historically we have had quite a
14 problem with the distribution being unequal.

15 DR. MACRAE: Exactly. So what I would like to see
16 is that we not have, you know, 1 investigator doing 40
17 percent of the cases or 50 percent of the cases and then
18 other investigators doing 1 or 2 cases.

19 MR. CALOGERO: The 25 percent limitation would
20 prevent that. Probably what we would run into if we reduced
21 that to 15 percent is the fact that with the Tier B study we
22 would have only 100 subjects. If you have that as a maximum
23 15 percent, then you have all of your investigators with no
24 more than 15 subjects and that is not a large enough sample
25 size to do a statistical analysis. In other places in the

1 document it basically cites a 20-subject minimum for a
2 statistical analysis. In the United States we generally use
3 something a little higher, say 25 or 30. So if you put that
4 limitation in all of the studies, then you force the
5 companies into a situation where they don't have sufficient
6 sample size for each investigator in Tier B studies to do a
7 statistical analysis.

8 DR. MACRAE: For the Tier B, realistically I don't
9 think you are going to be able to get a good scattering of
10 different investigators. It is going to be very difficult
11 to do that. But I think with 300-patient studies if you can
12 have a system where you encourage all the investigators to
13 do a reasonable number so that you get a relatively even
14 distribution, I think that would be desirable.

15 MR. CALOGERO: Okay. That certainly makes sense,
16 and I will need to think about some way of changing the
17 wording here and making another recommendation along those
18 lines.

19 The next item is the postop. reporting forms.
20 That is in your mailed out package. I believe it is under
21 Tab 3. It defines ISO/CEN subject examination dates. I
22 want to point out, as someone already pointed out, in terms
23 of the ISO/CEN clinical investigations, form 5 has dropped
24 off and what we currently have is form 6, which is now the
25 ISO form 5.

1 The reason for that is that it was felt that that
2 was really the form that provides the least useful
3 information in terms of the clinical investigation, and in
4 terms of balancing the additional requirements that we are
5 placing on the sponsors, they felt that they would eliminate
6 that form.

7 Now, in terms of the additional requirements, what
8 they have done is they have gotten away from having a cohort
9 study associated with the clinical investigation. All of
10 the patients in their clinical studies are core patients,
11 thereby all the subjects are required to have all the forms,
12 and it cites a minimum sample size at each form as the 300
13 subjects. That is one major change.

14 Then additionally, another change is that the
15 actual time frames associated with each form are tightened
16 in the ISO/CEN document. Take for example the form 1, in
17 the United States the form 1 is 1-6 days postop. It was
18 felt that this was too large a range and there could be a
19 large difference in terms of patient performance at day 1 or
20 2 as opposed to day 6. So that range was tightened to 1 or
21 2 days postop.

22 The form 2 was tightened to 7-14 days from the
23 U.S. 7-20 days. The form 3, as you can read on there, is
24 essentially the same: ISO/CEN 30-60 days; U.S. 21-55. Then
25 the rest are basically the same, with the exception of the

1 form 4 which truly starts at the conclusion of 4 months.
2 It's 1-21 days to 1-80 days, whereas in the United States a
3 form 4 for a normal study could be at day 56; for the
4 abbreviated Tier B study it could start at day 84. For
5 ISO/CEN it is essentially a month later than that, 1-21
6 days.

7 So those are the differences in terms of the
8 reporting forms and in terms of the time frames. Does
9 anyone have any feedback or comments on what was changed in
10 this document? Is this tightening acceptable to everyone?

11 DR. MACRAE: Nancy, most of our data is reported
12 as 12-month data, summary data?

13 MS. BROGDON: Yes.

14 DR. MACRAE: So it would be directly applicable to
15 form 5 of this?

16 MR. CALOGERO: Yes.

17 DR. MACRAE: So we could basically translate our
18 12-month data to this form 5 --

19 MS. BROGDON: That is right.

20 DR. MACRAE: -- and use that?

21 MS. BROGDON: Yes.

22 DR. MACRAE: Okay.

23 MR. CALOGERO: Now that we have finished the easy
24 parts, we move on to the actual changes that were made in
25 the FDA grid and also in the reporting forms. That is also

1 in your packet under attachment number 4. It is labeled
2 Annex A (normative), which are the acceptable levels,
3 essentially the grid levels that would be acceptable to the
4 clinical investigations under the ISO/CEN.

5 There are certain changes from what FDA has in
6 terms of the grid levels. I will point out and I will point
7 out the rationale that we used for making these changes, to
8 the best of my ability.

9 In terms of the complications that are in the
10 grid, it was felt that very infrequent complications should
11 be removed from the grid or this acceptable table. Two
12 examples of this are cyclitic membrane and vitritis. So
13 those two were removed. The complication rate that we had
14 listed in the grid for vitritis was 0.1 percent and for
15 cyclitic membrane also 0.1 percent, and less than 0.1
16 percent for posterior chamber lenses. It was felt that
17 these are complications that are almost never seen today and
18 it was safe to remove those, and it looks like everyone
19 agrees with that? Okay, very good.

20 DR. SUGAR: In the past have we called these
21 acceptance levels? I think that is sort of misleading. It
22 is really a rather loose comparison table rather than
23 acceptance levels.

24 MR. CALOGERO: Right. They have to be referred to
25 as acceptance levels in the standard document, and that is

1 why I am jumping back and forth between those two terms.

2 DR. SUGAR: But that makes them more than they are
3 I think.

4 MS. ROGERS: Yes, for the U.S. it is not a correct
5 term but since in Europe they won't have a particular
6 regulatory body reviewing every single study, they have to
7 have an acceptance level. It is a little different. They
8 don't have quite the regulatory arm to look it over. So in
9 the United States they haven't really been acceptance
10 levels. They have been more of a comparison.

11 MR. CALOGERO: To move on to the next change that
12 was made in the grid, hyphema was removed from the levels in
13 the grid. Hyphema had a cumulative rate of 5 percent with
14 anterior chamber and 1 percent with posterior chamber
15 lenses, and it was removed because it was felt that the
16 hyphema complication rate is generally almost always
17 dependent on the surgical procedure, and it is not really
18 related with modern lenses to the actual device. As a
19 result, it was deleted. Does anyone have any comments on
20 that deletion?

21 DR. MACRAE: I guess that the hyphema
22 complications that we see now basically are not considered
23 associated, for the most part, with a bad outcome. So it
24 would be reasonable to take those out. Most of the hyphemas
25 that are seen now are basically bleeding along the limbal

1 blood vessels or in the tunnel of the wound, and that
2 basically is the result of a blood vessel that is leaking
3 and somehow it gets retrograde into the eye. Those types of
4 bleeding episodes are not associated with a bad outcome. So
5 I think most of the Panel members would probably be
6 comfortable with excluding hyphema at this point.

