

FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
OPHTHALMIC DEVICES PANEL

Eighty-Seventh Meeting

(Open Session)

Monday,
January 13, 1997

Grand Ballroom
Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

IN ATTENDANCE:

Voting Panel Members

R. DOYLE STULTING, M.D., Ph.D., Panel Chair
MARK A. BULLIMORE, Ph.D.
EVE J. HIGGINBOTHAM, M.D.
MARIAN S. MACSAI, M.D.
JAMES P. McCULLEY, M.D.
RICHARD S. RUIZ, M.D.
P. SARITA SONI, O.D.
FRANK A. SPELLMAN, M.D., Consultant, deputized to vote
C. PAT WILKINSON, M.D., Consultant, deputized to vote

Non-Voting Panel Members

FREDERICK FERRIS, M.D., Liaison, National Eye Institute
JUDY F. GORDON, D.V.M., Industry Representative
MARK J. MANNIS, M.D., Consultant
ELEANOR McCLELLAND, Ph.D., Consumer Representative
WOODFORD S. VAN METER, M.D., Consultant

Food and Drug Administration Participants

SARA M. THORNTON, Panel Executive Secretary

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P R O C E E D I N G S (9:35 a.m.)

1
2 DR. STULTING: I'd like to call to order this
3 87th meeting of the Ophthalmic Devices Panel and turn the
4 floor over to Sara Thornton for introductory remarks.

5 MS. THORNTON: Good morning, everyone. Welcome
6 to all attendees. Before we proceed to the panel
7 introductions, I would like to note that since our last
8 meeting in July of 1996, we've made a few changes to the
9 panel:

10 The voting member term of Dr. Alexander
11 Brucker, a noted vitreoretinal surgeon, expired in October,
12 and we wish to take this opportunity to publicly thank him
13 for the many hours of review time he's contributed to our
14 panel during his years of service. His commitment to
15 bringing the best thinking to our deliberations will be
16 missed; however, we are happy to report that he will remain
17 on as a consultant to the panel.

18 Dr. Richard Abbott, a corneal and refractive
19 surgeon and valued voting member, was unable to continue
20 after only a short term. We wish to thank him also for his
21 many contributions, and while we regret his loss as a
22 voting member, we are fortunate to still retain his
23 expertise as a panel consultant.

24 ~~I would like now to introduce the three new~~

1 voting members whom we are welcoming today to the panel.

2 Dr. James McCulley is professor and chairman of the

3 Department of Ophthalmology at the University of Texas

4 Southwestern Medical School in Dallas, Texas. Dr.

5 McCulley's area of expertise is corneal and external

6 disease and refractive surgery. Dr. Eve Higginbotham, a

7 specialist in the treatment of glaucoma, is professor and

8 chair of the Department of Ophthalmology at the University

9 of Maryland School of Medicine in Baltimore, Maryland. Dr.

10 Mark Bullimore, a noted vision scientist, is an assistant

11 professor at the College of Optometry at Ohio State

12 University. Welcome to all three of you to our voting

13 member panel.

14 I would also like to take this time to

15 introduce a new consultant member to our group, Dr. Mark

16 Mannis. Dr. Mannis is an internationally recognized expert

17 on corneal and refractive surgery and is professor of

18 ophthalmology and director of the Corneal and External

19 Disease and Refractive Surgery Service at the University of

20 California Davis School of Medicine. Welcome, Dr. Mannis.

21 Will the remaining panel members please

22 introduce themselves, beginning with Dr. Judy Gordon.

23 DR. GORDON: I'm Dr. Judy Gordon. I'm with

24 Chiron Vision, and I'm the industry representative to this

1 panel.

2 DR. McCLELLAND: Eleanor McClelland, University
3 of Iowa College of Nursing. I'm consumer representative to
4 the panel.

5 DR. FERRIS: Dr. Frederick Ferris. I'm the
6 director of the Division of Biometry and Epidemiology at
7 the National Eye Institute, NIH.

8 DR. SONI: Sarita Soni. I'm a professor of
9 optometry and visional sciences at Indiana University, and
10 associate dean for research and endowed graduates program.

11 DR. MACSAI: Dr. Marian Macsai, associate
12 professor, West Virginia University School of Medicine.

13 DR. RUIZ: Richard Ruiz, chairman of the
14 University of Texas Ophthalmology Department, Houston.

15 DR. STULTING: Doyle Stulting, professor of
16 ophthalmology and director of the cornea service at Emory
17 University.

18 DR. WILKINSON: I'm Pat Wilkinson, chairman of
19 the Department of Ophthalmology at Greater Baltimore
20 Medical Center, and professor of ophthalmology at Johns
21 Hopkins.

22 DR. HIGGINBOTHAM: Dr. Eve Higginbotham,
23 University of Maryland.

24 DR. VAN METER: Woodford Van Meter, private

1 practice in Lexington, Kentucky.

2 DR. ROSENTHAL: Ralph Rosenthal, director of
3 the Division of Ophthalmic Devices, FDA.

4 MS. THORNTON: Thank you.

5 Before we begin the program, I would like to
6 ask you all to please note that on page 2 of the agenda for
7 today's session, there's an error in the PMA number being
8 presented by Dr. Saviola. The PMA number should read
9 P950008.

10 Just a short announcement that during the break
11 there will be a snack bar set up outside the room for the
12 public and FDA staff. At the lunch break following the
13 open session, there is reserved seating for the panel at
14 the Village Park Cafe just outside this room, down to your
15 left.

16 Now I'd like to move on to our open public
17 hearing portion of the meeting. Any speaker who wishes to
18 make a presentation before the committee is doing so in
19 response to the panel meeting announcement in the Federal
20 Register. The speaker who may wish to speak is not
21 specifically invited by FDA, nor are their comments, data,
22 or products endorsed by the agency.

23 There are no scheduled speakers today; however,
24 Dr. Stulting will recognize unscheduled speakers during the

1 open public hearing time. After a speaker has completed
2 their remarks, the chair may ask them to remain if the
3 committee wishes to question them further. Only the chair
4 and members of the panel may question speakers during the
5 open public hearing.

6 Dr. Stulting?

7 DR. STULTING: Does anyone wish to make a
8 public statement?

9 (No response.)

10 DR. STULTING: Don't hurt yourselves on the way
11 up. I think we're finished with that part. The public
12 session is declared closed, hearing no responses. The
13 public hearing period. Excuse me. I didn't get the words
14 quite right.

15 We'll move on to division updates, then. First
16 is a presentation by Dr. Rosenthal.

17 DR. ROSENTHAL: Mr. Chairman, ladies and
18 gentlemen, I have just a few very brief remarks. First, I
19 should like to thank the panel members for giving their
20 valuable time to come today and tomorrow, and particularly
21 to the primary reviewers on the panel, who I'm sure spent
22 countless hours reviewing the applications that were sent
23 to you. Thank you very much.

24 ~~Secondly, I'd like to thank my division members~~

1 who, for the past 6 months, have been tireless in their
2 propping me up against all the various onslaughts of issues
3 that have arisen, and in particular to Nancy Brogdon, who
4 has been a great tower of strength during my first 6 months
5 here.

6 I've asked my branch chiefs to give updates,
7 and I'd like to introduce Dave Whipple first, who will talk
8 about the 510(k) program.

9 MR. WHIPPLE: Well, good morning. For those of
10 you who don't know me by now, this is who I am, Dave
11 Whipple. I'm the associate director of the Division of
12 Ophthalmic Devices, and this is what I've been doing for
13 the past year as part of the reorganization for the
14 division. Back in 1995, when we reorganized, my job was
15 modified a bit to include a lot more division-related
16 functions across the board, and these are some of the
17 responsibilities that I have as the associate director.

18 Today Dr. Rosenthal has asked that I present a
19 little bit of an update on the 510(k) program, and that
20 also will include a little bit of information about the
21 third-party review pilot.

22 I did want to mention, though, that I will be
23 starting my 17th year with the Division of Ophthalmic

24 Devices, which means that I've been with the same team for

1 2 years longer than Cal Ripkin has been playing with the
2 Orioles, but I have missed a few days of work, where he
3 hasn't, so I think he's still got one up on me.

4 I'm going to start out by talking a little bit
5 about numbers. I will get into those first. This will
6 give you an overview across the board of what the 510(k)
7 program looks like within the division, and I thought it
8 would be nice to see a little bit of the history as I
9 presented it here regarding the 510(k) program in terms of
10 the fluctuations of numbers.

11 As you can see, in fiscal year 1996 our numbers
12 have gone down a bit from the past 4 years, and we believe
13 this is primarily due to a number of exemptions that we've
14 taken on in the division where we've exempted devices from
15 510(k). That doesn't mean we don't regulate them anymore,
16 it just simply means we don't receive an application prior
17 to marketing, and the numbers have gone down, as you can
18 see, to 279.

19 Now, this is a little bit of the breakout as
20 far as the branches within the division go. This gives you
21 a little bit of an idea how the workload flows within the
22 division.

23 Our Diagnostics and Surgical Devices Branch has
24 the majority of the 510(k)s within the division. As you

1 can see, they get approximately 35 a month, and that really
2 does fluctuate, it does go up and down, but that's an
3 average for fiscal year 1996. Most of theirs is the
4 hardware-type applications. They deal with the nuts and
5 bolts of the surgical products and the diagnostic products,
6 which is why they receive a lot of the 510(k) submissions.
7 We expect their numbers to actually go down as we exempt
8 more devices from 510(k), and hopefully we'll be doing a
9 lot more of that in the near future, especially if we can
10 exempt the sunglasses, which is a major part of that
11 particular program.

12 The Vitreoretinal and Extraocular Devices
13 Branch receives about 15 510(k)s on an average per month,
14 and that also fluctuates, and most of their applications
15 involve the contact lens 510(k)s for daily wear contact
16 lenses and some of the Class II care products. We expect
17 those numbers to actually go up as we reclassify contact
18 lens care products that are now in Class III, so we should
19 see that number actually rising.

20 Finally, our Intraocular Lens and Corneal
21 Implants Branch receives about six a month. That's a small
22 number for them, but most of their work is actually in the
23 implants area, so you wouldn't expect that particular
24 branch to be receiving a lot of 510(k)s, although we do

1 expect that number as well to go up when they take on the
2 reclassification of monofocal IOLs in the near future.

3 The numbers that we have are -- we're actually
4 sixth as far as divisions go in terms of the number of
5 510(k)s received in ODE. We're the lowest division. But
6 we have what I think is a pretty good workload, a pretty
7 hefty workload for a division as small as we are, so it
8 kind of balances out.

9 I thought I'd give you the last little
10 statistic slide as an overview of how we feel we've been
11 doing in the division so far across the board. You can see
12 our average response time is about 70 days for a 510(k)
13 once it hits the document mail center. This is actually
14 pretty good. We do a pretty good job on this. We'd like
15 to see that come down a little bit, but so far I think we
16 do real well on that.

17 About a third of the documents that come in of
18 that 510(k) workload does require that we get in a
19 supplement for additional information. That's why you see
20 the review cycles -- on an average we do require about a
21 third of these to send us additional information. That's
22 why you see the 1.3.

23 Total review time from start to finish when we
24 make a decision is about 92 days, and that's pretty good.

1 As a matter of fact, some of these numbers you see here are
2 actually some of the best in all of ODE. We'd like to see
3 still some of those numbers come down, but we're doing
4 pretty darn good as a division, and we're pretty proud of
5 that number.

6 We're also pretty proud of those last two
7 little stats that you see there. We have no backlog, and
8 we have currently no overdue 510(k)s. Occasionally one
9 will go overdue, but most of the time that's out of our
10 control, usually for a GMP-type issue, and there's nothing
11 we really can do about that. But currently we're doing
12 what I think is fairly well.

13 One of the reasons that we do so well is that
14 we're working to exempt a lot of devices from submission of
15 a 510(k), and you see in 1996 we took on four more. In
16 1994 and 1995 we did a huge amount of work in that area,
17 and as we move on in 1996 it's a little bit tougher,
18 because those are the more difficult ones, the ones that
19 need some criteria established in order to actually exempt
20 them. So we're going to be working -- there are probably
21 about a dozen or so that we've kind of targeted, and we
22 think we might be able to exempt them as well. The more we
23 can exempt, the more it frees up our resources to be able
24 to spend it on the more riskier types of devices.

1 We're really looking to get the non-
2 prescription sunglasses out of the division as an exemption
3 as well. We're trying to tweak that particular document as
4 it leaves in its final signoff phase through the center,
5 and you should be able to see that exemption hit the
6 Federal Register for comments probably at the beginning of
7 next month or so. So we're looking to exempt those.
8 That's a pretty good workload, sunglasses, that comes
9 through the DSDB group, and we're hoping to eliminate that
10 workload.

11 I want to talk a little bit now about the
12 third-party review pilot, which is part of the 510(k)
13 program in our division, and it certainly does affect our
14 510(k) process in the future.

15 Just as a little refresher for you all, this
16 particular third-party pilot was mandated as part of the
17 reinventing of government, and we were asked to
18 participate, and we're involved in it very heavily in terms
19 of the Class I devices and obviously the Class II devices
20 that we're seeking to get involved in as well.

21 The third-party pilot is really a feasibility
22 study of the 510(k) reviews by independent outside
23 organizations to see how well we can work with them to do
24 the reviews and free up some of our resources. The pilot

1 will be about 2 years long. It started back in August, and
2 all the Class I devices that we had and throughout ODE were
3 immediately eligible for review by third parties, and there
4 are also some selected Class II devices which will be
5 included, and they're being phased in as soon as guidance
6 documents are developed for them.

7 I do want to mention, though, that as far as
8 the pilot, FDA is not giving up its authority to actually
9 make the final decision in this case. We will get the
10 applications from the third parties sent to us, and then we
11 will make the final decision. So we're really treating
12 them as if they were like a reviewer for us, no different
13 than ones that are already in-house.

14 Currently the program is probably not going as
15 well as maybe it had been expected. We haven't seen any
16 third-party reviews in-house for any of the ophthalmic
17 devices, and I believe they've only seen maybe one, maybe
18 two -- I'm not sure -- throughout all of ODE, and we
19 believe that may be because the Class I devices that hadn't
20 already been exempted, the few that are remaining, that
21 really it's maybe not cost effective at this time to go
22 after them as a third-party review.

23 I want to show you a few of those Class I
24 ~~devices that we have that are participating in the third~~

1 party, and that's the list of them right there. As I said,
2 we have yet to see one of those come in from a third party.

3 Here are some of the Class II devices that
4 we've included, the phaco devices and the vitreous
5 aspiration cutting devices. We're currently working on
6 guidance documents for those particular products to see if
7 we can't give some guidance to third parties. Once those
8 guidances are completed, then we will include them, and
9 we're looking to get those guidances out sometime in the
10 beginning of February. So you'll be seeing those guidance
11 documents available, and they also will be available for
12 comment as well.

13 Moving on, these are some of the goals that we
14 have for fiscal year 1997, and I thought I'd spend a little
15 bit of time discussing those.

16 We do want to, obviously, improve our review
17 times. I think we do pretty good. I think the group has
18 spent extra special effort to keep our review times without
19 backlogs, no overdues, but we think we can get the review
20 times down from, say, 70 days, which you saw in the slide
21 earlier, to 60 days in response to originals. This is kind
22 of a target goal that we're shooting for. And certainly 30
23 days in response to supplements when additional information
24 comes in. That would give us a total cumulative review

1 time of 90 days, and if you remember the slide I showed you
2 earlier, I said 92 was our current average, so we're doing
3 pretty darn good even now, but we think we can do a little
4 better.

5 Certainly the use of the interactive review
6 process has helped us out an awful lot, being able to fax
7 information back and forth, and being able to talk out
8 certain problems and things with manufacturers and resolve
9 them immediately with the manufacturers over the phone has
10 been able to take our review times down quite a bit.

11 The improved consistency element is kind of a
12 toughie, because this isn't just something that involves,
13 say, consistency between reviewers within a branch or
14 between reviewers within a division. It cuts across all
15 the way through all of ODE, and it's even more of an issue
16 for us to try to get a grip on because we're getting a lot
17 more policies being handed down from the office level and
18 from the center level. So in order to implement those and
19 keep all the branches consistent throughout, it does take
20 some monitoring, and it's quite an effort.

21 We have a division QA/QC program that tries to
22 pick up all of those potential inconsistencies, not only
23 within the division, but across the board, and that
24 involves the management as it goes through the chain, but

1 we also have involved the actual reviewers within each
2 branch. We've had some focal points established in each
3 branch, and these people do a marvelous job of trying to
4 catch certain things within their own branch, or even they
5 begin to see how certain inconsistencies may be becoming
6 available or coming to the forefront across all of the
7 reviews within ODE. So we use them quite a bit, and we've
8 been able to keep a lot of our inconsistencies in-house and
9 resolve them before we ever go out and ask the manufacturer
10 for additional information. So we're really improving well
11 in that area as well.

12 Finally, we do want to go after more
13 exemptions. That's another goal that we have for this
14 coming year. We're hoping to exempt all the Tier I
15 devices. Those are the devices that are single-reviewer
16 devices, and those can be either Class I or II. The more
17 we can exempt those, again, the more we can free up
18 resources. Certainly if we can't exempt them, we're going
19 to try to write guidances for them, and the more guidances
20 we can write for non-exempt devices, the better off we'll
21 be in terms of consistency as well as in terms of review
22 times. They should all go down as well.

23 So that's basically the update of the 510(k)
24 program. I haven't mentioned anything about guidances,

1 about classifications or reclassifications, or about
2 national or international standards, which all can affect
3 or will have an impact on the 510(k) program in the future,
4 but we'll save that particular update for a later time.

5 Thank you.

6 DR. STULTING: Do you want to go ahead, Ralph,
7 and introduce the other folks?

8 DR. ROSENTHAL: Thank you. The first branch
9 update will be given by Donna Lochner, who is branch chief
10 of the Intraocular and Corneal Implants Branch.

11 MS. LOCHNER: Thank you, and good morning. I
12 have a brief announcement concerning the division's
13 classification efforts for Class III devices for which
14 we've been receiving 510(k)s.

15 Before I get to that, I'd like to take this
16 opportunity to publicly thank and acknowledge all the hard
17 work of all the members of the Intraocular and Corneal
18 Implants Branch during my extended leave in 1996. In
19 particular, I'd like to thank Ashley Boulware, Dr. Kesia
20 Alexander, and Claudine Krawczyk for so ably serving as
21 acting branch chief while I was on leave.

22 Now I'll turn to the two Class III ophthalmic
23 devices, eye valve implants and keratoprotheses, which we
24 currently regulate under 510(k)s. These are preamendment

1 devices. In other words, they were marketed prior to the
2 1976 Medical Device Amendments. As you know, FDA must
3 either call for PMAs for these Class III devices or
4 reclassify them into Class II or I and continue to receive
5 510(k)s. It could potentially impose a significant
6 regulatory burden on the manufacturers of the devices if we
7 were to require PMAs.

8 First, the eye valve implants, or, as we are
9 referring to them now, aqueous shunts for glaucoma. FDA
10 has received from several sponsors a summary of safety and
11 effectiveness data for their shunts. We have completed our
12 review of the data and are preparing our recommendation
13 regarding the classification of these devices. We are
14 currently preparing a homework assignment to the glaucoma
15 specialists on the panel to request their recommendation
16 regarding the classification of these devices. The
17 homework assignment will include the safety and
18 effectiveness data received by FDA and our classification
19 recommendations.

20 Next, the status of the keratoprotheses
21 classification review. The deadline for sponsors or any
22 interested person to submit safety and effectiveness data
23 for keratoprotheses is February 14, 1997. We recently
24 ~~sent a letter to keratoprotheses sponsors to remind them~~

1 of this deadline. Once the safety and effectiveness data
2 are received, we will prepare our recommendation and
3 consult the panel if needed. We strongly encourage
4 interested persons to submit safety and effectiveness data
5 for these devices and to contact the FDA if you need
6 guidance on the content of these submissions.

7 That was all I had for today. Thank you.

8 DR. ROSENTHAL: The next branch chief will be
9 Morris Waxler, who we have recently appointed as acting
10 chief of the Diagnostic and Surgical Devices Branch.

11 DR. WAXLER: Good morning. I have a few brief
12 comments.

13 First, an interim report on the reimported and
14 unique lasers. January 15th is the deadline for submitting
15 to FDA self-certification for reimported lasers and for
16 IDEs for these lasers and for unique lasers. Self-
17 certifications have been submitted by 10 owners of
18 reimported lasers. Eight of these self-certifications have
19 been determined to be inadequate and IDE submissions have
20 been requested. Two self-certifications require additional
21 information to be submitted to FDA for a determination of
22 adequacy. Three IDE applications have been submitted for
23 unique lasers.

24 ~~Because of the guidance for refractive surgery~~

1 laser and the training which has been provided on this
2 guidance, we have set a 10-day goal in the branch for
3 review of IDEs in this area. The statutory review time
4 remains 30 days. We conducted two 1-day training sessions
5 on the guidance for refractive surgery lasers. Thirty-five
6 individuals attended the training.

7 One point I want to emphasize is that
8 manufacturers may not distribute lasers without their own
9 IDE. Sponsors' investigators who submit an IDE for studies
10 at a manufacturer's investigational site should provide a
11 scientific rationale for the study which is distinctive
12 from the studies being conducted by the manufacturer,
13 obtain a letter of reference from the manufacturer and
14 letters describing mutual agreement that the data will be
15 provided to the manufacturer in support of a PMA.

16 We've received several suggestions for changes
17 in the guidance for refractive surgery. We are reviewing
18 these ideas. We would appreciate your views on these
19 issues at another meeting of the panel.

20 DR. ROSENTHAL: The final update will be given
21 by James Saviola, who's chief of the Vitreoretinal and
22 Extraocular Devices Branch.

23 DR. SAVIOLA: Thank you, Dr. Rosenthal.

24 ~~Good morning, panel members. In conjunction~~

1 with this meeting also being the annual closed session
2 update, there are a couple items in my branch update that
3 are for the open session that talk about what happened
4 during the whole year.

5 The first thing I'd like to do is introduce the
6 newest member of our branch, Dr. Bernard Lepri, who's
7 sitting over in the FDA section. It's with great pleasure
8 that I take this opportunity to introduce Dr. Lepri. He
9 recently joined our group in August, after having spent the
10 last 2 years in New Mexico, most recently affiliated with
11 the Talbot Medical Group in Albuquerque.

12 Dr. Lepri is a graduate of the Pennsylvania
13 College of Optometry, where he earned a Doctor of Optometry
14 and a Master of Science in vision rehabilitation. He also
15 holds a Master of Education in counseling psychology from
16 Temple University in Philadelphia.

17 Included in his prior employment experience is
18 1 year spent as a research optometrist with Bausch and Lomb
19 in the early 1980s, but in selecting Dr. Lepri for this
20 position, we realized that the statute of limitations on
21 any potential conflicts of interest had run out, so he was
22 clear to hire for this. He also spent 11 years on the
23 faculty of the Pennsylvania College of Optometry as both
24 ~~assistant professor and director of the externship and~~

1 clerkship programs.

2 During his brief tenure, he has been a valuable
3 clinical resource to the whole division by conducting
4 reviews not only for our branch, but for the Intraocular
5 and Corneal Implants Branch and also for the Diagnostic and
6 Surgical Devices Branch. We are very happy to have him on
7 board.

8 The next item I would like to update for the
9 panel and for the public is that Dr. Daniel W.C. Brown,
10 who, as you know, was executive secretary of the panel for
11 a number of years, was recently promoted to Grade 14 expert
12 reviewer for toxicology, with a specialty in contact lenses
13 and contact lens care products. This process of expert
14 review involves review by a peer committee within the
15 agency comprised of members from different centers within
16 FDA.

17 Dr. Brown has made many significant
18 contributions to ophthalmic device review and to contact
19 lens device review over the years, and his selection by the
20 committee reinforces this. I'd like to congratulate Dan on
21 that.

22 (Applause.)

23 DR. SAVIOLA: Next, I'd like to touch on the
24 ~~status of reclassification of the contact lens care~~

1 products. I'm sure people are wondering where it is and
2 when it's going to be out.

3 The special control guidance document that we
4 discussed at the July panel meeting has been revised. We
5 had set a goal of completing that revision by the second
6 week of October, and we completed it actually by the end of
7 October. It is currently in the process of receiving final
8 clearance within FDA prior to publication of the final rule
9 in the Federal Register. We had optimistically hoped for
10 this happening by the end of 1996, but now a more realistic
11 time frame is probably during the first quarter of 1997.

12 When this occurs, we'll mail a letter to all
13 PMA holders for these types of products notifying them of
14 reclassification. This is in addition to the publication
15 in the Federal Register. That letter will advise
16 applicants who have pending premarket approval applications
17 with the agency of their responsibility to determine
18 whether they should convert their application, in whole or
19 in part, to a 510(k) or withdraw it completely.

20 In terms of approvals for fiscal year 1996 and
21 early 1997, I had previously updated the panel in July of
22 two multipurpose contact lens care products that had been
23 approved, and I had mentioned at the April panel meeting
24 that the Perfluoron chemical manufactured by Infinittech for

1 vitreoretinal surgery had been approved.

2 In addition to those three, in September of
3 this year, September 25th, Allergan received approval for
4 P960012 for Refresh CL as a wetting and lubricating drop
5 for soft contact lenses. That application was filed on May
6 6th of 1996, so the total review time for the original PMA
7 was 142 days from filing to approval.

8 In addition, Bausch and Lomb recently received
9 approval for P960022 for a soft lens for 7-day extended
10 wear. This had previously been cleared under 510(k) as a
11 daily wear lens. It too was reviewed within a total time
12 of less than 6 months.

13 Dave gave you an update on the 510(k) program
14 earlier this morning, and there are just a couple of items
15 I want to touch on from our branch in terms of what's been
16 happening since we reclassified daily wear contact lenses
17 effective March 3, 1994.

18 There have been a total of 74 510(k)s for daily
19 wear lenses cleared since that time. These include a
20 variety of types of applications, most notably for
21 alternate designs for presbyopia, for manufacturing
22 changes, and in some cases for new generic materials which
23 require a USAN designation. Overall there have been 12
24 ~~510(k)s cleared out of the 74 for a brand new material~~

1 requiring the USAN-type designation. Since the beginning
2 of fiscal year 1996, we've cleared five of these types of
3 applications out of 36, going back to October of 1995, and
4 these are the types of applications which previously have
5 required an original PMA approval under Class III.

6 The last item I want to touch on involves the
7 clinical studies of significant risk devices. After having
8 the responsibility of coordinating the review of retinal
9 tamponade devices since the reorganization in September of
10 1995, it has really impressed me how different the level of
11 regulatory knowledge and expertise is between various
12 segments of the industry. This applies to companies,
13 investigators, and also to institutional review boards as
14 well. With that in mind, I would like to make this last
15 announcement for the benefit of those parties who may not
16 have a clear understanding of the medical device law:

17 This is a reminder that significant risk
18 medical device clinical studies require both local IRB
19 approval as well as FDA approval for investigational device
20 exemption, or IDE. According to the federal regulations,
21 when a practitioner begins a clinical investigation and
22 seeks IRB approval, the IRB should make the determination
23 or review the determination of whether it is a significant
24 risk study and, therefore, requiring an IDE approval.

1 Simply having FDA approval for one indication for use does
2 not provide for FDA approval to investigate a product for a
3 different indication or for an off-label use.

4 Now, these remarks aren't directed toward care
5 providers who prescribe a product off-label in the scope of
6 their medical practice. Rather, they're directed toward
7 practitioners such as those who recently published results
8 of a clinical study in the Journal of Retinal and Vitreous
9 Disease involving a perfluorocarbon liquid for use in
10 vitreoretinal surgery that was previously approved by FDA
11 for a different intended use, not for use in vitreoretinal
12 surgery. FDA is interested in working with clinical
13 investigators such as these so that they understand their
14 responsibilities.

15 The IRBs also have responsibilities under the
16 medical device regulation, and they can be subject to
17 review by FDA as well.

18 This announcement is strictly informational to
19 better inform those parties who may lack knowledge of this
20 process.

21 Thank you for your attention.

22 DR. ROSENTHAL: Thank you.

23 Thank you, Mr. Chairman.

24 ~~DR. STULTING: Thank you. We certainly~~

1 appreciate the updates.

2 Let me open the floor at this time to panel
3 members for questions or discussion of the presentations so
4 far.

5 DR. McCULLEY: Your last announcement, as I sat
6 here and listened to it, that means if I want to evaluate,
7 let's say, a device or a drug in a clinical trial for which
8 it has not been product labeled, I must have an IDE.

9 DR. SAVIOLA: Well, you normally would go to
10 your institutional review board to get clearance for that
11 study, and I'm trying to address not just your
12 responsibility as an investigator, but also that IRB's
13 responsibility.

14 DR. McCULLEY: Well, they should catch me if
15 I've not done it, is what I hear you saying.

16 DR. SAVIOLA: Correct. Yes, that's what I
17 said.

18 DR. McCULLEY: Right. And if they don't, then
19 they're potentially in trouble for not effectively doing
20 their job.

21 DR. SAVIOLA: Well, it's not trouble from a
22 punitive sense. Again, these are the regulations according
23 to the federal law, and we want to work with the
24 organizations so that they understand their

1 responsibilities.

2 DR. McCULLEY: I wonder how well the academic
3 and practicing communities understand this. I would not
4 have thought that I needed to -- I mean, it's just
5 ignorance, but if I wanted to take X device or drug and
6 evaluate it in a clinical setting with IRB approval, I
7 would have thought that would have been sufficient, but
8 from what I hear you saying, that is not.

9 DR. SAVIOLA: Well, technically the
10 investigational device exemption allows for intrastate
11 transportation of a particular product. So, for example,
12 if you're going to do it in the academic setting, I agree
13 with you, I'm sure that the majority of the time you're not
14 getting IDE approval. But if the manufacturer is sending
15 it to you and they're aware of the purpose of what you're
16 going to use it for, then in order to meet the regulations,
17 it should have effective clearance.

18 DR. McCULLEY: Well, suppose they're not
19 sending it to me. Suppose I'm purchasing it from a
20 pharmacy and distributing it to the patient or that I give
21 them a prescription, if it's a drug. I know this gets into
22 drugs, but it would apply, I assume, similarly to analogous
23 situations with IDEs.

24 DR. SAVIOLA: Again, the purpose of the IDE

1 regulation is to address safety for the subjects involved,
2 and the value that we add to the whole process is perhaps a
3 more objective review of the whole protocol, what the
4 endpoints are, what types of informed consent are being
5 conveyed over to the subjects.

6 DR. McCULLEY: But that's IRB --

7 DR. SAVIOLA: Those are all IRB, that's
8 correct. But there are many times when we see studies that
9 are proposed that may have gotten IRB clearance that we
10 have additional comments and would like some additional
11 information conveyed over to the subjects.

12 DR. McCULLEY: It seems stifling to me. Sorry.

13 DR. STULTING: I have to agree with Jim. I'm
14 not sure that that's the principle that is now being
15 followed in investigational work. If it's the intent of
16 the agency to inform people about that, I would suggest a
17 format might be a letter to practitioners or a letter to
18 IRBs -- probably to practitioners is a good idea -- to
19 provide that sort of information, because it's certainly
20 not widely known. I agree with Jim.

21 DR. McCULLEY: To me it's just going to kick in
22 the pants any investigation of devices or products for new
23 applications.

24 ~~DR. STULTING: Dr. Ferris?~~

1 DR. FERRIS: Well, I believe, if I understood
2 what you said and I understand the situation, that the
3 quirk in the way things are now is that if you want to use
4 this as an off-label indication, you're perfectly free to
5 use it for care, but if you want to study it, then you have
6 to get an IDE. So in some ways, as you point out, it has a
7 chilling effect on doing what probably ought to be done for
8 off-label uses, and that is to evaluate them. There's
9 another step that has to be gone through if you want to
10 evaluate it; if you just want to use it, go ahead.

11 DR. STULTING: Well, correct me if I'm wrong,
12 but the Food, Drug and Cosmetics Act addresses only
13 interstate commerce, so that if the manufacturer is unaware
14 of the use and a practitioner -- and interstate commerce
15 for the purpose of the study is not involved -- in other
16 words, as Jim says, if you give somebody a prescription for
17 a drug and they go a local drug store, or you provide them
18 a device from a local source or something like that, then
19 would that come under the jurisdiction of the FDA and
20 require an IDE, or would it be exempt from that process?

21 DR. SAVIOLA: Well, again, within the scope of
22 a practice, it's a different situation than when you're
23 actually going to investigate a product, develop a
24 protocol, study it. It's sort of akin, I guess, to the

1 idea of what's going on with the excimer lasers and
2 promotion and advertising issues.

3 The reason I brought this to attention in this
4 public forum was simply because of the publication of that
5 article, the fact that those products are used overseas,
6 but they're not approved within the United States, and from
7 the standpoint of what's been going on in the vitreoretinal
8 community in terms of products that people may use day to
9 day in practice but haven't gone through the regulatory
10 process and should be out there and approved.

11 My point was simply that if people are going to
12 pursue this endeavor and if they're going to try to develop
13 this type of compound for this particular use, then they
14 should be doing it within the established guidelines and
15 not try to circumvent them. As you'll see later in the
16 course of the discussion of this application, there were
17 some issues.

18 DR. STULTING: Dr. Rosenthal?

19 DR. ROSENTHAL: Mr. Chairman, I think the issue
20 relates to whether or not the risk of the device is a
21 significant risk or a non-significant risk. If there's a
22 significant risk of the device, then it is required by law
23 to submit an IDE, whether you like it or not, and there are
24 certain devices which are listed in the ophthalmic area as

1 significant risk devices, and one of them is retinal
2 tamponades, and that is the issue which Dr. Saviola is
3 addressing today.

4 The device that was used had never been
5 approved for ophthalmic use at all and was used as a
6 retinal tamponade and was outside the guidelines of the
7 agency, and I think it was very wise of him to bring the
8 issue up so that there's no misunderstanding in the future.