7 MR. CALOGERO: Okay, fine. Thank you.

8 DR. SERDAREVIC: Are you going to be saying some
9 other things that you are going to exclude, because in
10 relation with the hyphema I just wanted to mention that you
11 are removing hyphema because it is related to surgical
12 technique --

13 MR. CALOGERO: Right.

14 DR. SERDAREVIC: -- then you ought to consider
15 removing retinal detachment for that same reason.

16 MR. CALOGERO: Okay. So with modern lenses
17 retinal detachment is really never associated with the lens?

18 DR. SERDAREVIC: I think one thing that should be
19 on this list is posterior capsular opacification, which is
20 not on the list.

21 MR. CALOGERO: Yes, you are right.

22 DR. SERDAREVIC: And where you would have an
23 increased risk of retinal detachment would be either
24 surgical technique or if there is an increased incidence of
25 posterior capsular opacification. So I think you cover the

1 retinal detachment with posterior capsular and you leave out
2 the fact of due to surgical technique.

3 MR. CALOGERO: Okay. That is certainly a valuable
4 comment. In terms of adding a complication, the
5 opacification, is there any guidance? Are there any
6 literature articles that would give us a sense of rate that
7 we could compare to?

8 DR. SERDAREVIC: Well, certainly we were comparing
9 that when we were going over the literature as far as just
10 the last Panel meeting, in May, when we were looking at some
11 posterior capsular opacification rates, and I was thinking
12 why shouldn't we have this in the grid and, in point of
13 fact, there are articles in the literature where you could
14 go and get that information.

15 DR. DOUGHMAN: It has just been published in the
16 cataract guidelines and there is literature that talks about
17 it. There are certainly significant comparisons.

18 DR. SERDAREVIC: They are very valuable. There is
19 no question. It depends on the study but I think with the
20 background of the cataract guideline studies you can
21 certainly come up with some figure that you would consider
22 acceptable.

23 MR. CALOGERO: Okay, fine.

24 DR. DOUGHMAN: It is time related, of course. It
25 increases with time.

1 MR. CALOGERO: Right. Okay, well, that is
2 certainly valuable information.

3 DR. MACRAE: I would just like to say that I would
4 still like to see retinal detachment stay in the grid. It
5 may not be related to the particular lens implant, but it is
6 helpful in getting an overview of the surgical technique and
7 the clinical environment of the patients who are exposed.

8 MR. CALOGERO: Okay. The next complication that
9 we have removed from the grid is acute corneal
10 decompensation. There were large problems in terms of
11 essentially defining what this complication is, and it was
12 felt that if this is truly acute corneal decompensation, it
13 is occurring very rapidly, within a period of days, say,
14 after implantation, it is something that is really not seen
15 with modern lenses. So we didn't know if it actually was
16 that or if it was essentially a late onset of corneal
17 decompensation which just happened to occur a year or two
18 years out, where the patient came in one week and had a
19 clear cornea and then the next week it decompensated and it
20 could have been a long-term lingering inflammation process
21 that was subclinical and then suddenly the cornea couldn't
22 tolerate it any more.

23 So we ran into a definition problem with this, and
24 I think it was finally concluded that if this was, in fact,
25 acute corneal decompensation, something occurring very

1 rapidly in relation to the IOL, it is something that you
2 don't see anymore with modern lenses and, as such, it was
3 removed and the actual complication of corneal
4 decompensation was retained, but basically the European
5 ophthalmologists in my project group really saw no
6 definition difference between corneal decompensation and
7 corneal edema or persistent corneal edema. So as a result,
8 as you see in this Annex A listed under corneal
9 decompensation, what they have done is they have taken the
10 rate that we have in our grid for persistent corneal edema
11 and they now call persistent corneal edema corneal
12 decompensation.

13 Now, is this acceptable to the Panel members, what
14 has occurred in terms of this?

15 DR. DOUGHMAN: I think that is acceptable. It
16 makes more sense. The acute corneal edema is often due to a
17 surgical technique, not having anything to do with the lens.

18 MR. CALOGERO: Okay, fine.

19 DR. MACRAE: The term basically picks up
20 everything. (Inaudible).

21 MR. CALOGERO: Another change that was made to the
22 form was that intraocular infection was combined under
23 endophthalmitis because they were felt to be equivalent and
24 they additionally had the same complication rate. Is there
25 any problem with just having endophthalmitis listed?

1 Then secondary glaucoma was changed to raised
2 intraocular pressure requiring treatment -- persistent.
3 Does anyone have any problems with that change?

4 DR. DOUGHMAN: There you get into a definition
5 issue though. What is persistent and what is raised
6 intraocular pressure? Is that in the mind of the surgeon or
7 is that defined in the grid?

8 MR. CALOGERO: It is not defined any place in the
9 document. It is left up to the surgeon.

10 DR. DOUGHMAN: That is fine.

11 MS. BROGDON: The understanding that we have had
12 here in our grid is that persistent, by definition, means it
13 is occurring at one year.

14 DR. DOUGHMAN: Well, you could have had
15 significant damage for nine months and not started treating
16 until that time, and it would be elevated at one year but
17 too late to treat. So you are only counting any treatment
18 at one year as significant elevation if it didn't happen
19 before that time, or if it happened for nine months they
20 lost vision and that was the end of it. I mean this is
21 outside the realm of probability but it does occur.

22 MS. BROGDON: Maybe what is needed is a definition
23 of the term "persistent."

24 DR. DOUGHMAN: I would agree.

25 MR. CALOGERO: Okay, those are the major changes

1 to the grid. There were changes to the actual reporting
2 forms.

3 DR. STULTING: I have some more questions about
4 the grid, if you are ready.

5 MR. CALOGERO: Oh, yes.

6 DR. STULTING: It has been a while since I
7 reviewed an IOL application but, as I recall, when patients
8 had a secondary intervention involving removal of the
9 implant they were no longer carried in the calculation
10 beyond the point at which the implant was removed. Correct?

11 So every time I reviewed one of these applications
12 and wanted to figure out how many lens dislocations there
13 were, I had to go back and count up lens dislocations from
14 the pupil. Then I had to go down and count up secondary
15 surgical interventions, including suturing, removal for
16 corneal touch and some of the IOL replacements, in order to
17 figure out what the real incidence of dislocations of the
18 implant were.

19 I would suggest that the actual mechanism by which
20 they are calculated and reported be changed so that when a
21 patient has removal of an implant the complication is
22 carried as a persistent complication even though he has been
23 removed from the study, so that there is a reasonable basis
24 for comparing one-year results with all the lenses.

25 Otherwise, you selectively remove people with bad results

1 from the one-year calculations.

2 MR. CALOGERO: Right. Okay, if that is not
3 covered in the ISO/CEN document, then I will certainly make
4 that recommendation. I was told it is covered. All
5 patients in the document have to be accounted for and have
6 to be included in the final calculations.

7 DR. STULTING: I may be wrong but I know that I
8 have done that calculation over and over again to get the
9 real data for how many people had dislocations.

10 MS. BROGDON: Are you speaking of dislocations or
11 all of the removals for various causes, including
12 dislocations?

13 DR. STULTING: Correct me if I am wrong, but I
14 believe when a lens is removed they are no longer counted in
15 the numerator and denominator for subsequent reporting
16 periods.

17 MS. BROGDON: I am not sure but I do recall we had
18 trouble counting all the explantations.

19 DR. STULTING: Right. I think you need whatever
20 mechanism is required so that at the one-year reporting
21 interval you can include everybody who has had any
22 complication, especially those who have had lenses removed.
23 I don't think those people are now included in the
24 reporting.

25 MS. ROGERS: They are removed.

1 DR. STULTING: They are removed? Correct? Well,
2 I don't think that is a good idea.

3 DR. MACRAE: Those patients are not included in
4 terms of visual acuity.

5 DR. STULTING: They are removed from the study.

6 MS. ROGERS: That is correct.

7 DR. MACRAE: That is bad.

8 MS. ROGERS: We usually will have a worst case
9 analysis, which would capture the people who had their lens
10 removed. But when you are talking about the cohort, they
11 are removed.

12 DR. STULTING: Right.

13 DR. MACRAE: It seems like even in the best case
14 analysis (inaudible).

15 MS. ROGERS: The point is well taken and we will
16 go back at this point. But one of the things to keep in
17 mind is that we do monitor the overall loss to follow-up
18 rate. We make sure that we are not removing such a
19 significant portion that it is going to affect, you know,
20 the good data that you are looking at.

21 DR. STULTING: But it is very misleading, and
22 those data are what really gets translated to the labeling.

23 MS. ROGERS: That is right.

24 DR. STULTING: So if you look at the package
25 insert from lenses that have had lots of dislocations, if

1 the dislocations were removals then the dislocation rate
2 numbers in the labeling are very misleading. They are the
3 same numbers that we see in the PMA and I don't think that
4 is the way they ought to be reported.

5 DR. LYNDAHL: If I may comment on that --

6 DR. BROWN: Would you introduce yourself?

7 DR. LYNDAHL: My name is Eva Lyndahl, and I am a
8 Swedish ophthalmologist. I am the Swedish representative in
9 the ISO/CEN group and I have been involved in this
10 standardization effort.

11 There is a big difference between the way that the
12 FDA currently is evaluating data and the proposed way in
13 this document. That is, we are evaluating all patients that
14 are included in the study at any time point. So we are not
15 leaving anyone out at any point. So if they have had a lens
16 removed, that patient will still be in the study all through
17 and it will show up in the complication rates at any time
18 point. That is in accordance with the general rules for
19 conducting clinical trials in drugs, devices or anything.
20 So that has been taken care of.

21 DR. STULTING: Good. I have one more question.
22 That is, loop amputation for corneal touch. I don't believe
23 I have ever seen one of those happen in any of the
24 submissions. Are we going to leave that in there or is that
25 one of the things that is going to be out? You are throwing

1 things out; maybe that is something.

2 MS. ROGERS: Apparently, at one point when the
3 articles were being read, there must have been one of those
4 that occurred.

5 DR. STULTING: I am not familiar with the
6 procedure nor exactly what it would do, nor have I ever seen
7 or hear tell of one. If you have to take out a loop,
8 generally you take the lens out.

9 MR. CALOGERO: Okay. The one last item here was
10 changes that were made to reporting forms. The
11 postoperative reporting forms were updated --

12 DR. MACRAE: Don?

13 MR. CALOGERO: Yes?

14 DR. MACRAE: A couple of questions on the grid.
15 For the anterior chamber lens group, the corneal transplant
16 rate of 1 percent is pretty good.

17 MR. CALOGERO: It is one year.

18 DR. MACRAE: (Inaudible).

19 DR. STULTING: I have another general question.
20 Are we still going to use the numbers generated back in '83?
21 Are we still going to use those numbers as comparisons or
22 are we going to use more realistic numbers?

23 MR. CALOGERO: At this point, this is all we have
24 in the document. There has been a proposal from the English
25 delegation to update those values, and they have recently

1 completed a cataract patient survey in Great Britain on
2 about 1500 subjects and they have published the data. I
3 recently got the article and I am comparing the rates that
4 they have with their modern surgical procedure results with
5 the results in the grid, and that is going to be an item of
6 discussion at the next meeting, perhaps updating some or all
7 of the complication rates. Would the Panel members be in
8 favor of doing that if more recent data could be acquired?

9 DR. MACRAE: Yes.

10 DR. STULTING: Yes, I think these numbers are
11 outdated, and with current lenses this is really the minimal
12 performance and most of them perform better than this.

13 DR. MACRAE: Nancy, isn't Dave Worthen's data on
14 the modified grid available as well? Dave Worthen, a number
15 of years ago, looked at the complication rates and also
16 visual acuity, about four or five years ago.

17 MS. BROGDON: The grid that we have been using is
18 based on the Stark article. Dr. Worthen did some specific
19 analyses but I don't think that they were complete enough to
20 be called a grid.

21 DR. MACRAE: I know he had visual acuity data.

22 MS BROGDON: For what kind of lenses?

23 DR. MACRAE: For posterior chamber and anterior
24 chamber lenses.

25 MS. BROGDON: Is that when you were looking at

1 form 4 versus form 6?

2 DR. MACRAE: I don't recall.

3 MS. BROGDON: All we can say is that the Stark et
4 al. data is what we are currently using.

5 MS. ROGERS: Dr. Stulting, you had said that you
6 would want the data to be updated because you would consider
7 this to be sort of the minimally acceptable values. Does
8 that apply for anterior chamber lenses as well, that
9 statement?

10 DR. STULTING: Yes, I think so. We have had at
11 least one application that I can remember that has come
12 through for an anterior chamber lens that I think had
13 significantly better performance than perhaps the grid here.
14 I am not real sure exactly what the numbers are but, yes, I
15 think they all ought to be updated.