9 DR. McCULLEY: I wouldn't argue about the
10 situation in the example. What worries me is just how far
11 that could be taken. I could see if an instruction went to
12 an IRB that was not very explicit, if a person wanted to,
13 as would be appropriate, study an off-label use, that the
14 IRB would say, "Well, where's your IDE?" or "Where's your
15 IND?" and not allow what would otherwise be a good study to
16 go forward, which would be to everyone's benefit, but there
17 would be an assessment of whether it would be adding any
18 risk, but it wouldn't confuse that with an issue related to
19 a product coming from whether it's nationally or
20 internationally that has no approval whatsoever.

21 DR. ROSENTHAL: I think it has to do with the
22 product itself, the device itself, and if it carries a
23 significant risk label, it is required by agency dictate
24 that an IDE be presented, whether the IRB agrees or not.

1 There are certain devices which are listed that require
2 IDEs, and the IRB must go along with that.

3 DR. McCULLEY: Well, it needs to be made clear
4 to investigators and IRBs. I'm not sure I wasn't confused.

5 DR. STULTING: Dr. Wilkinson?

6 DR. WILKINSON: Dr. Rosenthal, I'm asked
7 frequently, "What's the risk to me as a physician?" As you
8 know, virtually all tamponades were used for other
9 purposes. Many experts for years signed releases saying
10 they were going to use this only in animals, et cetera, et
11 cetera. Is there any genuine risk to the physician to just
12 ignore the fact that he should have an IDE?

13 DR. SONI: Dr. Stulting, I have a question.

14 DR. STULTING: Well, wait a minute. I think we
15 have a question on the floor.

16 DR. SAVIOLA: Dr. Wilkinson, let me answer that
17 for Dr. Rosenthal.

18 DR. ROSENTHAL: Thank you.

19 DR. SAVIOLA: In the situation of a potential
20 liability issue, a malpractice claim filed against you, and
21 if you had signed a form to obtain a product for one intent
22 and then used it for a different intent, it kind of circles
23 back in my mind, knowing what I know about medical device
24 law and very little about tort law, that it goes to the

1 level of informed consent and what you tell your patient
2 before you use the product. Again, for tamponade products,
3 these folks are sort of at the last end of their ropes, and
4 whatever you're going to do to help them, hopefully they're
5 going to appreciate that and not turn against you if the
6 result isn't favorable.

7 But it does put into a situation of liability,
8 and going through the process -- again, I guess I wasn't
9 clear enough about significant versus non-significant types
10 of studies, but this does help to give you an extra
11 insulating layer against liability claims.

12 DR. STULTING: Dr. Soni?

13 DR. SONI: I wasn't trying to excuse the
14 question, but I was trying to probably change directions
15 for us maybe. Who is responsible to get the IDE? Is it
16 the investigator or the sponsor of the study, or is it the
17 IRB? Who is responsible for it?

18 DR. SAVIOLA: It can be an investigator-
19 sponsored IDE for a particular type of treatment study. If
20 the firm actually is intending to pursue marketing of the
21 product, then they may coordinate it and have many
22 investigators involved in the process. The IRB really
23 doesn't get the IDE for the applicant. The IRB is supposed
24 to be an overseeing body comprised of a certain number of

1 different individuals. And as I said, they do get
2 inspected from time to time by the agency to see that
3 they're meeting their statutory requirements as well.

4 DR. STULTING: Dr. Ferris?

5 DR. FERRIS: There was a long discussion of
6 this issue at the Eye Care Technology Forum. I'm not sure
7 any --

8 MS. THORNTON: Excuse me, Dr. Ferris. I'm
9 sorry. Could you speak into the microphone so we can
10 adequately record?

11 DR. FERRIS: There was a long discussion of
12 this at the Eye Care Technology Forum meeting several
13 months ago, and I think it would be interesting for those
14 who have some interest in the area to review the
15 discussion. I'm not sure there was a clear answer. The
16 main problem here is, you can use an off-label device or
17 drug. A physician can use it.

18 I gave an example at that meeting of a
19 physician who was sued for using 5FU for glaucoma after the
20 results were published in the Archives of Ophthalmology
21 because it was an off-label use, and the issue here is that
22 the company has little to gain by going through an IDE or
23 an IND process. Even when, for example, an NIH study was
24 done showing that 5FU was effective, they still had no

1 interest in getting it added to the label because there
2 wasn't anything in it for them.

3 So the issue here is who's going to sponsor it.
4 It won't be the company, so it's unlikely the company is
5 going to go get an IDE. So it's up to the investigator,
6 and then the investigator is put in the position that he or
7 she can just use it, or if they want to evaluate it, they
8 have to jump through a bunch of hoops.

9 DR. STULTING: That's a little bit of a
10 different issue than we've been discussing before, but I
11 think it's an important one, and that is, where is the
12 motivation to add an indication to labeling, even after
13 there has been a good, well-performed, published study? I
14 personally would like to see the agency be responsive to a
15 letter from a manufacturer, once such data are available,
16 to expand the labeling. I think that would be protective
17 for physicians, and it would make the use of the drugs for
18 those things more comfortable.

19 The example you cite is an excellent one.
20 Personally, if I were to receive a request from the FDA to
21 review a recommendation for addition to a labeling --
22 specifically, the example you gave -- then I would support
23 that. In other words, I think it ought to be easy for a
24 sponsor to have that so they can just write the agency, say

1 there has been a published NIH-supported study supporting
2 this addition to the labeling, and move forward with that
3 and get it done.

4 DR. FERRIS: Let me expand that a little bit
5 further. Walter Stark, at this particular meeting,
6 suggested that corneal glue, of which I know little, has
7 been used extensively for decades in an unapproved way.
8 His view was that there was enough data available that some
9 group ought to be able to gather together the data that's
10 available and either approve it or not approve it, but not
11 continue to use it as this totally off-label use.

12 DR. STULTING: I think I'm showing my age,
13 because I've been around long enough to know that we
14 actually approved that application some years ago, and it
15 hasn't completely received approval, as I understand.
16 Correct?

17 DR. SAVIOLA: I think I would refer those
18 remarks to Donna to complete, because it's within her
19 branch.

20 DR. STULTING: Anyway, I think we're into some
21 areas here that we maybe don't have time on the agenda to
22 discuss fully, but I think that your comments are well-
23 taken, and the opinions of the panel are also on the
24 record, and it probably should be addressed at a later

1 time.

2 Any other pressing comments about this?

3 DR. McCULLEY: A question for Dr. Waxler. This
4 may or may not be the time or place, you may be planning to
5 address it somewhere else, or you may not wish to address
6 it at all. But I would like to be educated -- and maybe
7 this isn't the time or place to do it -- relative to some
8 mailings I personally have received, and I'm sure other
9 panel members have, about a LASIK study where supposedly,
10 as I understand it, an IDE has been submitted and I can
11 join up for a LASIK study, or an investigator can, for a
12 fee of \$2,500.

13 I'm a little confused about all of that and the
14 propriety of it and the wisdom behind it, and I'm sure it's
15 just my ignorance, but I can stay ignorant if it's most
16 appropriate.

17 DR. WAXLER: Well, I can acknowledge that there
18 is an IDE for CRS. That is essentially the same situation.
19 ISRS, the International Society for Refractive Surgery, was
20 planning a study of LASIK, and we asked them to submit an
21 IDE, and they did so under the aegis of CRS, which is a
22 consulting firm. I can't discuss the IDE, but we have
23 approved an IDE for that group.

24 ~~DR. STULTING: Maybe that would be an~~

1 appropriate discussion for the closed session later today.

2 Any further comments?

3 (No response.)

4 DR. STULTING: Okay. I'd like to turn the
5 floor back over to Sara Thornton for discussion of
6 conflicts of interest prior to the consideration of the PMA
7 today.

8 MS. THORNTON: First of all, I'd like to call
9 forward, in addition to Dr. James Saviola, Deborah Falls
10 and Dr. Malvina Eydelman to be in place to present the PMA.
11 Before that, I'd like to read into the record the conflict
12 of interest statement for today:

13 "The following announcement addresses conflict
14 of interest issues associated with this meeting and is made
15 part of the record to preclude even the appearance of an
16 impropriety.

17 "To determine if any conflict existed, the
18 agency reviewed the submitted agenda and all financial
19 interests reported by the committee participants. The
20 conflict of interest statutes prohibit special government
21 employees from participating in matters that could affect
22 their or their employer's financial interests. However,
23 the agency has determined that participation of certain
24 ~~members and consultants, the need for whose services~~

1 outweighs the potential conflict of interest involved, is
2 in the best interest of the government.

3 "Full waivers have been granted to Drs. James
4 McCulley and Woodford Van Meter for their interest in firms
5 at issue that could potentially be affected by the
6 committee's deliberations. Copies of these waivers may be
7 obtained from the agency's Freedom of Information Office,
8 Room 12A-15 of the Parklawn Building.

9 "We would like to note for the record that the
10 agency took into consideration a certain matter regarding
11 Dr. Mark Bullimore. Dr. Bullimore reported that he was a
12 consultant on a 1-day study for which a firm at issue
13 donated money to his university. Since this is a past
14 involvement and unrelated to the issue before the panel,
15 the agency has determined that he may participate fully in
16 today's deliberations.

17 "In the event that the discussions involve any
18 other products or firms not already on the agenda for which
19 an FDA participant has a financial interest, the
20 participants should exclude themselves from such
21 involvement, and their exclusion will be noted for the
22 record.

23 "With respect to all other participants, we ask
24 in the interest of fairness that all persons making

1 statements or presentations disclose any current or
2 previous financial involvement with any firm whose products
3 they may wish to comment upon."

4 I'd like to read the statement of appointment
5 to temporary voting status. I would note at this time that
6 this statement does include Dr. Frank A. Spellman, who was
7 not able to be with us today due to a family emergency.

8 "Pursuant to the authority granted under the
9 Medical Devices Advisory Committee charter dated October
10 27, 1990, as amended April 20, 1995, I appoint the
11 following individual as a voting member of the Ophthalmic
12 Devices Panel for the duration of this meeting on January
13 13, 1997: Dr. C. Pat Wilkinson. For the record, this
14 person is a special government employee and a consultant to
15 this panel or a consultant or voting member of another
16 panel under the Medical Devices Advisory Committee. He has
17 undergone the customary conflict of interest review and has
18 reviewed the material to be considered at this meeting."

19 It's signed by Dr. D. Bruce Burlington, M.D.,
20 Director, Center for Devices and Radiological Health,
21 December 16, 1996.

22 I have one other thing that I would like to
23 read into the record regarding the panel recommendation

24 options for voting on the premarket approval application.

1 I will do that at the time we are ready to have the panel
2 vote on the application. I'd like to defer that until
3 later.

4 Dr. Stulting?

5 DR. STULTING: The next item on the agenda is a
6 discussion of PMA P950008, and I'd like to turn the floor
7 over to Jim Saviola for the agency's presentation.

8 DR. SAVIOLA: Thank you, Dr. Stulting.

9 As the panel members will notice from their
10 agenda, the sequence of presentations is a little bit
11 different this morning compared to what you've been used to
12 in the past. Most notably, the company will do the first
13 presentation of the PMA, and the FDA clinical review
14 presentation will follow that. This sequence and this type
15 of agenda order has been adopted across the whole office
16 and I guess is consistent for the way panels run across the
17 agency. It is, after all, the company's application, so
18 the burden is on them to present it to the panel, not have
19 the agency present it.

20 I will focus on some administrative items in my
21 introductory remarks, and then turn it over to Deborah
22 Falls for the overall introduction.

23 I would like to also thank the primary panel
24 reviewers for taking the time out of their busy holiday

1 season to review this application. As you know, we mail
2 these applications out to the primary reviewers 6 weeks
3 ahead of the meeting so that their reviews can be received
4 back and included in the general mailout, which goes out 3
5 weeks in advance of the meeting. We also have to make some
6 decisions on our agenda about 8 weeks ahead of the meeting
7 so that they may be published in the Federal Register.
8 These time frames highlight some of the preparation which
9 is necessary in order to bring an application to you for
10 review.

11 I mention these time frames and preparation
12 because in the case of this application, the firm has been
13 preparing for this meeting for over a year. At previous
14 panel meetings it has been stressed again and again that
15 the quality of clinical studies brought for review to the
16 panel is somewhat difficult to evaluate. There has been
17 criticism for lack of patient follow-up and other issues
18 that have been highlighted by panel reviewers.

19 In considering this application for panel
20 review, our branch in DOD has taken these comments very
21 seriously, and we have worked with the company to get the
22 clinical data sets for this application in the best shape
23 possible. We did not bring this application for your
24 ~~review until we thought we had maximized data~~

1 accountability. We have reached a comfort level that we
2 feel is sufficient for panel clinical review.

3 The gaps that existed prior have been filled in
4 to address the questions of those subjects who were treated
5 with the device. The result is a rather large data set
6 which has been established, far beyond what would normally
7 have been necessary for the study to be evaluated for PMA.

8 I would also like to touch briefly on the data
9 analysis method. In compiling the data set, the sponsors
10 utilized data from the 6-month exam and the last visit to
11 evaluate safety and efficacy. This has been utilized in
12 literature and is sufficient to determine approvability of
13 a product from an efficacy standpoint.

14 However, the last visit data analysis we feel
15 is not strictly appropriate from a safety standpoint in
16 terms of an ability to write product labeling. The
17 protocol for the study called for a number of scheduled
18 follow-up visits; however, data were not reported for each
19 of those visits at less than 6 months. The sponsor has
20 committed to FDA that they will report these data to
21 complete the follow-up visit profile, and that is going to
22 remain an outstanding issue to be addressed following panel
23 review.

24 ~~FDA feels that this additional information is~~

1 necessary from a safety standpoint so that appropriate
2 information may be included in product labeling when it's
3 finally written.

4 In terms of process control, I must acknowledge
5 that the study was not well controlled compared to what we
6 are currently doing to monitor projects. Initial patient
7 data were not captured by the sponsor in a timely manner,
8 and also, as I mentioned, this was a larger study than had
9 been designed under the original IDE. In conducting a
10 review of the product, we came to realize that there were
11 also issues concerning the distribution and accountability
12 of devices sent out into the field.

13 In response to these items, the firm was issued
14 a warning letter by the Office of Compliance regarding the
15 conduct of the study and distribution of investigational
16 devices. That fact is part of a publicly available record
17 of the submission. Also, some investigators received
18 warning letters from the Office of Compliance. These
19 warning letters to the company and the selected
20 investigators could have resulted in this product not
21 reaching the panel for review by undermining the validity
22 of the data set. Ultimately, however, following additional
23 auditing procedures, the data set has been validated, and
24 we feel confident in presenting it for your review.

1 As we noted in the cover letter for the general
2 mailout, you will be hearing about the additional
3 difficulty concerning the need to change raw material
4 suppliers during the study and the additional data
5 necessary to address that issue. Please remember that
6 although the majority of clinical data are from silicone
7 oil manufactured by the original supplier, the only product
8 that will be made available will be that manufactured from
9 the new supplier. This is a case of two different sources,
10 but it is not a case of two different formulations. The
11 formulations are the same.

12 In terms of the overall review process
13 following panel recommendation, I must remind everyone that
14 this product cannot receive a final approval until all
15 clinical and preclinical issues have been adequately
16 addressed. In addition, the manufacturing processes need
17 to be evaluated by the Office of Compliance and receive a
18 final clearance, which is standard procedure for any
19 original Class III application. This will involve an
20 inspection by FDA prior to issuance of the final decision.

21 Having touched on some of these issues, I must
22 commend the sponsor for considerable effort in order to
23 overcome the obstacles to get to this point today. The
24 follow up data that has been verified is roughly 70 percent

1 at 6 months and 50 percent at 12 months for the non-CMV
2 patients.

3 As you will hear in a moment, this has been an
4 expedited device, and we have always had as a goal to
5 solicit panel input as soon as we possibly could, in order
6 to minimize any further delays in the review process.

7 I would like to introduce the team leader for
8 this application at this point, Ms. Deborah Falls.

9 MS. FALLS: Thank you, Dr. Saviola.

10 Good morning, members of the Ophthalmic Devices
11 Advisory Committee, Ms. Thornton, Dr. Rosenthal. My name
12 is Deborah Falls, and I'm the team leader for PMA P950008.
13 Silikon 1000, the subject of this PMA, is an intraocular
14 fluid with low viscosity and is intended for use as a
15 retinal tamponade in complicated retinal detachments.

16 As background information, this PMA was filed
17 on February 22, 1995, and was granted expedited review at
18 that time. Expedited review was granted on the basis of
19 its use for AIDS patients and its lower viscosity, allowing
20 easier installation and removal of the device than the
21 approved 5000 centistoke.

22 This PMA contains clinical data from silicone
23 oil manufactured from two different raw material suppliers.

24 ~~The clinical data on the finished silicone oil produced~~

1 from both raw material suppliers will be discussed this
2 morning. To date, the sponsor has provided FDA with the
3 majority of the information necessary to demonstrate the
4 preclinical equivalency of the two raw material oils and
5 the finished silicone oil product. However, certain issues
6 concerning the final product specifications and quality
7 control processes remain.