16 DR. DOUGHMAN: I think they need to be updated.
17 There are data coming out all the time. Claims are being
18 made also all the time about the complication rates, trying
19 to favor a certain lens or technique. I think it would be
20 very helpful to the Panel, realizing that the data aren't
21 always very accurate. For instance, right now there is
22 (inaudible) hospitals comparing anterior and posterior
23 chamber lenses in certain situations and they are going to
24 have a lot of prospective data on anterior chamber lenses in
25 that particular model.

1 MS. CALOGERO: Okay, thank you. We will certainly
2 look, for the purposes of this document anyway, into
3 updating the grid levels in the ISO/CEN document.

4 Then one other major last topic was the change in
5 the reporting forms. Those revised reporting forms were
6 included under Attachment number 5. Dr. Lavell (phonetic)
7 had done most of the work with the other ophthalmologists in
8 the group in terms of revising and updating those reporting
9 forms.

10 Included in this package is Dr. Lavell's letter --
11 if I can find it -- and it describes the changes that were
12 made to the preop. and operative reporting forms. I don't
13 exactly know how to handle it. There were a lot of minor
14 changes that were made to the forms to update them. Do you
15 want us to go through each of the changes that were made, or
16 do you want to simply skim through the letter and let me
17 know if you have any problems with any changes that were
18 made?

19 DR. SUGAR: In reading this previously, I
20 disagreed on page 4, paragraph 3 that fistular blebs are
21 only as a result of glaucoma filtering surgery and if they
22 were inadvertent blebs they would be detected as wound
23 leaks. That may be a definitional thing but, certainly
24 inadvertent filtering blebs occur where there may not be a
25 wound leak in the sense that some people would define as low

1 pressure and so forth.

2 DR. LYNDAHL: What we have seen there is a problem
3 because it is reported as fistular blebs and then you
4 realize that the patient has undergone glaucoma surgery, and
5 then you don't know if it is a complication or if it really
6 should be there. So that is why I suggested that we would
7 take it out.

8 DR. SUGAR: It is also unlikely to be related to
9 the implant surgical technique.

10 MR. CALOGERO: In this document it says that a
11 non-constrict pupil was removed but, in actuality it was put
12 back because someone felt strongly that it is potentially a
13 complication with modern lenses. Is it possible to get
14 Panel members' feedback as to whether or not they think that
15 non-constrict pupils should remain on the form, or is that
16 simply a complication of lenses years ago? Is that
17 associated with PC or AC lenses?

18 DR. SUGAR: Yes, as fixed eyelid pupils. There is
19 a series published by Beck in the literature and it occurs.
20 It is not clear at all what it is related to though in the
21 case reports in that one series. Whether it is related to
22 the implant or whether it is related to the elevated
23 intraocular pressure after surgery, inflammation or
24 sphincter damage and so forth is not clear.

25 DR. LYNDAHL: Do you feel that it is important to

1 keep in the reporting forms and register it in every case?
2 Or do you think it is likely that we would catch it under
3 the other complications? There is a line for "other"
4 complications for those very unusual things.

5 DR. SUGAR: Open-ended questions tend not to be
6 answered.

7 DR. LYNDAHL: That is true.

8 DR. SUGAR: So if it is significant, it should be
9 a forced choice question but it probably is uncommon enough
10 so that it is not worth (inaudible).

11 MS. BROGDON: Dr. Sugar, if there were a posterior
12 chamber lens that was a disc lens that was fairly large,
13 would that be more likely to cause this complication?

14 DR. SUGAR: I don't think anybody knows that. It
15 can be a significant complication if you have small disc
16 lenses or small haptic lenses. It can be maybe of
17 significance in terms of glare, in terms of multifocal
18 lenses, in terms of getting the effect that you would like
19 for pupil constriction for some zone, and so forth. It may
20 be important but it is a fairly rare complication and
21 probably not directly caused by the lens.

22 DR. LYNDAHL: Can I ask you one more question? We
23 have had a problem about lens dislocation. It is a semantic
24 problem, and being an international group trying to
25 standardize this, we have had problems. Within the forms

1 there has been lens dislocation, lens malposition and lens
2 decentration. In the grid the term was lens dislocation.
3 Then we decided to clarify that and call it lens dislocation
4 from the pupil, and I just want to know if that is what was
5 meant in the grid, is that when the optic has actually left
6 the pupillary area? Is that what the old grid value
7 reflects?

8 DR. STULTING: That was one of the problems in
9 evaluating the PMAs, that the definition was not
10 standardized.

11 DR. LYNDAHL: No. We sometimes get lenses that
12 are decentered 0.5 mm registered as dislocated, and then we
13 end up with a very high number.

14 DR. STULTING: I might offer a suggestion that
15 what is important is the frequency with which the lens is
16 sufficiently far from its normal location to either cause
17 visual symptoms or to necessitate removal. So I think those
18 are the things that we need not to miss and the definitions
19 need to be designed so that those cases are all captured.

20 DR. MACRAE: In the 1983 grid, I think when
21 someone reported lens dislocation they were reporting a lens
22 dislocation. The dislocations were much more dramatic than
23 we tend to see now. So we are dealing with two different
24 types of problems and maybe we should have two categories so
25 that it clarifies it, one for dislocation of lenses that are

1 actually unstable, and the other for decentration where the
2 lens is not centered optically.

3 DR. LYNDAHL: If we can find some good, reliable
4 data to compare with. But we have decided to use the old
5 grid value that is called lens dislocation. We are using
6 that for dislocation from the pupillary area. I just wanted
7 to make sure that we are talking about the same thing. But
8 we are also registering lens decentration on the new forms,
9 and trying to say how much it is decentered.

10 DR. MACRAE: That would be helpful in terms of
11 multifocal lenses.

12 DR. LYNDAHL: Yes.

13 DR. SERDAREVIC: One other question regarding
14 that, it seems as though there are really three categories.
15 There is dislocation, decentration and there is also the
16 tilt factor. So perhaps one could combine the tilt and
17 decentration because those affect more the actual visual
18 outcome as opposed to a major problem that requires surgical
19 intervention, such as dislocation.

20 MR. CALOGERO: So it would be acceptable to use
21 the grid value for dislocation, whereas decentration and
22 tilt is probably going to be much higher then.

23 DR. STULTING: But, again, the grid rate is not
24 reliable because the grid is derived from PMAs that remove
25 patients from the analysis when they have their lenses

1 removed. So these rates for decentration and dislocation do
2 not reflect the actual data.

3 DR. LYNDAHL: Do you suggest that we remove the
4 grid value for dislocation?

5 DR. STULTING: No, I am not suggesting that you
6 remove the value. I am just saying that if you are
7 searching for a number to use as a performance standard you
8 can't get it from the grid because the numbers in the grid
9 have those patients who had severe dislocations removed from
10 the study before form 6.

11 DR. LYNDAHL: That is true. So it may be that
12 that value is not really reliable. So we should not refer
13 to it. I mean we are going to have much, much lower
14 incidences.

15 DR. STULTING: Yes, it is unreliable for a number
16 of reasons. One of those Scott referred to. Back in the
17 '80s, when you talked about a dislocated lens it meant it
18 was in the anterior chamber in the vitreous, and we don't
19 see that very much. So the definition is different.

20 Furthermore, the persistent rates are skewed by
21 the fact that patients who had severe dislocations are not
22 included in the analysis at those late time points.

23 DR. SERDAREVIC: But some of those might be useful
24 though when we are looking at intraocular lenses that are
25 used for refractive purposes, such as the anterior chamber

1 lenses. I am particularly thinking of the anterior chamber
2 IOLs for myopia where, when you have dislocation, you will
3 then have secondary problems sometimes and that is a
4 dislocation that is unrelated to tilt and decentration. So
5 I think dislocation should be a separate category but we
6 just should find better values for it.

7 MR. CALOGERO: I assume there are no other
8 comments on the reporting forms. Then I just have two other
9 questions for the Panel members. The change in optic size
10 that FDA has historically had as a Tier I modification was
11 between 5.5 and 7.5 mm. I am thinking in terms of updating
12 that. We haven't really seen a 7.5 mm optic in a very long
13 time and my question is are they currently used? Is it
14 reasonable to have 7.5 mm optics still as a modification of
15 the parent lens?

16 DR. SERDAREVIC: Well, certainly for several
17 procedures we certainly like having as large an optic as
18 possible so that in terms of what a company might want to
19 do, I mean, I don't see -- and I certainly would want to
20 keep 7; I don't know about 7.5. But it is not as though we
21 want to get rid of large optics because, you know, there are
22 indications --

23 MR. CALOGERO: Exactly, there is a large number of
24 lenses that are 7 mm optic size.

25 DR. SERDAREVIC: So you are asking about 7.5?

1 MR. CALOGERO: But 7.5, does anyone have 7.5 mm?

2 DR. STULTING: No, but I don't see too much
3 concern raised by it. You have other performance standards
4 for overall length and I am having trouble conceiving a
5 major risk from having an optics of 7.5 mm. There are risks
6 for having smaller ones, including 5 mm, but I see no major
7 risks for 7.5.

8 MR. CALOGERO: Okay. Then the last question I
9 have deals with the Tier A modifications for clinical
10 studies. What I mean to say is that currently we have
11 clinical investigations where a company may combine the
12 parent model and a Tier A modification of that model in the
13 same clinical study. We have come across instances where a
14 company will have a Tier A modification of the parent model
15 in a 500-subject clinical study and that Tier modified lens
16 will only have one subject. But by the definitions and all
17 the rules that we have, that modified lens with one subject
18 now becomes a clinical parent that they can modify other
19 lenses off.

20 That really doesn't seem -- it has only occurred
21 once so it really doesn't seem reasonable and I was going to
22 make a proposal that that be changed in the ISO/CEN document
23 and also the FDA that for any Tier A modified lens in a
24 clinical study, it has to have a minimum level of perhaps 20
25 or 30 subjects so a sponsor can perform a statistical

1 analysis between the performance of the modified lens and
2 the general parent population.

3 That was my final comment. Thank you very much
4 for your comments on these documents.

5 MS. ROGERS: I think we have done a good job of
6 getting the Panel back on track with the agenda. We should
7 be back on the regular time.

8 (Laughter)

9 But I would like to open the floor to the
10 audience, if they are still awake, if they would like to
11 make any comments that we could either carry with us to the
12 November meeting or to the Panel.

13 MS. GARVEY: I am Patricia Garvey, from Allergan
14 Medical Optics, and I have a question for Dr. Lyndahl. It
15 really concerns the presentation of the results after a
16 clinical investigation. On page 8, number 6, it talks about
17 the data analysis shall include a statistical analysis
18 comparing the results from the clinically evaluated IOL at
19 the final reporting form to the acceptable IOL clinical
20 performance data contained in Annex A, which is basically
21 the grid.

22 However, you made a statement earlier on that you
23 would be collecting the data on all 300 patients and you
24 would present all of the data in the final report, and I
25 don't understand how that would work if you are going to do

1 a one-year analysis only.

2 DR. LYNDAHL: The idea is to include enough
3 patients --

4 DR. BROWN: Once again, identify yourself please.

5 DR. LYNDAHL: I am Eva Lyndahl, from Sweden.

6 DR. BROWN: Thank you.

7 DR. LYNDAHL: The idea is to include enough
8 patients to have 300 patients left at 1 year, or 3 years if
9 it is a 3-year study, and actually to have enough patients
10 also to allow for the occasional missing visit because we
11 know that when we do clinical trials we can never get every
12 patient back at every scheduled visit. There will be a few
13 visits that are missing. But we have said that we want to
14 see at least 300 patients reported from each of these
15 visits. So if we want to see 300 patients at 1 year, we
16 need to include 390 and then we believe we will have 300
17 forms at each of the visits.

18 MS. GARVEY: But there is no mechanism for interim
19 reporting analyses. Is that correct? So you don't have any
20 interim results presented within the technical dossier, for
21 example. Those data will be available to the firm but there
22 will be no final presentation of those results. Am I making
23 myself clear?

24 MR. CALOGERO: What you are saying then is you
25 would have a core study rather than a cohort study, which is

1 differently associated with IOLs. I think the feeling was
2 that clinical studies typically don't have cohort
3 populations. Typically, the subjects are followed at each
4 reporting form. We wanted to make the clinical study more
5 in alignment with other clinical studies that are in
6 existence today and, additionally, to have the 300 subjects
7 at each reporting form is useful because in the document it
8 allows for a company to make an analysis as to whether or
9 not a complication is device related, and by having more
10 powerful clinical data at each of the reporting forms, it
11 was felt that it would be easier to discern whether or not a
12 complication was truly device related. I think those were
13 the two rationales that were used to move away from the
14 cohort study with this clinical investigation and go to a
15 true core study.