8 The panel members will be asked to provide your
9 review and recommendation on the clinical data reported in
10 the PMA, with the understanding that the sponsor will
11 resolve the remaining preclinical issues with internal FDA
12 review staff. This PMA, as Dr. Saviola pointed out, cannot
13 be approved by the agency until all the reviews are
14 completed and until all deficiencies are adequately
15 addressed.

16 Contained in your panel packet are the revised
17 list of clinical questions for panel discussion. Please
18 note that these have been edited from the draft list
19 previously sent to you. You will be asked to address these
20 questions during the discussion.

21 At this time I would like to recognize the FDA
22 team members for this PMA -- our chemists, Ms. Ming Shih
23 and Mr. Nelson Lau; our microbiologist, Ms. Karen
24 Warburton; our toxicologist, Dr. Everett Beers; and our

1 statistician, Mr. Mel Sideman -- for their expert
2 contributions on this application.

3 The clinical reviewer for this PMA is Dr.
4 Malvina Eydelman, who will present her review of this
5 application after the sponsor concludes their presentation.

6 At this time, I would like to introduce Mr.
7 Richard Wood of Burdett & Radzius, the FDA consultant for
8 the sponsor of this PMA, Richard-James.

9 Mr. Wood?

10 MR. WOOD: Good morning, ladies and gentlemen
11 of the panel, Dr. Rosenthal, FDA, and guests. I can say
12 prefatorily that it's very interesting, being a regulatory
13 type, to sit and hear the regulatory discussion I heard
14 today. It made me feel like I was in my office fielding
15 calls from people such as yourself.

16 We're here to discuss, as has been mentioned,
17 the PMA for Silikon 1000 intraocular fluid. I'd like, if I
18 may, to go over what we're going to cover in the next 30 to
19 40 minutes.

20 I will give an introduction and background.
21 After that we will hear from Dr. Stanley Azen, a
22 statistician at the USC medical school. I can also say he
23 was involved in the NEI silicone oil study, of which you
24 will hear discussion this morning. We're also very lucky

1 to have with us two clinicians, both of whom were principal
2 investigators in the study we'll be discussing today, at, I
3 might also add, two of the largest sites who contributed
4 data to the data set you'll see.

5 I want to say that none of the presenters have
6 a proprietary interest in Richard-James. If they have
7 other statements -- I'm sure they're having their expenses
8 covered for coming to the meeting today.

9 MS. THORNTON: Excuse me, Mr. Wood, could you
10 speak a little more into the microphone? The air handling
11 system just came on, and it's difficult to hear you.

12 MR. WOOD: Thank you. We will also ask to have
13 questions, if at all possible, held to the end of the
14 presentation.

15 Next slide, please. We will be presenting data
16 today on Silikon 1000, the starting material for which is
17 polydimethylsiloxane. Polydimethylsiloxane undergoes a
18 proprietary multistep purification process during
19 manufacturing. It's important to note that that process
20 has not changed at any time during the production of this
21 material for the PMA and the IDE studies. The finished
22 product, which looks like this, is highly purified, as I
23 mentioned, by the proprietary process. It's optically
24 clear. Viscosity is 1000 centistokes. It's particulate

1 free, sterile, and non-pyrogenic.

2 Next slide, please. Let me amplify a little
3 bit, if I may, the statement concerning the source of the
4 silicone that we'll be discussing that was used in the IDE
5 study. This, as I mentioned, is the finished product, and
6 it will look something like this in the finished form. The
7 material that was used to produce the finished product
8 originally came from United Chemical Technologies. During
9 the course of the clinical trials, UCT, following the lead
10 of many other companies in this country, determined that
11 they would no longer supply silicone material for medical
12 uses. It, therefore, became necessary for Richard-James to
13 find a new source.

14 A source that was identified was NuSil
15 Technology, one of only two companies that will still
16 supply this material to medical use, and I can add that
17 they are also a supplier of this substance to NASA. The
18 Silikon 1000 that will be used in marketed product
19 following approval of this PMA will be supplied by NuSil.

20 Next slide, please. I won't dwell a lot on
21 this, because it was referenced by the FDA reviewers prior
22 to my presentation. The clinical trial discussed here was
23 initiated in August 1991, the PMA was filed in February
24 1995, the most recent update filed in November 1996. I can

1 also add that audits of good clinical practices, both by
2 FDA and independent auditors of the leading study centers,
3 have been conducted, and as Dr. Saviola mentioned, the data
4 set has been validated. All observations arising from
5 those audits have been addressed.

6 Next slide, please. Let me now discuss the
7 summary of the indications for which approval is being
8 sought. Silikon 1000 is an operative tool indicated for us
9 as a prolonged retinal tamponade in selected cases of
10 complicated retinal detachments, including CMV, PVR, PDR,
11 giant tears, and trauma.

12 Next slide, please. I would now like to
13 introduce the statistician for the clinical study, Dr.
14 Stanley Azen. He's a professor and director of biometry at
15 the Department of Preventive Medicine, USC. Dr. Azen has
16 performed statistical analysis of the RJ study and has
17 published 150 peer-reviewed articles, including 11 on the
18 NEI silicone oil study, and he was also statistical
19 director of that study.

20 I now introduce Dr. Azen.

21 DR. AZEN: Thank you, Dick, and good morning
22 everybody. It's my pleasure to describe the overview of
23 the study results for the clinical study of Silikon 1000.

24 ~~Next slide, please. I would like to just~~

1 review the study design, if I may. This is a multicentered
2 study conducted in the United States. The enrollment
3 period was between August 1991 through September 1996, and
4 the final analyses were conducted in November of 1996.

5 There are two primary patient study groups -- namely, CMV
6 retinitis and a non-CMV group which are characterized by
7 four primary etiologies -- namely, eyes with proliferative
8 vitreoretinopathy, PVR; proliferative diabetic retinopathy,
9 PDR; giant tears; and trauma -- and we will summarize the
10 outcomes for not only the CMV and non-CMV groups, but these
11 subgroups as well.

12 Next slide, please. One of the outstanding
13 features of the study is the numbers of eyes that have been
14 treated in this study. This study has enrolled and treated
15 2,754 eyes. Seven hundred and fifty-seven of those eyes
16 were CMV retinitis eyes. The other 1,816 eyes were non-CMV
17 retinitis eyes, and 181 eyes are characterized as "other."
18 These were a small group of non-CMV eyes with rare diseases
19 that were also treated with Silikon 1000 for retinal
20 detachments.

21 In the non-CMV group, it's important to point
22 out that the number of eyes with PVR was 935, which is four
23 times the number of eyes that were treated and seen and
24 followed in the silicone study funded by the National Eye

1 Institute. Furthermore, the number of eyes in the other
2 etiological groups -- PDR, giant tears, and trauma -- are
3 substantially large.

4 Next slide, please. Now, this slide summarizes
5 the principal study centers in the Richard-James Silikon
6 1000 study. In particular, this graph shows the 10 study
7 centers which treated and followed eyes for 75 percent of
8 the study cohort, and it's important to point out that six
9 of these 10 study centers were study centers for the
10 silicone oil study funded by the National Eye Institute,
11 and two of the investigators of that study, Dr. Topping and
12 Dr. Flynn, will be commenting about the clinical relevance
13 of the data after my presentation.

14 Next slide, please. I now will summarize the
15 endpoints, the primary outcomes of the study. The efficacy
16 endpoints are the traditional endpoints, which are
17 established not only in the silicone study, but also in the
18 Lucke-Laqua studies -- namely, anatomic success as
19 characterized by both macula attachment and complete
20 retinal attachment, and visual acuity as characterized by,
21 first of all, ambulatory vision, which is defined to be
22 visual acuity greater than or equal to 5/200 -- that is the
23 same cutoff that was used in the silicone study -- and
24 ~~preservation of vision, which is characterized by either~~

1 improved or maintained vision postoperatively.

2 I should also like to point out that the
3 primary time at which these endpoints are ascertained is 6
4 months, which is the classical time at which the efficacy
5 of the treatment is evaluated, but we also will be looking
6 at these data over a longitudinal period of 12 and 24
7 months.

8 Next slide, please. The safety endpoints,
9 again, are the classical and traditional endpoints --
10 namely, whether or not there's any oil emulsification
11 observed; two endpoints characterizing intraocular pressure
12 -- number one, as to whether there's elevated intraocular
13 pressure, IOP, which is defined to be greater than or equal
14 to 30 millimeters mercury at any given visit; and hypotony,
15 which is defined to be less than or equal to 5 millimeters
16 mercury -- any corneal opacity or abrasion; and whether or
17 not there's cataract formation in the phakic eyes.

18 I would just like to point out that the
19 definition of corneal opacity and abrasion was broad and
20 rigorous in this particular study and included not only
21 band keratopathies, but also corneal edemas and any
22 indication of unopacity.

23 Next slide, please. Patient follow-up. In the
24 non CMV group, 71 percent of the patients were followed 6

1 months or more, and the average follow-up period was over a
2 year -- namely, 13 months. With regard to the CMV patient
3 group, 60 percent of the patients were followed 3 months or
4 more. The average follow-up period was 4 and a half
5 months, and it's very important to point out that 44
6 percent of the patients died prior to the 6-month period
7 due to the HIV infection.

8 Next slide, please. As pointed out earlier by
9 Dr. Saviola and by Mr. Wood, the issue of the equivalency
10 between the suppliers of the silicone oil -- namely, UCT,
11 United Chemical Technologies, and NuSil -- it was important
12 to establish at least from a statistical point of view the
13 equivalency between these two suppliers, and this slide
14 highlights the rates of outcomes at 6 months for the non-
15 CMV patients for both the safety and efficacy parameters
16 and establishes whether or not there are statistically
17 significant differences between the two groups.

18 Just to comment about several of them, for the
19 UCT group at 6 months, the rate of macula attachment was 89
20 percent, and it was 91 percent for NuSil, and there was no
21 statistical difference between these two rates. The P
22 value is .86. Similarly for retinal attachment, the rates
23 were 70 percent versus 70 percent, and there is no
24 statistical difference between those.

1 If you examine the column of P values, the last
2 column, you'll see that basically there were no
3 statistically significant differences between the two
4 suppliers for any of the clinical endpoints at 6 months for
5 the non-CMV patients. For that reason, all outcome data
6 will be presented for the combined UCT and NuSil groups for
7 ease of presentation and because equivalency was
8 established on the S&E parameters.

9 This first slide is the result of evaluation of
10 macula attachment for both CMV, on the left-hand side, and
11 non-CMV eyes, and shown are four bars. The first bar in
12 each cluster represents 6-month data. The second bar, the
13 green bar, represents 12-month data. The red bar
14 represents 24-month data, and for completeness, the last
15 examination is given in the last of the four bars. Along
16 the vertical axis are the rates observed at each of those
17 time points, as I said before, for both CMV and non-CMV
18 eyes, and the sample sizes associated with each of those
19 follow-up time points is summarized at the bottom of the
20 slide.

21 This slide demonstrates the efficacy of macula
22 attachment, and for the CMV eyes, that rate is 95 percent,
23 and for the non-CMV eyes, it's 89 percent. The other
24 important thing to notice here is the stability over time,

1 that the rates are constant across the time periods of
2 follow-up.

3 Next slide, please. I'm going to also show you
4 the rates of macula attachment at 6 months and the last
5 exam for each of the non-CMV etiological groups. So I'm
6 repeating the total non-CMV here, and then PDR, giant tear,
7 PVR, and trauma. That will give you a sense of the rates
8 associated with each of the etiological groups.

9 Now, going along at a faster pace, the next
10 slide shows the same relationships for CMV and non-CMV eyes
11 for complete retinal attachment, and, again, efficacy for
12 this anatomic endpoint is established and is stable over
13 time.

14 Next slide, please. This, then, shows complete
15 retinal attachment for 6 months and the last exam,
16 stratified by each of the non-CMV etiological groups.

17 Next slide, please. Now, with regard to
18 preserved vision, which is vision equal to or better than
19 the preoperative vision, we see for the non-CMV group that
20 84 percent had preserved vision at 6 months and that it's
21 stable across the time points, and for the CMV group, 46
22 percent had preserved vision at 6 months, and there's a
23 slight declination across time.

24 ~~Next slide, please. This shows the preserved~~

1 vision rates for the various etiological categories in the
2 non-CMV group.

3 Next slide, please. Now, with regard to
4 ambulatory vision, which is defined to be vision greater
5 than or equal to 5/200, we see that 64 percent of the CMV
6 eyes have ambulatory vision. I'm sorry. This slide also
7 shows -- in addition to the 6, 12, 24, and last month
8 visits, it shows the rates preoperatively. Sixty-four
9 percent of the CMV eyes had ambulatory vision
10 preoperatively and at 6 months. Postoperatively, 65
11 percent had ambulatory vision. With regard to the non-CMV
12 eyes, 38 percent had ambulatory vision at 6 months
13 postoperatively, but it's important to notice that only 14
14 percent had ambulatory vision preoperatively, so there is a
15 3-fold increase in ambulatory vision after the operation,
16 and there was stability across time.

17 Next slide, please. This shows ambulatory
18 vision for the various etiological categories of the non-
19 CMV eyes.

20 Next slide, please. Now we're dealing with the
21 safety parameters here. We're showing the rates of
22 emulsification at the 6-, 12-, and 24-month examinations as
23 well as the last examination. It's important to point out
24 a very low, exceedingly low rate of emulsification in the

1 CMV eyes. Only 1 percent of the eyes had emulsification,
2 and anywhere from 3 to 5 percent in the non-CMV eyes over
3 time had oil emulsification.

4 Next slide, please. This shows the same thing,
5 stratified by etiological categories.

6 Next slide, please. Associated with
7 emulsification is the potential for elevated intraocular
8 pressure, defined to be greater than or equal to 30
9 millimeters mercury, and, again, there is a very
10 exceedingly low elevated IOP rate for both the CMV and non-
11 CMV cohorts.

12 Next slide, please. Same thing with regard to
13 the various non-CMV etiological categories.

14 Next slide, please. With regard to hypotony,
15 there is a 6 percent rate for hypotony in the CMV group at
16 6 months, but there was a 6 percent rate in hypotony
17 preoperatively. With regard to the non-CMV eyes, there was
18 a 19 percent hypotony rate at 6 months, but preoperatively
19 that rate was larger, 22 percent, and the hypotony rates
20 were stable across time.

21 Next slide, please. Six-month and last exam
22 data for the various etiological categories.

23 Next slide, please. Corneal opacities are
24 presented in this slide, and the rate of opacities for the

1 non-CMV group was 26 percent at 6 months, 19 percent
2 preoperatively. There is an increasing trend, which I've
3 seen in the silicone study also. This increasing trend is
4 fully expected due to band keratopathy and oil left in
5 phakic eyes, as well as hypotony, and I think that the
6 ophthalmologists will be able to make further comments
7 about that.

8 Next slide, please. This shows the
9 opacity/abrasion rates at 6 months and the last exam, and I
10 also want to reemphasize that this is a very broad
11 definition of opacity and abrasion, broader than that used
12 in the silicone study, which included only band
13 keratopathies.

14 Next slide, please. Cataract in phakic eyes is
15 presented here. At 6 months 63 percent of the phakic eyes
16 had cataract, as contrasted to 56 percent. There is a
17 slight increase in cataract, but this is due to the natural
18 result of vitrectomies.

19 Next slide, please. This is the cataract in
20 the phakic eyes, broken down for the various etiological
21 categories.

22 With that, I'd like to turn over the podium to
23 Trexler Topping. Dr. Topping is at the Mass Eye & Ear at
24 Harvard University in Boston.

1 Dr. Topping?

2 DR. STULTING: Excuse me just a minute, Dr.
3 Azen. I may have missed this, but for the record could you
4 please state your relationship to the company and any
5 financial interest, and we'll ask the further speakers to
6 do the same when they begin.

7 DR. AZEN: Okay. I'm sorry. I have no
8 proprietary interest with the Richard-James company as
9 primarily a consultant for the company.

10 DR. STULTING: Do they pay you?

11 DR. AZEN: As a consultant.

12 DR. STULTING: Okay. Thank you. That's what
13 we need.

14 DR. TOPPING: Good morning. I have no
15 proprietary interest in the Richard-James company.

16 DR. STULTING: Are you a paid consultant?

17 DR. TOPPING: I am not a paid consultant. I
18 trust my airfare here is covered.

19 (Laughter.)

20 DR. STULTING: What you need to say is that
21 you're a consultant and if you get paid for your time and
22 if they paid your expenses for coming up here, just for the
23 record so that people understand what your relationship is.

24 ~~DR. TOPPING: Expenses are paid.~~

1 DR. STULTING: Okay.

2 DR. TOPPING: As a tertiary vitreoretinal
3 surgeon over the last 20 years, I am proud to stand in
4 support of the Silikon 1000 study reported by Richard-
5 James.

6 Next slide, please. Vitreoretinal clinicians
7 are well aware of the value of silicone oil. This
8 substance is an absolutely needed adjunct to vitrectomy in
9 the management of complex retinal detachments. We all know
10 that silicone oil enables the salvage of previously lost
11 eyes. The use of silicone oil markedly improves the
12 outcomes of complex retinal detachments of diverse causes.
13 Over the last decade, we have all been struck by a marked
14 increase in retinal detachments caused by necrotic
15 retinitities, especially CMV retinitis in the AIDS
16 population.

17 Silicone oil is the most effective and the most
18 widely used mechanism of management of CMV retinal
19 detachments, and indeed, importantly so, it is also the
20 most compassionate means of treating AIDS retinal
21 detachments. It is compassionate in that it enables the
22 most rapid rehabilitation of the visual process to these
23 patients. In addition, it avoids the necessity for face-
24 down positioning for a considerable portion of the short

1 remaining life in these individuals.

2 Next slide, please. As a clinician, I would
3 like to summarize what I feel are the clinically important
4 highlights of this Silikon 1000 study for the non-CMV eyes.
5 Number one, it works. Retinal attachment at 6 months is at
6 the 70 percent number, and not only does it work in the
7 short term, but as time passes there is stability, in that
8 69 percent of the retinas are totally attached at 2 years.

9 But retinal attachment alone is not important.

10 Also, it has to be coupled with functional vision.

11 Ambulatory vision was obtained in 38 percent of the
12 patients at 6 months, and indeed was even maintained with
13 stability at 31 percent at 2 years.

14 But as you're using an agent, it not only needs
15 to be efficacious, which it is, but it also needs to be
16 safe, and I think from a clinical perspective
17 emulsification of the oil is, I feel, the most important
18 because it relates so directly with the other complications
19 one sees. This oil has an extremely low rate of only 3
20 percent emulsification at 6 months, and, amazingly, only 5
21 percent at 2 years.

22 Next slide, please. Thus, the Silikon 1000 oil
23 has some specifically important characteristics. It
24 enables us to achieve postoperative tamponade goals, it

1 gives long-term stable outcomes, and it displays a low
2 clinical toxicity with good safety for the patients.

3 Next slide, please. In order for silicone oil
4 to be of use, it must be placed inside the eye. This is
5 1000 centistoke silicone oil. The 1000 centistoke oil is
6 less viscous than 5000. The 1000 oil may be instilled into
7 the eye either with manual injection or by a mechanical
8 pump. Because of its lower viscosity and because of the
9 difficulty of viscous fluids going through the injection
10 canula systems, one obtains much better control of the
11 intraocular pressure and pressure of injection during the
12 injection process.

13 On the other hand, 5000 centistoke oil, of
14 course, is more viscous. Because of the higher viscosity
15 and because you're going through the same size canulas and
16 small openings into the eye, this usually requires a
17 mechanical pump. Mechanical pumps require added cost to
18 the operative facility, which may be a problem in smaller
19 facilities.

20 In addition, higher pressures are required to
21 push the oil into the eye through the delivery systems.
22 These higher pressures have themselves certain potential
23 problems and complications. Initially, because of the high
24 pressure required and the slow flow, the intraocular

1 pressure in the eye may be quite low for an extended period
2 of time, raising the probability of interoperative
3 choroidal hemorrhage during the early injection phase.

4 Later on during injection, as the pressures are so high in
5 the infusion systems, there is potential for high pressure
6 in the eye at the completion, with potential optic nerve
7 damage.

8 In addition, because of the high pressures that
9 one sees during infusion, it is a common experience among
10 surgeons that the infusion lines with 5000 centistoke oil
11 break, spraying oil throughout the OR, which is itself not
12 terribly important, but the important thing is that during
13 that interval, the intraocular pressure drops to zero, with
14 attendant potential complications.

15 Next slide, please. Of course, silicone oil
16 may be removed. There is marked increased ease of the
17 removal process with the 1000 centistoke oil. The oil is
18 gooey enough that it can be removed by displacement. Fluid
19 may be able to percolate into the eye, and passively the
20 oil exits the eye. On the other hand, the much more
21 viscous 5000 centistoke oil usually requires high active
22 suction for removal. Because of this high active suction
23 where the suction devices are placed within the eye, there
24 is a risk of retinal incarceration in suction devices, with

1 potential retinal tears and detachments.

2 I would like now to introduce Dr. Harry Flynn
3 of the Bascom Palmer Eye Institute, University of Miami.

4 DR. FLYNN: My name is Dr. Harry Flynn. I'm a
5 professor of ophthalmology on the full-time faculty at the
6 Bascom Palmer Eye Institute and director of the retina
7 service at our hospital. I do not have a financial or
8 proprietary interest in this product, and I assume that my
9 airfare will be covered by the company for coming here
10 today.

11 During the past 19 years on the faculty at
12 Bascom Palmer, I have been a principal investigator on two
13 silicone oil trials. The first of these was the NEI-
14 sponsored trial of PVR, with the use of C_3F_8 gas and
15 silicone oil, which recruited patients between 1985 and
16 1990 and has been reported in 11 publications. The second
17 trial is the current study of Silikon 1000, which began in
18 1991 and completed recruitment in 1995. I will summarize
19 the current Silikon 1000 study and compare these results to
20 other published studies.

21 Next slide, please. When should we use
22 silicone oil and not C_3F_8 gas? I've listed these reasons
23 on the slide. The first of these is failure for surgical
24 success with gas tamponade. The second issue is inability

1 of the patient to maintain the appropriate face-down
2 positioning necessary with gas. This applies to children,
3 patients with mental retardation, physically handicapped,
4 and patients unable to comply with 4 to 6 weeks of face-
5 down positioning. The next issue is the need for air
6 travel. Patients with gas may be unable to travel for 4 to
7 6 weeks after surgery, making alternative methods of
8 surgery necessary. Finally, early visual rehabilitation.
9 For those patients with CMV retinitis and AIDS, this is a
10 very important issue.

11 Next slide, please. The previously approved
12 and studied substitutes are listed on this slide. Adatosil
13 5000 was approved in November 1995 and is the only
14 currently available oil in the United States for use in
15 this situation. The NEI study of PVR enrolled and followed
16 patients between 1985 and 1990, and we are now about to
17 report 72-month follow-up of this study in the Archives of
18 Ophthalmology demonstrating the safety and efficacy of oil
19 use in this study. The final report is that of the Lucke-
20 Laqua group published in 1990 from Germany using 1000
21 centistoke silicone oil. This is the commonly used oil in
22 Europe today.

23 Next slide, please. This slide is the most
24 ~~important slide of my presentation and compares efficacy~~

1 outcomes in PVR eyes. We chose PVR because this is the
2 largest subgroup of non-CMV patients, and it is also the
3 group of eyes most commonly reported in the literature for
4 which comparison is available.

5 On the left-hand column, you will see the
6 efficacy outcomes listed, which include retinal attachment
7 rates, macula attachment rates, ambulatory vision, and
8 preserved vision. On the horizontal axis, we see a
9 comparison of the oils, the current Silikon 1000 compared
10 to the only alternative approved oil, and that is Adatosil
11 5000 centistoke, the NEI study of PVR, and the Lucke-Laqua
12 study. Notice that the number of patients in the Silikon
13 1000 group is 677. This is approximately six times greater
14 than any other reported study, and notice in the footnotes
15 that in the current study 76 percent had prior vitrectomy,
16 compared to 100 percent in the NEI study and 20 percent in
17 the Lucke-Laqua study.

18 Reviewing the data, macula attachment was
19 achieved in the current study in 93 percent of cases,
20 compared to 75 percent in the Adatosil group and 80 percent
21 in the NEI study, but it was not reported in the overall
22 Lucke-Laqua study. These rates certainly compare favorably
23 to the two other studies.

24 ~~Complete retinal reattachment was achieved in~~

1 76 percent of the current study, compared to 64 percent of
2 the Adatosil study, and, again, compares favorably to the
3 two other published large studies.

4 Ambulatory vision, again, defined as 5/200 or
5 better vision, was achieved in 40 percent of the Silikon
6 1000 group, compared to 34 percent in the Adatosil 5000
7 oil. Again, this is the only other alternative oil in the
8 United States. These rates compare similarly to the NEI
9 and Lucke-Laqua studies, which were much smaller studies,
10 and, again, the NEI study excluded eyes with confounding
11 diseases, such as preexisting glaucoma, macular
12 degeneration, or other disease processes which might affect
13 visual outcome.

14 Preserved vision, as covered by Dr. Azen,
15 occurred in 86 percent of patients, comparing favorably to
16 the Lucke-Laqua study of 60 percent.

17 Next slide, please. This slide summarizes the
18 safety outcomes in PVR eyes in the various studies. The
19 safety endpoints listed on the left column include
20 emulsification, hypotony, elevated pressure, corneal
21 opacity, and cataract. We compared the current study
22 Silikon 1000 with Adatosil 5000, NEI 1000 oil and gas.
23 Emulsification rates were very low in the current study, as
24 previously described, and were reported at 17 percent in

1 the 5000 Adatosil study.

2 Hypotony rates were 19 percent in the current
3 study, but preoperatively in this study 22 percent of eyes
4 had hypotony. In the Adatosil study, 5 percent had
5 hypotony postoperatively, but it's important to recognize
6 that only 1 percent of that group had hypotony prior to
7 surgery. These rates compare favorably to the oil group
8 from the NEI study and are certainly better than the
9 alternative, which is C₃F₈ gas, having a rate of 31 percent
10 hypotony.

11 Next, looking at elevated intraocular pressure,
12 only 2 percent of the Silikon 1000 group had elevated
13 pressure, compared to 10 percent in the Adatosil group and
14 similar low percentages in the other studies.

15 Moving next to corneal opacity, corneal opacity
16 of any degree occurred in 25 percent of the current study
17 and was not reported in the Adatosil group for the overall
18 range of corneal opacities. Only band keratopathy was
19 reported in this particular group. This 25 percent
20 compares favorably to the oil used in the NEI study and
21 also to gas.

22 Finally, cataract is another endpoint, and 52
23 percent of Silikon 1000 patients had cataract

24 postoperatively, again, comparing favorably to 71 percent

1 of the Adatosil group.

2 Next slide, please. The question comes, why
3 approve Silikon 1000 oil? As the preceding speakers and I
4 have shown, this oil allows the surgeon the ability to
5 achieve surgical goals, which are reattaching the retina
6 and improving visual acuity. Number two, this oil achieves
7 equal or better clinical outcomes compared to other oils.
8 Numbers three and four, as shown by Dr. Azen's
9 presentation, the long-term effects and outcomes are
10 stable, and there is low clinical toxicity.

11 Next slide. In conclusion, Silikon 1000 is a
12 safe and effective operative tool indicated for use as a
13 prolonged retinal tamponade in selected cases of
14 complicated retinal detachments shown in the categories
15 below. On behalf of vitreoretinal surgeons practicing in
16 the United States, I would like to request and urge this
17 panel to approve Silikon 1000.

18 This completes our presentation. Thank you.

19 DR. STULTING: Thank you very much.

20 At this point, we've reached the time in the
21 agenda for a brief break. I'd like to remind panel members
22 that there should be no discussion of the application or
23 any other panel business outside of the room.

24 Thank you very much.

1 (Recess.)

2 DR. STULTING: I'll reconvene the meeting,
3 please.

4 Is anybody terribly uncomfortable with the
5 temperature in this room? Who thinks it's too hot?

6 (Show of hands.)

7 DR. STULTING: Who thinks it's too cold?

8 (Show of hands.)

9 DR. STULTING: People who think it's too hot
10 need to stand over there, and the ones that think it's too
11 cold need to congregate in this area.

12 (Laughter.)

13 DR. STULTING: We'll move forward with the
14 presentations. I think Dr. Eydelman is next. Go ahead.

15 DR. EYDELMAN: Good morning.

16 DR. STULTING: I'm sorry. What is the panel's
17 desire about questioning the sponsor? Are there any
18 questions, or would you prefer to wait until later? The
19 consensus is to wait until later? Okay. Let's go ahead.

20 DR. EYDELMAN: This morning I would like to
21 just highlight a few of the points from my review. As was
22 mentioned several times, this is one of the largest studies
23 that we have seen under an IDE. It involves 2,754 eyes,
24 and 182 physicians were involved, 78 sites, 5 years.

1 During this study, Richard-James found it
2 necessary to change its raw material supplier from United
3 Chemical Technologies to NuSil. Thus, the data in this PMA
4 involves analysis of UCT oil use, NuSil oil use, comparison
5 of UCT and NuSil data, and combined UCT and NuSil analysis.
6 Only oil manufactured from NuSil is currently available for
7 commercial distribution and will be the only oil used after
8 the approval is obtained.

9 The objective was to establish safety and
10 effectiveness of Silikon 1000 as a retinal tamponade, and
11 the study was non-comparative, open label.

12 The study's accountability can be analyzed in
13 several different ways. You can do it by two oils, by
14 emergency/non-emergency, by the diagnosis, by the amount of
15 follow-up the subjects received, or by seven subgroups
16 which arose secondary to numerous data accountability
17 issues in this PMA.

18 In order to try to understand the evolution of
19 the seven subgroups comprising the baseline population, one
20 must consider it in the historical perspective of this PMA.
21 The original submission of 282 eyes was received in January
22 of 1995. Six months later another group of 402 eyes, non-
23 CMV diagnosis, was submitted to the agency. Those two
24 ~~submissions comprise the first subgroup.~~

1 However, analysis of this data revealed several
2 accountability problems, and in order to address these
3 issues, Subgroup 2, consisting of 903 additional eyes
4 treated with UCT oil, was provided in January of 1996. In
5 order to address the remaining numerous accountability
6 issues and to submit the data generated from several site
7 audits, the remaining subgroups emerged and were submitted,
8 bringing us to today's total of 2,573 eyes.

9 This table I think clearly demonstrates the
10 enormous amount of work done by both the sponsor and the CA
11 in the last year and a half in order to locate and analyze
12 the missing data. Please note that the number of eyes
13 analyzed has grown almost 10-fold since the first
14 submission.

15 As you heard before, this PMA in its current
16 form contains data on 2,754 eyes, 2,573 of which represent
17 the baseline population. Out of 2,573, the records of any
18 follow-up examination were available for 2,493 eyes. These
19 eyes are referred to as core, and no postoperative data at
20 all was available for 80 eyes, which is 3.1 percent.

21 One thousand five hundred and thirty eyes had
22 the minimum pre-op and a 6-month post-op report form and
23 are defined as cohort. Thus, overall 60 percent of
24 subjects had a 6 month follow-up. One has to take into

1 consideration, however, that some of these were AIDS
2 subjects who died prior to their 6-month follow-up.

3 As I mentioned before, you can look at the
4 baseline population, broken out by CMV and non-CMV, and see
5 that there were 1,816 non-CMV eyes analyzed in this PMA.

6 For the purposes of a statistical analysis of
7 the cohort, the data were coded and entered into the data
8 base for 6 months, 12 months, and 24 months. For the
9 analysis of the core data, data were entered for the last
10 exam only. With the above data entry coding, there is no
11 data available in the data base for cohort eyes prior to 6
12 months. For the core eyes, data prior to 6 months is
13 available in the data base only if the subject's last visit
14 occurred prior to that point.

15 It was not evident until recently that these
16 data were not entered into the data base. In a recent
17 teleconference, FDA became aware that the data coding also
18 omitted entry of preoperative surgery status into the data
19 base. The sponsor was informed that all data collected
20 under the IDE must be entered into the data base and
21 analyzed to ascertain that it does not present any
22 additional safety concerns. The sponsor has agreed to
23 enter all the data and submit it as an amendment to the
24 PMA.

1 My analysis is a little bit different than the
2 sponsor's this morning, in that I've focused separately on
3 the UCT and NuSil oil. As you see, 2,551 eyes were treated
4 with UCT alone, out of which 2,387 comprised the baseline
5 population. Out of all the UCT-treated CMV eyes, 31
6 percent reached a 6-month exam, 45 percent of whom,
7 however, died prior to reaching 6 months. Out of non-CMV
8 eyes treated with UCT, 71 percent reached a 6-month exam,
9 and 20 percent were lost to follow-up.

10 This is a summary slide of some of the efficacy
11 endpoints for UCT oil. As you can see, complete attachment
12 for CMV/non-CMV was 77 and 70 percent, respectively.
13 Preserved vision was 45 percent in CMV and 84 percent in
14 non-CMV.

15 This is the efficacy endpoints plotted for each
16 one of the non-CMV diagnoses -- specifically, PDR, giant
17 tear, PVR, and trauma.

18 The overall safety of the UCT oil showed a
19 quite low percent of emulsification of only 1 percent in
20 CMV and 2 percent in non-CMV eyes. Cataract formation was
21 at 64 and 61 percent. There was some difference between
22 corneal opacity and hypotony rates for CMV and non-CMV
23 eyes, at 5 percent for CMV and 19 percent for non-CMV for
24 hypotony, and 5 percent and 26 percent for corneal opacity.

1 These are the safety for non-CMV by diagnosis.
2 As was mentioned by the sponsor this morning, for non-CMV
3 eyes the percentage was 7 percent at 6 months. As
4 demonstrated in this graph, the attachment rates were
5 stable across the three follow-up periods, at 6, 12, and 24
6 months.

7 For CMV eyes the percentage of eyes with
8 complete attachment was 77 percent at 6 months, 75 percent
9 at 12 months, and 84 percent at 24 months. The percentage
10 of eyes with macula attachment were 94 at 6 months, 92 and
11 89, respectively. For non-CMV, UCT efficacy also remained
12 stable.