16 DR. BROWN: Don Calogero is going to the back to
17 talk to Dr. Walter Sloane, our in-house ophthalmologist.
18 Dr. Sloane is incapacitated. He broke an ankle, I
19 understand, probably playing football. I am only joking,
20 Walter, and trying to fill in the interim of time --

21 (Laughter)

22 MR. CALOGERO: Walter just had a minor question
23 which we will address at a later date. Are there any other
24 questions from the audience?

25 DR. BROWN: Is that the end of your presentation?

1 MR. CALOGERO: Yes.

2 DR. BROWN: Thank you very much.

3 MR. CALOGERO: You are welcome.

4 DR. BROWN: As Donna has said, we are finally
5 caught up with our time schedule on our agenda. However, we
6 are still off about 35 minutes but let's go ahead and take a
7 coffee break at this time. Come back, please at 3:15.

8 (Brief recess)

9 DR. BROWN: I think we need to get started. We
10 have a couple of Panel members that are taking care of
11 business on the telephone, and Dr. Wilkinson had to leave
12 early, going back to Baltimore. He had a call that required
13 him to go back. I would like Dr. Harris then to continue as
14 Chairperson to get us started in the afternoon. Could you
15 again open us up?

16 DR. HARRIS: Thank you, Dr. Brown. This
17 afternoon, Mr. Dave Whipple, the Associate Director of
18 Contact Lens Devices, will give an overview of the topics
19 that will be discussed in the contact lens section
20 presentation. I would like Dave to make his introductory
21 remarks.

22 DR. WHIPPLE: Thank you, Dr. Harris.

23 DR. BROWN: Dave, get closer to the mike please.

24 DR. WHIPPLE: All right. I am sure you will be
25 glad to know that we have a fairly short contact lens

1 presentation today. We have no PMAs to discuss but we do
2 have several key announcements that we would like to make.

3 The first one involves an issue that I have been
4 dealing with for about ten years, and kind of waiting ten
5 years to make this announcement. It deals with the issue of
6 reclassification of contact lenses. The issue of
7 reclassification of contact lenses has had a long history
8 within the Agency and is about to begin a new chapter.

9 Just to refresh our memories, in 1976 when medical
10 device regulations were enacted, soft hydrophilic and rigid
11 gas permeable contact lenses were considered to be
12 traditional devices and were automatically regulated as
13 Class III, subject to premarket approval.

14 In the early 1980s, the Contact Lens Manufacturers
15 Association petitioned FDA for reclassification of contact
16 lenses. The Agency and the Ophthalmic Devices Panel at that
17 time fully supported reclassification of contact lenses.
18 However, the Agency's attempt to reclassify the lenses was
19 unsuccessful due, in large part, to the fact that the key
20 data that were needed to support reclassification were
21 contained in PMAs and were not publicly available for use.
22 Despite this unsuccessful attempt, the Agency and the Panel
23 maintained its belief that contact lenses should be
24 reclassified.

25 During the mid to late 1980s, the Agency had an

1 ongoing program to streamline the PMA process for contact
2 lenses whenever it was consistent with the protection of
3 public health. Numerous policies and procedures, including
4 our 1989 guidance document for Class III contact lenses,
5 were developed during this time to minimize the regulatory
6 burdens placed on manufacturers of Class III lenses, and
7 laid the groundwork for any future reclassification.

8 When the Safe Medical Device Amendments Act was
9 passed in November, 1990 Congress included a specific
10 requirement that was in three years from the date of the Act
11 FDA would reclassify daily wear plastic contact lenses into
12 Class II, unless the Agency could justify keeping them in
13 Class III.

14 During these past three years, the Agency and this
15 Panel continued their support for reclassification. Indeed,
16 the Agency made no attempt under SMDA-90 to argue for
17 continued regulation as a Class III device. Instead, the
18 Agency has been working behind the scenes during this time
19 to identify the special controls mandated by SMDA-90 that
20 must be in place at the time of any reclassification.

21 Congress asked that these special controls be in
22 place to ensure continued safety and effectiveness of daily
23 wear contact lenses when regulated as a Class II device.
24 The Agency has also invested time and resources in
25 evaluating the potential for including extended wear contact

1 lenses and all lens care products within the
2 reclassification effort.

3 Having considered all options, I would like to
4 announce at this time that the Agency will issue an order
5 reclassifying Class III transitional daily wear hydrophilic
6 and non-hydrophilic plastic contact lenses into Class II, as
7 outlined in SMDA-90. The effective date for
8 reclassification will be the date the order is to be
9 published in the Federal Register, which will be November 28
10 of this year.

11 This order applies only to daily wear contact
12 lenses. It does not include extended wear contact lenses
13 nor lens care products, which will remain in Class III for
14 the time being.

15 Regarding extended wear contact lenses, there are
16 issues that remain with these lenses at this time. The
17 Agency is in the process of reevaluating information on the
18 safety and effectiveness of these lenses. In addition,
19 criteria are changing for clinical studies involving
20 extended wear contact lenses. Until these and other issues
21 have been resolved, and sufficient special controls
22 identified and established, the Agency believes the safety
23 and effectiveness of extended wear lenses should continue to
24 be evaluated through the PMA process.

25 Regarding lens care products, it is the Agency's

1 intent to initiate a reclassification of these devices as
2 soon as possible following the reclassification of daily
3 wear lenses. It is important to note that the
4 administrative process for reclassifying lens care products
5 will differ from those involving daily wear lenses because
6 lens care products were not included as part of SMDA-90.

7 A notice of intent to reclassify lens care
8 products will be published in the Federal Register and will
9 outline the process, and the data needed to support a
10 reclassification of these accessory devices.

11 Regarding special controls mandated by SMDA-90,
12 the reclassification order will also include a notice of
13 availability of a draft 510(k) guidance document for Class
14 II contact lenses. This comprehensive guidance document,
15 prepared by the contact lens branches, will outline the
16 minimum necessary information and data needed for submission
17 of a 510(k) for daily wear lenses. The document outlines
18 data requirements recommending testing involving chemistry,
19 manufacturing, toxicology, microbiology, clinical studies
20 and a fill-in-the-blanks type labeling section in that
21 document.

22 In addition, this document includes a section on
23 modifications requiring submission of a new 510(k),
24 procedures for adding finishing laboratories for rigid gas
25 permeable lens manufacturers, procedures for adding color

1 additives, and procedures for making packaging changes for
2 lenses.

3 This guidance document is currently circulating
4 within CDRH for review and comment. We will be sending
5 copies of this document to Panel members within the next
6 week or so. This document will be available at the time
7 that the reclassification order is issued or earlier, if
8 possible, and can be used by applicants for submission of
9 510(k)s. Interested persons can obtain copies of this
10 guidance document from our Division of Small Manufacturers
11 Assistance, and I urge you to check with this office on or
12 after November 15 regarding the availability of the guidance
13 document.