13 Even though this study was a non-comparative
14 study in its design, the comparison of the results was
15 performed to the known data from the literature, and this
16 is a plot of the efficacy at 6 months of UCT-treated PVR
17 eyes versus various retrospective silicone oil studies.
18 This was done for the last visit as well, as summarized
19 previously by the sponsor. Safety was compared as well
20 with those parameters that were available in the
21 literature.

22 Now, as you heard, the sponsor had to change
23 the raw material supplier. The clinical study with a new
24 source of oil was designed as a confirmatory study only,

1 given that the sponsor demonstrates preclinical equivalency
2 of oil from UCT and NuSil. This equivalency has not been
3 established as of today; however, the clinical data
4 analysis is being presented for panel review, with the
5 provision that the preclinical equivalence will be
6 adequately established.

7 Two hundred and three eyes were treated with
8 NuSil, out of which 186 comprised the baseline population
9 of CMV and non-CMV eyes. At the time of approval for
10 subjects treated with NuSil under the IDE, it was pointed
11 out to the sponsor that they should make every effort to
12 have 100 percent accountability for this small group of
13 patients in order to have enough data to make any judgment
14 on the clinical safety and efficacy of this new source.
15 Seventy-three percent accountability for the non-CMV
16 subjects at 6 months was achieved, 41 percent for CMV eyes.

17 Here the NuSil efficacy endpoints are plotted,
18 and as you can see, they're quite close to the UCTs. This
19 is non-CMV by diagnosis at 6 months efficacy endpoints.
20 Emulsification for NuSil also was quite small, 6 percent
21 for CMV eyes, 4 percent at non-CMV; cataract formation of
22 62 and 70 percent; and hypotony of 8 percent and 15
23 percent. Corneal opacity was 19 percent for CMV and 28
24 percent for non-CMV.

1 This was the safety, again, plotted by the
2 various diagnoses. Even though I created this graph of
3 NuSil efficacy over time, I would like to remind you that
4 long-term follow-up available is quite limited. There are
5 only 17 non-CMV eyes at 12 months available for analysis at
6 this point, and two CMV eyes.

7 Both UCT and NuSil populations had a large
8 percentage of pediatric cases. There were 251 eyes treated
9 with UCT in subjects less than 20 years of age, and there
10 were 19 for NuSil.

11 Comparing UCT and NuSil efficacy endpoints at 6
12 months, there was no statistically significant difference
13 in any of the efficacy outcomes. Here you see I plotted
14 CMV, UCT and NuSil, and non-CMV and non-CMV by the two
15 various oils next to each other, and you can see there's
16 really not much difference.

17 When we look at a safety endpoint, for CMV eyes
18 the 6-month rate of corneal opacity was greater for the
19 population of NuSil eyes than it was for UCT, 19 percent
20 versus 5 percent, with a P of .05. However, the 19 percent
21 rate of corneal opacity for NuSil CMV eyes was less than
22 that reported for non-CMV eyes treated with either NuSil or
23 UCT.

24 ~~When we look at the same analysis at the last~~

1 exam, we see that the corneal opacity rates were equivalent
2 between the population of NuSil and UCT eyes, 6 versus 4
3 percent, with a P of .65. There were no other
4 statistically significant differences found.

5 From this analysis, the sponsor concludes that
6 the two suppliers, UCT and NuSil, of Silikon 1000 are
7 clinically equivalent.

8 Now for some additional overall safety
9 considerations. For UCT oil, 46 CMV and 209 non-CMV eyes
10 had a single reinjection. From the two oils, two CMV and
11 10 non-CMV eyes had a single reinjection. Most
12 reinjections occurred prior to the 6-month exam with both
13 UCT and NuSil.

14 Oil removal took place prior to 6 months in 232
15 non-CMV eyes treated with UCT and 17 eyes treated with
16 NuSil. At this point, we have limited information about
17 oil removal, but the sponsor has committed to provide a
18 thorough analysis of oil removal cases to FDA, and my
19 understanding is that the amendment has been received
20 today.

21 Just to turn your attention to the labeling,
22 this is indications for use as stated in the labeling: as
23 a prolonged retinal tamponade in selected cases of
24 ~~complicated retinal detachment where other interventions~~

1 are not appropriate, and in AIDS-related CMV retinitis and
2 other viral infections.

3 I would like to direct your attention now to
4 the questions which you have in your packet. Question No.
5 1: Does the data analysis of the clinical endpoints
6 reported in the PMA provide for the determination of
7 reasonable assurance of safety and efficacy of Richard-
8 James Silikon 1000 silicone oil for the labeled indications
9 for use? If not, are there additional data analysis which
10 would be recommended for the information currently
11 presented in this PMA?

12 Question No. 2: Currently the methodology to
13 demonstrate absolute chemical equivalency of silicone oils
14 used for retinal tamponade has not been validated;
15 therefore, a confirmatory study was requested of the
16 sponsor to adequately demonstrate comparable clinical
17 outcomes from the two raw material suppliers, UCT and
18 NuSil. Does the data set with the available follow-up
19 provide for an adequate determination of safety and
20 efficacy for the NuSil-based Silikon 1000 oil for the
21 labeled indications for use? If so, is the follow-up
22 period adequate, or would additional follow-up data be
23 recommended? If the current data set is not adequate to
24 demonstrate clinical comparability, what are your

1 recommendations?

2 Question No. 3: Do the indications, warnings,
3 and precautions in the current draft labeling adequately
4 reflect the data and experience with this silicone oil? If
5 not, what additional language would be recommended?

6 Question No. 4: With the large percentage of
7 pediatric subjects treated with Silikon 1000, would a
8 separate analysis for pediatric cases be warranted to
9 better assess risk/benefit ratio for this population? Is
10 this analysis recommended even if the sponsor does not want
11 to include in the labeling any specific information about
12 pediatric use?

13 Finally, Question No. 5: The Adatosil 5000
14 silicone oil was approved with a condition that a
15 postapproval study be conducted on the rate of oil removal.
16 Do you believe that the issue of oil removal has been
17 adequately addressed in this application, or should an
18 additional study be performed after the device has received
19 market approval?

20 Thank you very much for your attention.

21 DR. STULTING: Is the presentation of the
22 agency's comments completed?

23 DR. SAVIOLA: That concludes our presentation.

24 DR. STULTING: Okay. Then, for the record, you

1 may leave the table, and the discussion portion of the
2 meeting is open, and I'll ask Dr. Wilkinson to begin by
3 presenting his comments.

4 DR. WILKINSON: Thank you, Mr. Chairman. I'm
5 going to condense my written comments.

6 First of all, for the record, I think the
7 agency should be applauded for sticking with this
8 application. I think what you've just seen in terms of how
9 these data were acquired should make it obvious to everyone
10 that the agency has gone through a tremendous amount of
11 effort to keep this PMA alive. Those of us who are used to
12 hearing the FDA bashed should remember this. On the other
13 hand, it should be noted that the sponsor has finally come
14 up with sufficient information for us to judge the PMA, and
15 for that I'm very, very thankful.

16 The data which are available demonstrate that
17 the performance of this device is comparable to that
18 reported for other silicone oils, one of which has been
19 approved, and in spite of a lack of optimal follow-up of
20 all cases, the literal number of eyes examined at 6 months
21 was large, and this is a very definite strength of this
22 PMA.

23 The data demonstrate no surprising findings.

24 ~~The device appears to be relatively safe and effective,~~

1 based upon the retinal reattachment rates and the frequency
2 of complications which are known to be associated with the
3 use of silicone oil.

4 We all would acknowledge it's unfortunate that
5 a different producer of the raw material is now in place.
6 This is, as you know, a sign of the times and certainly
7 related to the malpractice situation, the silicone oil
8 breast situation in our country. I nevertheless think that
9 for the purposes of this panel we should go along with the
10 assumption that the preclinical equivalency will be
11 discussed between the sponsor and the agency. I think that
12 we as panel members should, for the purposes of this
13 clinical discussion, assume that these devices are
14 considered equivalent on a preclinical basis, and if that's
15 the case, I believe that the two cohorts can be combined,
16 as the sponsor has suggested.

17 I've mentioned to the agency and would like to
18 see in future applications the data stratified for cases in
19 which surgery is successful. I don't think it's
20 particularly helpful to know how many eyes have cloudy
21 corneas if they're blind anyway. On the other hand, I
22 think it would be very helpful to all of us if we knew for
23 eyes that were reattached and doing relatively well, what
24 the incidence of subsequent corneal opacification might be.

1 I think the labeling appears to be generally
2 appropriate; however, under adverse reactions, I think some
3 statements should be modified. In Amendment 18 there's an
4 implication that no complications other than emulsification
5 are due to the oil. I think that's probably incorrect, and
6 yet this is not a big deal, and these things can be
7 modified quite easily.

8 I do not believe a separate analysis for
9 pediatric patients is in order.

10 I do not believe the issue of oil removal
11 should be studied further. I think that's a nightmare. I
12 discussed this over a year ago with the previous oil which
13 was approved. The problem is that oil removal is only
14 attempted in eyes that look relatively good, and you just
15 don't even know where to start with any sort of data
16 analysis.

17 Mr. Chairman, in conclusion, I would recommend
18 that this PMA be considered for approval.

19 DR. STULTING: Thank you.

20 I'll ask Dr. Ruiz to add his comments.

21 DR. RUIZ: Mr. Chairman, I'm just going to read
22 my written report.

23 I've reviewed the materials sent to me on
24 Richard James Silikon 1000. By way of introduction,

1 silicone has been widely used in ophthalmic surgery since
2 the 1960s. There has been an ongoing discussion and debate
3 over the advantage of various viscosities. In the past,
4 there were also some questions as to the purity of the
5 product.

6 The use of intraocular silicone has been
7 reserved for clinically desperate cases consisting of
8 proliferative vitreoretinopathy, failed retinal detachment
9 surgery, giant retinal breaks with detachment, and other
10 complicated cases not amenable to conventional treatment.
11 The ocular complications of intraocular silicone are well
12 known, but these complications are far exceeded by the
13 advantages in the use of this material in these clinically
14 desperate cases. Intraocular silicone is usually reserved
15 as a last line of defense in eyes which are otherwise
16 doomed to certain blindness.

17 In evaluating Richard-James Silikon 1000, I've
18 focused my attention on product purity, toxicity,
19 contamination and potential contamination, as well as any
20 unusual complications which have not been previously noted
21 with the use 5000 centistoke silicone. In addition, I've
22 noted the efficacy and success rate with this product
23 compared to silicone 5000.

24 ~~It's my opinion that the data submitted by the~~

1 applicant provide reasonable assurance of safety and
2 efficacy of Richard-James Silikon 1000 silicone oil for use
3 as a prolonged retinal tamponade in selected cases of
4 complicated retinal detachments, and also for primary use
5 in retinal detachments due to AIDS-related CMV retinitis
6 and other viral infections. Further, the current data set
7 for the non-CMV eyes provides, in my opinion, sufficient
8 data to determine safety and efficacy for the NuSil-based
9 Silikon 1000 oil, and that additional follow-up data are
10 not needed.

11 Even though there is a large percentage of
12 pediatric patients treated with Silikon 1000 oil, I do not
13 feel a separate analysis for these cases is warranted. The
14 risk/benefit ratio for this population should not vary
15 sufficiently from those of the adult population, and in
16 view of the fact that there is no alternative effective
17 therapy, I would feel that no specific labeling or
18 additional data is needed. One must consider that although
19 complications of glaucoma, cataract, corneal clouding, and
20 hypotony are all significant, they are offset by the fact
21 that there is no alternative treatment in these desperate
22 cases in which the eye will surely go blind without the use
23 of silicone.

24 In summary, it's my opinion, based on the data

1 supplied and the analysis of that data, that Richard-James
2 Silikon 1000 shows a degree of safety, toxicity, and purity
3 equivalent to that of silicone 5000, that it appears to be
4 just as efficacious as silicone 5000, and that it is
5 unquestionably easier to manipulate and use than silicone
6 5000, making it a product which will benefit both patients
7 and ophthalmic retinal surgeons without introducing
8 additional risks or complications.

9 DR. STULTING: Thank you.

10 Any other comments from the panel?

11 DR. RUIZ: Can I make a few additional
12 comments? I'm sort of perplexed by the use of the word
13 "clinically equivalent" in a product that should be easy
14 enough to analyze to be exactly the same, whether it's from
15 one manufacturer or another. It seems to me like we've
16 complicated the issue here by making a big deal out of the
17 silicone coming from two different sources, when really the
18 analysis of that silicone ought to be a truly scientific
19 thing that's easy to do vis-a-vis a clinical study, which
20 is very difficult to do.

21 I'd like to ask some of the clinicians a couple
22 of questions. The intraocular pressure data, was that with
23 or without treatment at 6 months, at 12 months, at 24
24 months?

1 DR. FLYNN: With treatment.

2 DR. RUIZ: With treatment. So those
3 percentages are patients that are on therapy and still
4 exceed 30 millimeters mercury.

5 DR. STULTING: For the record, Dr. Flynn, you
6 should come up and sit at a microphone and introduce
7 yourself so that the record will reflect who answered the
8 question and how it was answered.

9 DR. FLYNN: This is Dr. Harry Flynn from the
10 University of Miami School of Medicine. The answer to the
11 question was that these eyes were on treatment at the time
12 that these pressure determinations were recorded.

13 DR. RUIZ: So let me ask a follow-up question.
14 How many eyes were on treatment that didn't exceed 30
15 millimeters of mercury? What percentage of eyes were
16 needed to be treated for any elevated pressure?

17 DR. FLYNN: I'm not sure I can answer that
18 question.

19 DR. RUIZ: Quite a few?

20 DR. FLYNN: I would say that it's probably a
21 relatively low number, because the number of eyes with
22 grossly elevated pressure was low, and by that I mean
23 greater than -- our endpoint was greater than or equal to
24 30. But most of these eyes had low pressure. As you know,

1 in the National Eye Institute study and in our study,
2 hypotony was a preoperative condition in, certainly, the
3 range of 25 or 40 percent, and then after surgery hypotony
4 was a much greater problem than elevated pressure. But I
5 cannot give you a number on exactly how many patients were
6 taking glaucoma medications.

7 DR. RUIZ: Trex?

8 DR. TOPPING: I would agree, but the data
9 points were collected as that number of patients who had
10 elevated pressure at that given examination interval. If
11 the patient had indeed had normal pressure up until, let's
12 say, the 6-month interval and was measured as elevated at
13 that one point, it would appear as a blip as a positive for
14 elevated IOP, even though that patient may then be treated
15 with topical agents and normalized within the next several
16 weeks.

17 DR. RUIZ: I mean, the way the data is
18 presented, I would almost interpret it to say that this was
19 the percent that were not controllable, because you're
20 talking about a level of 30 on medication.

21 DR. FLYNN: I might clarify for the committee
22 that this endpoint -- this, again, is Dr. Harry Flynn
23 speaking -- that this was a one-time determination. This
24 was one event recorded during the postoperative course.

1 That could have been at 1 week, it could have been at 6
2 months, or at a later time. So it would require evaluation
3 of the subset of when that pressure elevation occurred. We
4 have that data, but most of the pressure rise occurred at 1
5 week to 1 month after surgery, and then on long-term
6 follow-up the pressure was usually controlled or low.

7 DR. RUIZ: I think the important fact that I'd
8 like to have is how many of these patients required
9 glaucoma management afterwards, not how many of them had
10 one spike to 30 sometime during their lifetime.

11 Let me ask another question. What were the
12 percent of scleral buckles that were done in conjunction
13 with the use of the silicone?

14 DR. AZEN: This is Dr. Azen speaking. We do
15 have that information, but I would need to look for it.

16 DR. RUIZ: Can you shoot from the hip? I don't
17 need it precisely. While you're looking for that, let me
18 just make a few other comments, Mr. Chairman, if I can.

19 You know, I heard Jim Saviola say that we're
20 going to place the burden of presenting the data on the
21 sponsors, and I think that's fine. But then do we have to
22 go over all the data again from the FDA? If we're going to
23 put the burden of the data on the sponsor, let's don't
24 listen to it all again 5 minutes later.

1 On the labeling aspect, it seems to me that we
2 need to make a distinction, as we do here in this product,
3 over this and, for instance, refractive surgery, in which
4 you're talking about a very different kind of a market.
5 The labeling for lay people or for general physicians I
6 think is one thing, and the label for maybe 1,000 retinal
7 surgeons in the whole world that will be using this product
8 is another thing.

9 The last thing I'd like to say is, I'd like to
10 thank the sponsor for persisting in this to the benefit of
11 all of our patients, because I can't imagine that this is a
12 very profitable endeavor, number one, or a very profitable
13 product.

14 DR. AZEN: Sir, I've found the data related --

15 MS. THORNTON: Excuse me. Could you identify
16 yourself, please, for the record?

17 DR. AZEN: This is Dr. Azen speaking again.
18 Dr. Ruiz, I have found in our eyes in the initial injection
19 that 25 percent also had a scleral buckle. Some of the
20 eyes had previous vitrectomies, and there was a revision of
21 the buckle.

22 DR. RUIZ: The only reason I was interested in
23 that is that Dr. Topping said that it was a humane way to
24 treat patients, for instance, with AIDS, and I certainly

1 agree with that. The surgical procedure itself has a lot
2 less morbidity and so on than a massive scleral buckling
3 operation.

4 Thank you very much.

5 DR. STULTING: Dr. Higginbotham?

6 DR. HIGGINBOTHAM: I have two questions. First
7 of all, I'd like to thank Dr. Topping and Dr. Flynn for
8 sharing their clinical experience with us, and it's to
9 these two esteemed colleagues that I'd like to direct my
10 first question.

11 As a glaucoma specialist, I've seen a lot of my
12 own procedures gravitate from inpatient to outpatient, and
13 it's my understanding that this 1000 centistoke vehicle
14 could be used as an outpatient. Could you comment on that,
15 and if you do agree that it could be used as an outpatient,
16 would you anticipate that the efficacy and safety issues
17 might change as a result?

18 DR. TOPPING: I'm Trex Topping. For the last,
19 I would say, 3 years, virtually every silicone oil
20 operative procedure I have carried out has been as an
21 ambulatory procedure, many of them in an ambulatory
22 surgical facility setting. We have looked at outcome
23 analysis, not specifically for silicone oil patients, but
24 for retinal patients in general, in both the hospital

1 operative setting versus the ambulatory setting and in an
2 ambulatory setting surgery center versus ambulatory surgery
3 in a hospital OR, and have found no significant
4 differences.

5 I wouldn't anticipate any difference in any of
6 the parameters of safety or efficacy that are monitored
7 here. I'd only comment that patients often find it easier
8 to work through ambulatory surgery.

9 DR. FLYNN: Dr. Flynn commenting on the same
10 question. In more than 80 percent of our patients, we now
11 perform vitreoretinal surgery as an outpatient procedure.
12 The factors that influence our decision to bring a patient
13 into the hospital would include coexisting medical
14 diseases, inability to use their medications because of
15 blindness in the fellow eye, and general status of the
16 patient.

17 As far as the primary procedure, again, there
18 may be a coexisting scleral buckle and it may be a longer
19 operation, which may also influence our decision. But in
20 terms of removal of silicone oil, this is routinely an
21 outpatient procedure in 100 percent of patients.

22 DR. HIGGINBOTHAM: Thank you.

23 I had one other question. This question is
24 directed to Dr. Azen. I think you mentioned in your review

1 that you did not separate out those patients that had
2 hypotony that might have contributed to the corneal
3 opacification. Is that right? That there's probably some
4 overlap?

5 DR. AZEN: Right. That's true.

6 DR. HIGGINBOTHAM: Do you have a sense in terms
7 of how many patients did not have hypotony but still had
8 corneal opacification?

9 DR. AZEN: Well, we do have a line listing of
10 all the complications of the patients, and we could count
11 that for you. I don't have a sense for it on the spot.

12 DR. MACSAI: Dr. Azen, I was wondering if you
13 had separated out the patients that had corneal opacity by
14 those who are phakic, aphakic, or pseudophakic.

15 DR. AZEN: The analysis I've presented presents
16 opacities only for the phakic eyes. So at any given time
17 we count the denominator as the number of eyes that are
18 phakic, and then we look at opacities.

19 DR. MACSAI: So, then, your 42 percent at 24
20 months follow-up is in phakic eyes?

21 DR. AZEN: Only in phakic eyes, yes.

22 DR. MACSAI: Thank you.

23 DR. AZEN: Oh, I'm sorry. I think there's
24 going to be a revision of that answer. Maybe you can

1 clarify that.

2 DR. TOPPING: I'm sorry. I think you're
3 discussing cornea versus cataract opacities.

4 DR. MACSAI: Right.

5 DR. TOPPING: But we do have stratification, I
6 would trust, of that data, but --

7 DR. AZEN: I'm sorry, I misunderstood your
8 question. Would you rephrase it, please?

9 DR. MACSAI: Okay. The question as previously
10 intended to be stated was, have you stratified the number
11 of patients with corneal opacity on the basis of their lens
12 status being either phakic, aphakic, or pseudophakic?

13 DR. AZEN: We have not.

14 DR. FLYNN: This is Dr. Flynn commenting on
15 that. I would say the rate of corneal opacity in phakic
16 eyes with successful retinal reattachment is
17 extraordinarily low. Similarly, in pseudophakic eyes, in
18 which there's no emulsification of the oil and the retina
19 is reattached, the incidence of corneal complications is
20 equally low. However, in the setting of recurrent retinal
21 detachment or hypotony or chronic glaucoma, corneal opacity
22 rates go way up, and these factors are intermingled. I
23 can't give you any data, but I would say that all of these
24 clinical factors contribute to the status of the cornea.

1 DR. WILKINSON: I think, again, this just
2 points out the fact that the sponsor could do mankind a
3 great good deed if you could restratify these complications
4 on a basis of anatomical success or at least macula
5 reattachment in, obviously, phakic and pseudophakic versus
6 aphakic.

7 DR. AZEN: Right. We do have some of those
8 analyses, Dr. Wilkinson. Would you like us to show those?

9 DR. WILKINSON: Not for the purposes here. I
10 just think in terms of particularly the labeling that this
11 in fact would be of interest to the 1,000 vitreoretinal
12 surgeons that Dr. Ruiz mentioned.

13 DR. MACSAI: More importantly, I think it may
14 be of interest to some of the patients in whom this will be
15 used, because if they're aphakic preoperatively and the
16 incidence of corneal decompensation is 90 percent, that
17 might be involved in surgical planning.

18 DR. STULTING: Any other questions of the
19 sponsor? Dr. Ferris?

20 DR. FERRIS: I guess this is more of a comment
21 than a question, and Sandy Brucker is not here, but his --

22 DR. STULTING: I hope you're not going to speak
23 for him.

24 (Laughter.)

1 DR. FERRIS: I would never consider speaking
2 for Sandy Brucker. However, I know he and I share a point
3 of view with regard to this -- I guess you could call it a
4 study, and the point of view is that this could have been
5 done at much less cost, I suspect, because I'm sure there
6 was a huge cost going back and gathering all of that data
7 that were gathered retrospectively, that it would have been
8 done much better if there had been some sort of appropriate
9 study design from the beginning.

10 There's this big pile of stuff, boxes that come
11 to me to look at. I don't know what the study design was.
12 It looks to me like the study design was, "We'd like to get
13 an idea of whether this stuff works," and that's the
14 hypothesis. It seems to me that in this day and age we
15 could easily go beyond that. There was a silicone oil
16 study. You could have done, "We want to know if this lower
17 viscosity oil had comparable results to the higher
18 viscosity oil. Here are the endpoints that were studied in
19 the silicone oil trial, and we're going to study those same
20 endpoints."

21 For example, I don't know exactly what the
22 definition of "cataract" is. Glaucoma was discussed here,
23 pressure greater than 30, uncontrolled before attempts at
24 control. I don't know whether you'd call that glaucoma or

1 not. Corneal opacities. What was the definition of a
2 corneal opacity?

3 Having been in this business for a long time, I
4 know these things aren't easy, but at least if I knew this
5 is what the clinicians had -- I suspect the clinicians
6 didn't have anything. They had little boxes that they
7 checked yes or no, when they checked them at all.

8 There's one final comment, and that's with
9 regard to what appears to be a common practice in these
10 studies, and that is that there's some final follow-up
11 time, like 2 years. I don't know what the final follow-up
12 time in this study was. However, I know that there are
13 patients that should have been available for follow-up for
14 4 or 5 years.

15 It seems to me that once a study stops, that at
16 least attempts should be made to continue to follow
17 patients for as long as the process goes until it's
18 approved. I don't think that's too big of a burden.
19 You're following the patients anyway, and with regard to
20 the variables that I talked about, such as cataract,
21 glaucoma, corneal opacity, I think it would be of not just
22 passing interest to know what the 3- and 4-year rates are,
23 to the extent that they exist. Granted the sample size
24 problems.

1 So I suppose that the comment eventually comes
2 down to my strong recommendation that a good study design
3 be developed at the beginning, and I don't know whether the
4 agency can be more proactive in assuring that there is a
5 study design, that outcome variables are defined, that
6 there is some sort of comparison group or at least some
7 number that is being shot at.

8 I'm finished, and I hope Sandy wouldn't
9 disagree too much.

10 DR. RUIZ: Rick, let me ask you a question. I
11 think one of the problems is that you try to go back and
12 pick up all the data. As retinal surgeons, we've all been
13 there where you're just desperate to do anything you can
14 do, and my question, Rick, is, this would have taken really
15 not a very large sample. You probably could have done it
16 with 100 or 200 patients with a laid-out plan, as he's
17 saying. So you've got 1,000 patients, and you don't have
18 any answers, and you say, "We want to get some answers;
19 therefore, for the next 250 of them, we're going to do it
20 this way," and then you have a really good study, and you
21 get the answer.

22 DR. FERRIS: I suspect Stan Azen would agree
23 with me that the only way to deal with losses to follow-up
24 is to not have them, and other than that, you can guess as

1 to what happened to those that were lost to follow-up, and
2 you can do some analyses that look at baseline
3 characteristics and say they were generally comparable.

4 But ongoing quality control as part of the
5 study is the critical feature, and if a doctor can't get in
6 a data form at the appropriate study visit, I don't think
7 he should be allowed to use the drug or device the next
8 time. And that's the way the company can -- the company
9 says they can't control these doctors. Well, to a certain
10 degree that's true, but they can control who gets the
11 stuff.

12 DR. STULTING: Procedurally, we should ask all
13 of our questions of the sponsor, and then allow the sponsor
14 to return to the audience, so let me ask one more time, are
15 there any additional questions of the sponsor at this time?

16 Go ahead, Dr. Soni.

17 DR. SONI: I would like to address the loss to
18 follow-up even in the NuSil part of the study, the 17
19 percent loss. Is that a normal loss with these sort of
20 patients, or is it an unusual loss? Can you comment on
21 that?

22 DR. AZEN: This is Dr. Stan Azen speaking. Was
23 the 17 percent associated with the non-CMV eyes at 6
24 months?

1 DR. FERRIS: That's the non-mortality rate.
2 One of them was 17 percent, and one of them was higher than
3 17 percent.

4 DR. SONI: One is higher, yes.

5 DR. FERRIS: We'd all agree that if the patient
6 dies, it's not a loss to follow-up in that sense, but --

7 DR. FLYNN: May I? This is Dr. Flynn from
8 Miami. I wanted to comment, since I've worked with Dr.
9 Ferris on at least three coronary-constricting NEI studies
10 during my career.

11 I just wanted to say that we did have a
12 protocol for this study, and it did designate intervals for
13 follow-up, and Dr. Ferris is entirely correct that it was a
14 check mark for corneal edema opacities; it was a pressure
15 determination, which could have been determined by a
16 tonopin or an aplanator, and it wasn't designated in the
17 protocol how the pressure was measured; and we did have a
18 criteria for a set number of follow-ups, which was extended
19 to 2 years, as approved by our individual IRBs.

20 Now, obviously, all of us in our clinical
21 practices have patients we've followed for 5 years, and we
22 continue to follow the patients, but according to the study
23 design, 2 years was the approval time that this study
24 mandated. In the silicone study, we altered the protocol

1 to allow 72-month follow-up on patients, so that, as I
2 mentioned in my presentation, will be reported in terms of
3 1000 centistoke oil for complex PVR detachments.

4 As Dr. Ferris pointed out, we did have
5 deficiencies in these studies, because on an annual basis
6 we as physicians need to be reminded when our follow-up is
7 not complete, and we need to be reminded where our
8 deficiencies are and what we need to do, and that was not
9 always done in this study. As a result, we had to gain
10 many of these endpoints at times that were not absolutely
11 consistent with the protocol.

12 But since May of 1996 at Bascom Palmer we have
13 hired a full-time coordinator to work on this study, and we
14 have completed the available follow-up on about 80 percent
15 of the patients. Now, some of the patients do not yet have
16 a 2-year follow-up, so we are continuing to follow those
17 patients.

18 So that concludes my comments regarding our
19 mutual concern with Dr. Ferris.

20 DR. STULTING: Any other questions?

21 (No response.)

22 DR. STULTING: Okay. Thank you very much. You
23 may return to your seats in the audience.

24 ~~The floor is now open for further discussion~~

1 among panel members of the PMA.

2 (No response.)

3 DR. STULTING: Seeing no comments, I'll take
4 just a moment to try to summarize what I heard as the
5 responses to the FDA's questions for panel discussion that
6 are found in the panel's agenda. What I'd like to do is
7 summarize what I believe to be the consensus, and then
8 after I'm finished we can discuss whether there are any
9 corrections or misinterpretations on my part.

10 The first would be that the data analysis is
11 sufficient to allow for a determination of safety and
12 efficacy, subject to the comments about the quality of the
13 study and the application that have been discussed at
14 length.

15 Second is that the clinical data that we have
16 received and any other that might be obtained should not be
17 the primary determinant of equivalency of the product from
18 the two suppliers, and that instead this should be based on
19 a determination of chemical equivalence conducted by the
20 agency.

21 Third is that the labeling is adequate, and
22 that it particularly should reflect the indications for use
23 by experienced retinal surgeons for specific indications in
24 desperate cases.

1 Fourth, that a separate analysis for pediatric
2 cases is not warranted, and, fifth, that the issue of oil
3 removal is adequately addressed, and that no additional
4 study is necessary.

5 There were several comments during the
6 discussion about subgroup analyses and addressing certain
7 questions, such as the number of patients that required
8 long-term glaucoma treatment and the incidence of corneal
9 opacities in phakic and pseudophakic eyes. It's my
10 understanding from the discussion that these were merely
11 recommendations for the sponsor and for the group's
12 consultants to publish this information for the usefulness
13 of the ophthalmic community, but that this information
14 would not be necessary for a decision about safety and
15 efficacy.

16 Is what I have just stated correct? Are there
17 comments or corrections?

18 (No response.)

19 DR. STULTING: Okay. Hearing no comments at
20 this point, I'll now ask the FDA if there are any questions
21 that we have not addressed or any information that you
22 would like to have brought out in the discussion or
23 comments from the panel.

24 DR. SAVIOLA: This is Jim Saviola. We have no

1 additional questions for you to discuss. Based on your
2 comments, it's my understanding that the labeling -- these
3 additional subgroup analyses will not be something that you
4 recommend being included in final product labeling. You
5 stated that you would recommend that they be published in
6 the literature. Could you clarify that, please?

7 DR. STULTING: That was my understanding from
8 the panel, but I would imagine that if the data were
9 available, that physicians would like to see it in the
10 labeling. That would be an efficient way of getting it
11 into the hands of the end users.

12 DR. FERRIS: They better put it in the
13 labeling, because this may not be publishable.

14 DR. MACSAI: I would say that I would want the
15 cornea information in the labeling, assuming it's
16 available.

17 DR. STULTING: Okay.

18 DR. WILKINSON: And the adverse reactions list
19 should be altered. It's not accurate as written.

20 DR. STULTING: Okay. So those are some things
21 that we can also include as --

22 DR. SAVIOLA: So that goes back to my earlier
23 comments about the need for the additional follow-up so
24 that we could write the labeling and include that

1 information in the package labeling. That sort of comes
2 full circle.

3 DR. STULTING: So we probably should make that
4 a provision in the recommendation.

5 DR. SAVIOLA: Right.

6 DR. FERRIS: Well, one other comment about the
7 labeling. Should there be something in the label about
8 allergic response to silicone? I mean, that was the one
9 really bad outcome, and it may be there, but I didn't see
10 it if it's there.

11 DR. SAVIOLA: Okay.

12 PARTICIPANT: That will be included.

13 PARTICIPANT: Is there something in there? I
14 didn't see it.

15 DR. RUIZ: If that was really an allergic
16 response. It didn't sound like it to me.

17 DR. FERRIS: I don't know how to deal with it,
18 because it was presented that way, and I was surprised.

19 DR. RUIZ: Yes. It did not, just reading it,
20 sound like a true allergic response. On the basis of one
21 case, I sure wouldn't put it in the labeling.

22 DR. FERRIS: I'm not so sure about that. If
23 there is an idiopathic response to silicone -- if a patient
24 has had some sort of bad response to silicone, at least I

1 would think that you would need to take that into
2 consideration. I would want to make sure that the patient
3 -- if they came to me and said they had some response to a
4 buckle or their breast implant, for that matter, it would
5 seem to me that it would be important to tell the patient
6 there was one patient that had a negative response.
7 Obviously, the patient's options are difficult, but I think
8 it's fair warning.

9 If it's not in the label, how will the
10 physician even know?

11 DR. RUIZ: Reading that, it sounded like an
12 inflammatory response, not an allergic response.

13 DR. SAVIOLA: So currently there's a warning
14 concerning silicone intraocular lenses, and there's some
15 discussion regarding your recommendation for including the
16 potential for silicone allergy.

17 DR. STULTING: Well, would it be appropriate to
18 have some standard verbiage that says you shouldn't use
19 this device in someone who has a history of allergic
20 reaction to silicone in the past? That sort of makes sense
21 to me. If they haven't ever had an allergic reaction,
22 you're not going to know if they're allergic anyway.

23 DR. SAVIOLA: Okay.

24 DR. STULTING: All right. This would be a good

1 time for a motion.