14 FDA realizes, however, that there may be
15 substantive comments regarding the content of this guidance.
16 Therefore, it will be considered a living document, open for
17 comment and revisions as we proceed with the transition
18 phase of reclassification of lenses.

19 It is anticipated that a discussion of this draft
20 guidance will occur at the February, 1994 Ophthalmic Devices
21 Panel meeting. Comments on this document should be sent to
22 my attention as soon as possible so they can be evaluated
23 prior to the February meeting.

24 Regarding the transition phase during
25 reclassification, it should come as no surprise that there

1 are administrative complexities associated with this
2 reclassification. Therefore, we have included in the order
3 a section on the transitional issues surrounding daily wear
4 lens reclassification. This section will describe processes
5 and procedures for how to handle PMAs currently under review
6 in-house involving daily wear lenses. These PMAs will have
7 to go through administrative procedures to be either
8 converted to 510(k)s, withdrawn or resubmitted as 510(k)s,
9 depending on the circumstances involved.

10 These issues will be more completely addressed in
11 the FR notice, and I urge manufacturers with pending PMAs
12 involving daily wear lenses to read this section carefully
13 as we intend to make you active participants in this
14 process.

15 In closing, I am sure we all recognize that this
16 transitional phase will be challenging and complex, but we
17 have waited a long time for reclassification to occur. I
18 hope we can all work together, be patient and understanding
19 as we enter a new phase in the regulation of contact lenses.
20 Thank you.

21 DR. HARRIS: Thank you, Dave. Are there questions
22 or comments from the Panel? If not, I will ask you to
23 continue with the next topic, please.

24 DR. WHIPPLE: All right. At this time, I would
25 like to introduce Jim Saviola who has several key

1 presentations to make as well. Dr. Saviola?

2 DR. SAVIOLA: Thank you, Dave. I am going to
3 discuss two different topics this afternoon. The first is
4 an update on extended wear lens, the RAISE Project, the
5 reanalysis of information on safety and effectiveness. Then
6 I will follow with a presentation on a policy development
7 regarding monovision fitting technique to be added to the
8 contact lens labeling.

9 Regarding the first topic, the extended wear lens
10 and the RAISE report, as you have just heard, the
11 reclassification will include daily wear contact lenses
12 only. Extended wear contact lenses will remain in Class
13 III.

14 At the February Ophthalmic Devices Panel, we
15 presented an update on the RAISE report regarding extended
16 wear lenses. Since that time, we have circulated the report
17 to the Panel members for their comment and their input, and
18 I would like to thank them for their comments at this time.

19 After receiving a number of specific comments, the
20 RAISE group reconvened to discuss them and to redraft the
21 final report. The re-edited report is currently going
22 through a final review internally before it will be sent to
23 Dr. Burlington.

24 At this point, I realize that many people are
25 probably getting impatient and are wondering what type of

1 action the Center may take regarding extended wear. I can
2 only say that the recommendations to the Center Director
3 will be consistent with the types of actions which the
4 Center is either considering or involved in for other
5 prescription devices.

6 The idea that certain devices have a degree of
7 risk and that the persons who use those devices should be
8 informed and have an understanding of the risk applies to
9 extended wear contact lenses as much as it does to other
10 devices, and we hope to be able to provide you with some
11 more detailed information later on on this topic.

12 Does anybody have any specific questions about
13 RAISE at this time?

14 DR. BOUCHER: Do you have a timetable?

15 DR. SAVIOLA: Well, we certainly hoped to be able
16 to have something more definitive to present at this
17 meeting. It is kind of difficult. As you know, we have
18 been working on this project for over a year and when we
19 presented this in February we thought we would have
20 something to say at this October meeting. I could be
21 optimistic and say I would expect to have something within a
22 month, or I could be more realistic and say that at the
23 February meeting we could probably be specific.

24 DR. HARRIS: Any other questions or comments on
25 this topic?

1 (No response)

2 DR. SAVIOLA: All right, thank you. I will now
3 provide background information and report on a policy being
4 developed for contact lens manufacturers to include a
5 monovision fitting technique in the contact lens labeling.

6 The first thing to address is why we are involved
7 in this activity with so many things currently going on. I
8 can imagine that some people are wondering don't we have
9 enough to do with all the reclassification activities and
10 guideline development? Well, I have to admit that I,
11 myself, ask that question sometimes too.

12 However, the Contact Lens Branch was approached by
13 a firm which requested a PMA supplement to add the
14 monovision fitting technique to the labeling of a single-
15 vision contact lens to manage presbyopic patients. That
16 supplement has subsequently been approved, but there were a
17 number of issues which developed and needed to be addressed
18 during the review. Discussions were held within the
19 Division of Ophthalmic Devices and with the program
20 operations staff of the Office of Device Evaluation as to
21 whether we should even entertain that type of labeling
22 request since it was for a fitting technique.

23 It was determined that we should, indeed, review
24 the application. In addition, the basis for the use of
25 monovision existed in publicly available scientific

1 literature involving clinical studies of single-vision
2 lenses. This technique was not specific to a particular
3 contact lens. Therefore, it was determined that a policy to
4 address this for the entire contact lens industry needed to
5 be developed. This is a generic issue since any single-
6 vision contact lens can be used safely and effectively to
7 manage presbyopia using the mono-vision technique, with the
8 appropriate labeling.

9 We explored this request through consultation with
10 Panel members and obtained input on potential labeling that
11 should be included. Again, I would like to express my
12 thanks and appreciation to the Panel for their work on this
13 issue.

14 It was determined that correction for presbyopia
15 by monovision could not be added to the indications section
16 since no lens design changes were made. In the case of
17 monovision, presbyopia is managed by the prescription of a
18 lens by the eye care practitioner. Presbyopia is not
19 corrected in the same manner as it is with the bifocal
20 contact lens.

21 We anticipate that many or perhaps all
22 manufacturers of single-vision lenses may want to revise
23 their labeling to take advantage of this, and we want to set
24 up a mechanism to efficiently process these applications in
25 a consistent manner, given the fact that the basis for his

1 approval can be found in the publicly available literature.
2 Therefore, we plan to provide holders of PMAs for single-
3 vision contact lenses an opportunity to update their
4 labeling to include the monovision fitting technique for
5 managing presbyopia.

6 We have prepared pertinent sections to be added to
7 contact lens manufacturers' labeling to include this
8 technique. These labeling suggestions were developed by the
9 Division in consultation with the Ophthalmic Devices Panel.

10 Our expectation is that a PMA supplement for this
11 revised labeling will be submitted as a 30-day PMA
12 supplement, as provided under 21 CFR Section 814.39 Subpart
13 (b) (2) of the PMA regs. with some particular provisions:
14 that the supplement does not include any additional changes
15 in the labeling, other than the addition of the suggested
16 language to include the monovision fitting technique; and
17 that no significant deviations are made in the suggested
18 language.

19 Any 30-day PMA supplement that does not meet the
20 final policy requirements would not be filed as a 30-day
21 supplement and, therefore, could not be deemed approved 30
22 days after receipt, as stated in that part of the
23 regulation.

24 Also monovision labeling suggestions will be
25 included in labeling guidance which will be developed for

1 Class II contact lenses.

2 We believe use of these labeling suggestions will
3 provide the contact lens industry with appropriate guidance
4 to ensure consistency and uniformity, presenting eye care
5 practitioners and contact wearers relevant and important
6 information pertaining to monovision.

7 Currently, the final policy is undergoing review
8 in the Office and will be forthcoming. Are there any
9 questions?

10 DR. HARRIS: Any questions for Jim on this issue?
11 Comments?

12 (No response)

13 DR. SAVIOLA: All right. At this time I would
14 like to introduce Dr. Ronda Balham, who will discuss another
15 developing policy in our Division.

16 DR. BALHAM: Thank you, Jim. This afternoon I
17 would like to present to you some background information on
18 a developing policy on the use of saline as a rinse with
19 rigid gas permeable contact lenses.

20 The issue of the use of saline as a rinsing agent
21 for use with rigid gas permeable contact lenses has been
22 discussed by prominent contact lens specialists worldwide,
23 as well as in peer-reviewed journals. This publicly
24 available information discusses the use of saline as a
25 viable option to the use of tap water.

1 The clinical standard for rigid lens care since
2 the very early days of PMMS has included practitioner
3 recommendations for the use of tap water as a rinse during
4 RGP lens cleaning. In fact, the Ophthalmic Devices Panel
5 has reviewed and recommended approval for RGP lens care
6 products which includes the use of tap water as a rinse,
7 after cleaning, prior to the soaking step.

8 It is not our intention to bring into question the
9 safe use of tap water as a rinsing agent with rigid lenses.
10 However, there exists a regulatory anomaly between the
11 current saline product labeling and the recommendations of
12 those practitioners and the desires of those patients who
13 consider a prepared saline to be a preferred alternative to
14 a tap water rinse.

15 It is known that the composition of tap water
16 differs in different parts of the country. It is also known
17 that tap water arising from a well can present patients with
18 a different set of concerns which may lead them on their own
19 to search for an alternative. There is also a concern with
20 the availability of potable fresh water in some foreign
21 countries where RGP patients may travel.

22 Compared to other Class III medical devices that
23 the FDA regulates, salines for use with contact lenses are
24 not life-supporting for that intended use and are certainly
25 not implantable. In fact, the sole reason that this product

1 shares its lofty regulatory status is that it is an
2 accessory to a product which is regulated as a Class III
3 device. Therefore, from a biocompatibility standpoint, it
4 has a rather low risk concern.

5 Over the years, the Agency has gained experience
6 with the use of sterile saline with hydrogel lenses. In
7 most analyses, hydrogel lens exposure to saline can be
8 viewed as the worst case for biocompatibility with RGP
9 lenses.

10 The idea of ocular surface exposure to saline from
11 residual carryover through absorption by the hydrogel lens
12 has been demonstrated to focus primarily on interactions of
13 preservatives in the solutions. However, with the hard,
14 glassy RGP polymers, there is no absorption of saline. Any
15 carryover to the eye is secondary to adsorption or what is
16 intentionally left on the lens surface.

17 In order to reconcile this regulatory anomaly
18 which exists between those who desire an alternative to tap
19 water and the lack of available saline products which are
20 labeled for use with rigid gas permeable lenses, the
21 Division is currently involved in evaluating the currently
22 available data and developing a policy to provide an avenue
23 for saline manufacturers and/or RGP lens manufacturers to
24 obtain approval for the use of saline as a rinsing agent
25 with RGP lenses. The reviewers are considering the issue of

1 focusing on chemistry and compatibility data to support the
2 use. The FDA is aware that certain ingredients present in
3 other RGP contact lens solutions, such as polyvinylalcohol,
4 may interact with ingredients in the saline solution, such
5 as the borate buffers, thereby creating precipitates.

6 At this time we are not prepared to issue a policy
7 since we are still exploring the possible options available.
8 The options being considered include, number one, a 30-day
9 PMA supplement as provided for under 21 CFR 814.39
10 Subsection (e) (2) of the PMA procedural regulation, or
11 number two, inclusion in the sponsor's next annual report,
12 or number three, Tier I labeling reviews requesting use with
13 RGP lenses.

14 At such time as a policy is issued, we plan to
15 provide the types of data, such as chemistry and
16 compatibility, that manufacturers would be required to
17 submit.

18 Finally, we wish to emphasize that it is not our
19 intention to call into question the use of safe tap water as
20 a rinse with rigid gas permeable contact lenses. Our
21 intention is to address labeling inconsistencies between
22 current saline product labeling and the recommendations of
23 eye care practitioners.

24 Are there any questions from the Panel?

25 DR. HARRIS: Any comments or questions?

1 MR. GREEN: Yes, I just have a comment. Since our
2 nation is so heterogeneous and since lens wearers also have
3 languages that are heterogeneous, I wondered if the consumer
4 health and safety information would be bilingual, or even
5 trilingual if possible.

6 DR. BALHAM: That sounds like a very good plan
7 that we will certainly take into consideration. Thank you.

8 DR. HARRIS: Other questions or comments?

9 (No response)

10 Thank you.

11 DR. BALHAM: Thank you.

12 DR. HARRIS: At this time I would like to ask if
13 there are members of the audience who would like to comment
14 on any of the topics presented by the contact lens group.
15 If so, would you please stand at the microphone and state
16 your name? Seeing none, I will turn the meeting back to Dr.
17 Brown.

18 DR. BROWN: I see someone getting up but they are
19 going the wrong way; they are going out the door. So that
20 probably means that the meeting is adjourned at 3:45. Thank
21 you very much.

22 (Whereupon, at 3:45 p.m., the Panel adjourned, to
23 reconvene on Friday, October 29, 1993 at 8:30 a.m.)

C-E-R-T-I-F-I-C-A-T-E

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

Soza Gavrisheff (K)