2 DR. RUIZ: I move approval.

3 DR. STULTING: We have a motion on the floor
4 from Dr. Ruiz. Do you want to modify that with any
5 verbiage about the labeling?

6 DR. RUIZ: Why don't you state that for me, Mr.
7 Chairman.

8 (Laughter.)

9 DR. STULTING: Dr. Wilkinson has a comment.

10 DR. WILKINSON: I'm going to propose a couple
11 of amendments to the recommendation that this be approved.

12 DR. STULTING: Just a minute. We've had a
13 motion for approval. First, we need a second for that.

14 DR. WILKINSON: Second.

15 DR. STULTING: Okay. Now it's open for
16 discussion, and now, if you would like, you can offer an
17 amendment.

18 DR. WILKINSON: Mr. Chairman, Dr. Ruiz, I would
19 suggest adding a couple of caveats: first of all, that the
20 new device is proven biochemically equivalent on the basis
21 of preclinical studies, which will not get into any sort of
22 clinical data; secondly, the labeling should reflect the
23 incidence of accepted classical complications of silicone
24 oil and stratify the incidence of these complications as a

1 function of anterior segment status and posterior segment
2 success.

3 DR. STULTING: Okay. We now have an amendment
4 that has been offered. Do we have a second for the
5 amendment?

6 DR. MACSAI: Second.

7 DR. STULTING: It's been moved and seconded
8 that the original motion be amended as stated so that the
9 recommendation is contingent on proven biochemical
10 equivalence of the two products from the two suppliers and
11 labeling that includes the incidence of certain
12 complications, with stratification. Any discussion?

13 (No response.)

14 DR. STULTING: Okay. Those in favor of the
15 amendment --

16 DR. McCLELLAND: Excuse me, Mr. Chair. From a
17 consumer standpoint, I would certainly support that
18 amendment. I think it's important to have that
19 information, whether it be in labeling or, as with the
20 earlier discussion this morning -- and we'll be talking
21 about that later, apparently -- regarding devices with
22 risk, whether that is part of the informed consent.

23 It seems to me that that's an important issue,
24 ~~even if there were only one incident and the etiology not~~

1 completely known, that a potential patient determining
2 whether or not they wish to go forward with this procedure
3 should have that information. So I would just strongly
4 support the action in regard to that amendment.

5 DR. STULTING: Okay. Other comments?

6 (No response.)

7 DR. STULTING: Those in favor of the amendment
8 as stated, please raise your hands.

9 We need to make sure that everybody who's
10 voting knows they're voting. Voting members on this PMA
11 include Dr. Bullimore, Dr. Higginbotham, Dr. Macsai, Dr.
12 McCulley, Dr. Ruiz, Dr. Soni, and Dr. Wilkinson. So those
13 of you who are on that list need to be voting, and the
14 other panel members who are not on that list are here for
15 discussion only today.

16 So those that are capable of voting, please
17 raise your hand if you're in favor of the amendment.

18 (Show of hands.)

19 DR. STULTING: Those opposed?

20 (Show of hands.)

21 DR. STULTING: Okay, the amendment passes.

22 Now, is there any further discussion on the
23 main motion? The motion is to recommend approval of the
24 PMA, with the contingents in the amendment.

1 (No response.)

2 DR. STULTING: I see no further discussion.
3 Then, we'll move to a vote on the main motion. Those in
4 favor, please signify by raising your hands.

5 (Show of hands.)

6 DR. STULTING: That's seven in favor, and there
7 are seven people supposed to be voting. So the motion
8 carries unanimously.

9 We are now supposed to poll the panel members
10 so that each person who votes has an opportunity to say why
11 they voted for or against the motion. Is that correct?

12 We're being reminded that we need to read the
13 voting options, which we didn't before, so why don't you
14 read them so that we know them.

15 PARTICIPANT: Thank you, Mr. Chair.

16 MS. THORNTON: Thank you, Doyle.

17 DR. STULTING: Can we rearrange the transcript
18 at a later time?

19 (Laughter.)

20 MS. THORNTON: I'm going to read the voting
21 options at this time for clarification. Your recommended
22 options for the vote are as follows:

23 Approvable, meaning there are no conditions
24 attached. If the agency agrees with the panel

1 recommendation, an approvable letter will be sent to the
2 applicant.

3 Approvable with conditions. You may recommend
4 that the PMA be found approvable subject to specified
5 conditions, such as a resolution of clearly identified
6 deficiencies which have been cited by you or by FDA staff.
7 Prior to voting, all the conditions are discussed by the
8 panel and listed by the chair. If the FDA agrees with the
9 panel recommendation for approvable with conditions, an
10 approvable-with-conditions letter will be sent.

11 If the panel were to have recommended not
12 approvable, that would have meant that the data do not
13 provide reasonable assurance that the device is safe under
14 the conditions of use prescribed, recommended, or suggested
15 in the proposed labeling; or reasonable assurance has not
16 been given that the device is effective under the
17 conditions of use prescribed, recommended, or suggested in
18 the labeling; or based on a fair evaluation of all the
19 material facts in the discussion, the panel believed the
20 proposed labeling to be false or misleading.

21 If the panel were to have voted on a not
22 approvable recommendation, the agency, if they agree with
23 the panel's recommendation, would send a not approvable
24 letter. This is not a final agency action, however. In

1 that case, the amended application, after the sponsor had
2 an opportunity to amend the PMA, would then be reviewed
3 again by the panel at a future meeting date.

4 Thank you.

5 DR. STULTING: Let me make sure that no one
6 would like to change his or her votes on the basis of what
7 you have just heard. If anyone does, please speak up.

8 (No response.)

9 DR. STULTING: I hope that repairs the
10 transcript adequately for the transcript police.

11 Is there any further business for the morning
12 session?

13 DR. ROSENTHAL: Mr. Chairman, could I just get
14 you to clarify that it is approvable with the conditions in
15 the amendment?

16 DR. STULTING: Okay.

17 DR. ROSENTHAL: I don't want there to be any
18 misunderstanding of what went on.

19 DR. STULTING: The panel has just voted to
20 recommend approval of P950008 for silicone oil, with two
21 conditions. One is that there be proven biochemical
22 equivalents of the products that are manufactured, using
23 raw materials from two separate suppliers; and, to be
24 clear, that this equivalence is to be based on chemical

1 analysis, not additional clinical studies.

2 The second condition is that the labeling
3 reflect the incidence of complications that are seen with
4 this material, as with other silicone oils, and that there
5 be stratification, as discussed during a panel meeting.

6 Now, we still have to poll people so that you
7 can say why it is you voted for this. Is that okay, Dr.
8 Alpert, that we don't do that?

9 DR. ALPERT: I believe what you can do is go
10 around. If anyone has a comment to make about their
11 voting, they can do that. But it is an opportunity that we
12 like to provide to every panel member.

13 DR. STULTING: Okay, then, if you're happy with
14 the proceedings and the statements so far, you don't have
15 to say anything. If you do, then you can say it now.
16 We'll start on the right, Dr. Bullimore.

17 DR. BULLIMORE: No comment.

18 DR. McCULLEY: No comment.

19 DR. HIGGINBOTHAM: No comment.

20 DR. WILKINSON: No comment.

21 DR. RUIZ: No comment.

22 DR. MACSAI: No comment.

23 DR. SONI: I wish Sandy was here. No comment.

24 (Laughter.)

1 DR. STULTING: He was clearly here in spirit,
2 because Dr. Ferris helped us with that. So as I understand
3 it, we have received six-and-a-half no comments, and then
4 one about one of our previous panel members. But
5 basically, there's no substantial comments so far.

6 Dr. Macsai?

7 DR. MACSAI: Well, in Dr. Brucker's absence, I
8 have to say this. I just want to say that, since this is a
9 drug -- excuse me -- a device that has obviously got a
10 desire to have expedited approval for compassionate use in
11 AIDS patients, the sponsors of this and any other device of
12 this sort wishing expedited approval should bear in mind
13 that with much fewer numbers, and in more complete data
14 collection and data follow-up, the process could be
15 expedited considerably.

16 DR. STULTING: Dr. Alpert?

17 DR. ALPERT: This is Dr. Susan Alpert. I'm the
18 Director of the Office of Device Evaluation.

19 I want to thank the panel for making their
20 comments about clinical trial design. We at the agency
21 share your concern that trials be the appropriate size for
22 the questions to be addressed in that clinical trial.
23 We're working hard, both internally and with the industry,
24 through guidance documents and a series of workshops to

1 assure that all of us understand the criteria upon which
2 clinical trials for medical devices need to be designed.

3 I would make one comment to a comment Dr.
4 Ferris, I believe, made during the discussion. That is
5 that one should continue to follow patients until approval.
6 I would raise the concern in the following way. Where you
7 have patients who are going to be exposed for either a
8 permanent implant, or where a product of this sort may be
9 instilled in eyes over the lifetime of the patient, I think
10 it is appropriate to determine at the beginning of a trial
11 that you want to follow either all of the patients or a
12 subset of patients over a longer duration.

13 However, it is very difficult in most clinical
14 trials to say the trial ends at two years, and then
15 everybody ought to be followed longer. We need to be very
16 clear, again for the burden of proof for the issues that
17 need to be addressed, that we identify those products where
18 we need long-term follow-up when we begin, recognizing that
19 patients and investigators commit for the term of the
20 trial. If we believe going into a trial that it needs
21 longer-term follow-up, that we can make a determination
22 about safety and effectiveness with an interim timeframe
23 but would like to have longer-term annual follow-up, or
24 there are questions that need longer term follow up, I

1 think we need to decide that early.

2 It's very difficult, and indeed very
3 burdensome, both for patients and companies, to have that
4 decision made later in the process. So I think, in
5 response to your concern, that if that is in fact an issue
6 up front, then we need to design the trials to have that
7 type of follow-up in them. But not every product needs
8 that type of trial. I just wanted to make sure that that
9 comment got in the record.

10 There are devices where that is an appropriate
11 type of follow-up. There are other situations in which
12 that kind of annual follow-up is not necessary. We need to
13 help, and you need to help us make those decisions. But we
14 do welcome the comments of the panel on trial design and
15 hope to in fact get the panel more involved in IDE trial
16 design as we move forward.

17 Thank you.

18 DR. STULTING: Thank you.

19 Dr. Ferris?

20 DR. FERRIS: I don't want to respond to that
21 because I think we share the same point of view.

22 I did have a question, though, regarding the
23 chemical composition of this product and whether it will be
24 problematic for the agency if I presume this product is

1 not 100 percent this oil. Maybe it is, but maybe it's
2 99.4, or whatever. Will it be a problem for the agency if
3 the other .06, or a small percentage, isn't identical
4 between the two? Is that going to create a problem?

5 DR. STULTING: I don't know how to deal with
6 that. Our decision so far was to rely on chemical
7 equivalents. The only issue for us is, do we want a
8 clinical study, or do we not want a clinical study?

9 Are there comments from the agency?

10 DR. ALPERT: Yes. I would like to comment on
11 that as well. I think there's a great deal of difference
12 between chemical equivalence, or reasonable comparability,
13 and identity. When it comes to products that are sourced
14 like silicone, where there is a family of sizes of material
15 in the source itself, it is impossible to have identity, if
16 you will. That's true of most materials.

17 So we try to determine what the definition of
18 the material is that supported the studies and make sure
19 that the new source -- and this goes across the board,
20 whether it's silicone or it's a type of metal or plastic,
21 whatever the issue is, and have no new questions, no
22 issues, no new content, no new materials in the source
23 material that raise concerns about safety and
24 effectiveness.

1 When it comes to something of the sort of these
2 types of oils where the short-chain molecules have been of
3 concern to the scientific community in terms of their
4 safety, sometimes we can't answer the question with a
5 chemical identity and have in fact turned to a small
6 clinical trial as confirmation that there is no high-level
7 risk introduced by the differences in the source material.
8 That's a very important question here. It's how you define
9 what comparability is. We will look very carefully at your
10 recommendations and very carefully at how one can define
11 these types of products to assure that, as sources change,
12 which they do, that we don't lose the safety and
13 effectiveness of the product.

14 DR. STULTING: Are you saying that the FDA is
15 reasonably comfortable that they can perform that type of
16 analysis on the silicone oils and that they don't think
17 there's a need for additional clinical data?

18 DR. ALPERT: As I said, one of our questions to
19 the panel was whether the panel had any additional
20 concerns. We feel that there are times when clinical is
21 what you need to answer the question, when you cannot
22 answer the question either chemically or in animal studies.
23 It happens very rarely, but it does happen.

24 ~~Our question to you was whether there were any~~

1 concerns on the part of the experts here at the table about
2 silicone oils based on what you were told this morning
3 about these oils, whether you had any additional concerns
4 that were coming forward, and whether you felt that, as we
5 look at new sources -- and again, this is not just for this
6 product, but we have, as was pointed out, other products.
7 When sources change, whether clinical confirmation,
8 clinical studies are always necessary, or whether it is at
9 the discretion of the agency, depending on the chemical
10 comparability and the information, the pre-clinical
11 information that we have on those oils.

12 DR. STULTING: Comments on that?

13 DR. RUIZ: I'm not in a position to answer that
14 question. I mean, if you tell me that, as far as possible,
15 these two things are equivalent, within physical
16 capabilities they're equivalent, then I don't think we need
17 to do clinical studies. If on the other hand you say as
18 far as we can tell they're equivalent, but we're only this
19 good at it, then I think you have to double-check it with a
20 clinical study.

21 DR. ALPERT: That is exactly where I think I
22 was hearing you this morning. Thank you very much.

23 DR. STULTING: I think it would be correct to
24 state that the panel members are unaware of any known

1 complications that occur because of typical contaminants in
2 this type of product. But none of us, as far as I know,
3 are chemists that are well-enough educated to really give
4 you good information on that. So I think the consensus is
5 that there's no clinical data to raise concern. But we
6 would be relying on chemical analysis to understand that
7 these are equivalent in the reasonable sense of the word.

8 I saw some hands. Are there other comments?

9 DR. WILKINSON: Well, one thing we mentioned,
10 the wording was biochemically equivalent, not identical.
11 Secondly, there are not a substantial but certainly a
12 significant number of eyes that have had the new device.
13 There appear to be no red flags. We've been through this
14 with intraocular lenses before. There must be some broad
15 guidelines that the agency uses. If it looks like it's the
16 same stuff, I don't think we should make a tremendously big
17 deal of it.

18 These eyes are sick eyes to begin with, for the
19 most part. This material is not tolerated perfectly by an
20 eye. It's very, very difficult to study these eyes. I
21 think that there is sufficient data that do not raise
22 concern, that unless there is some glaring lack of
23 equivalency, that we should let it be.

24 DR. VAN METER: I have a question for

1 discussion. Is the low incidence of emulsification that we
2 witnessed in some of these patients arranged from 1 to 3
3 percent in any way possibly due to a quality issue? It
4 wasn't stratified between the two suppliers?

5 DR. RUIZ: Now, Woody, why are you waiting
6 until now to bring that up?

7 DR. VAN METER: Because I don't use the
8 silicone oil.

9 DR. RUIZ: Does anybody know why you get
10 emulsification?

11 DR. STULTING: Now, wait a minute. We have to
12 get some order here. We've had the floor open for
13 discussion and there were multiple chances to add comments
14 and continue discussion, and we have voted. I think we
15 should move on, unless there are serious concerns about the
16 opinions that we've rendered thus far.

17 Are there any of those serious concerns?

18 (No response.)

19 DR. STULTING: Okay. Any other comments from
20 the agency? Dr. Alpert, are you reasonably happy with what
21 we've done?

22 Is anybody else in the agency unhappy with what
23 we've done?

24 ~~Are there any panel members that are unhappy~~

1 with what we've done?

2 Okay. Then I will turn the floor over to Ms.
3 Thornton for some closing comments before we end the
4 morning session.

5 DR. THORNTON: Since this is the end of the
6 open session for today, I would like to make a few short
7 announcements. For the remainder of the 1997 panel meeting
8 season, we have tentatively scheduled meetings for March
9 27th and 28th, July 10th and 11th, October 20th and 21st.
10 Please stay tuned to your Web site, your hotline, or you
11 can call me.

12
13 The dates that are on the FDA Web site are
14 accessible at <http://www.fda.gov>. Changes or cancellations
15 of those dates will appear, as well as draft agendas of the
16 planned meetings. Information on planned meetings can also
17 be obtained from the panel hotline number, which is
18 1-800-741-8138. The Ophthalmic Panel code, when prompted
19 by the recording, is 12396.

20 I would like to again thank the panel, and
21 particularly the primary reviewers, and to thank our FDA
22 staff who have worked so hard on this presentation this
23 morning. I would like the panel to leave on the table
24 ~~materials to be returned to the agency and put your panel~~

1 packets with your agenda for the closed session this
2 afternoon on your chairs. Anything left on the table will
3 be destroyed.

4 (Laughter.)

5 DR. THORNTON: I believe Dr. Stulting is going
6 to close the open session now and give us our time for
7 reassembling for the closed session this afternoon.

8 DR. STULTING: The morning session is
9 adjourned, and the afternoon session will begin at 2:00
10 p.m. promptly, please.

11 (Whereupon, at 1:00 p.m., the open session was
12 adjourned.)

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