

TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

OPHTHALMIC DEVICES PANEL

NINETY-NINTH MEETING

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Pages 1 thru 237

Gaithersburg, Maryland
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

OPHTHALMIC DEVICES PANEL
NINETY-NINTH MEETING

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Friday, May 12, 2000

8:30 a.m.

Hilton Hotel
Salons A & B
620 Perry Parkway
Gaithersburg, Maryland

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C O N T E N T S

	<u>Page No.</u>
Call to Order: James P. McCulley, M.D.	4
Introductory Remarks: Sara M. Thornton	4
Conflict of Interest Statement: Sara M. Thornton	7
Open Public Hearing: David J. Spalton, M.D.	9
TOPIC A: POSTERIOR CAPSULE OPACIFICATION	
Introduction: Donna R. Lochner	31
Overview of Discussion: Sheryl L. Berman, M.D.	37
Primary Panel Reviews	
Clinical Endpoints: Joel Sugar, M.D.	40
Study Controls: Jayne S. Weiss, M.D.	76
Methodology: Mark A. Bullimore, MCOptom, Ph.D.	97
Clinical Protocol: Frederick L. Ferris III, M.D.	113
Open Public Hearing: Wiley Chambers, M.D.	135
TOPIC B: REFRACTIVE IMPLANTS	
Introduction: Ashley Boulware	143
Panel Discussion of Questions	149
Open Public Hearing: John Sheets, M.D.	231

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

2 Call to Order

3 DR. McCULLEY: I would like to call to order the
4 second day of the Ninety-Ninth meeting of the Ophthalmic
5 Devices Panel and turn the floor to Sara Thornton for
6 comments.

7 **Introductory Remarks**

8 MS. THORNTON: Good morning and welcome to the
9 second day of the meeting here of the Ophthalmic Devices
10 Panel. As I did yesterday, and some of you have heard this
11 before, I will proceed with today's agenda but I do have to
12 make a few short announcements and remind everyone who is
13 joining us for the first time today to sign in on the
14 attendance sheet in the registration area just outside the
15 meeting room. Those of you who are returning, please do the
16 same.

17 Messages for the panel members and FDA
18 participants and information or special needs should be
19 directed through Ms. AnnMarie Williams or Ms. Carol Coy who
20 are available in the registration area just outside the
21 meeting room. The phone number for calls to the meeting
22 area is 301-977-8900.

23 In consideration of the panel, the sponsor and the
24 agency, we ask that those of you in the audience and at the
25 table with cell phones and pagers either turn them off or

1 put them on vibration mode while in this room.

2 Lastly, will all participants speak into the
3 microphone. Give your name clearly so that transcriber will
4 have an accurate reading of your comments.

5 At this time, before I ask the panel to introduce
6 themselves, I would like to, again, extend a special welcome
7 and introduce to the public who is joining us today, the
8 panel, the FDA staff, a panel consultant member who is with
9 us for the first time today. That is Dr. Anne Louise
10 Coleman who is here on my right today next to Dr. Rosenthal.
11 She is an Associate Professor of Ophthalmology and Director
12 for the Center for Eye Epidemiology at the Jules Stein Eye
13 Institute of the University of California at Los Angeles
14 School of Medicine.

15 She has published and lectured extensively and is
16 internationally recognized for her expertise in the
17 diagnosis and management of glaucoma.

18 I will now ask the others at the table to
19 introduce themselves starting with Dr. Yaross.

20 DR. YAROSS: Marcia Yaross, Director of Regulatory
21 Affairs and Medical Compliance, Allergan, Irvine,
22 California, and industry representative to that panel.

23 MS. MORRIS: I am Lynn Morris. I am the Deputy
24 Director for the State Department of Consumer Affairs in
25 California and I am the consumer member on the panel.

1 DR. GRIMMETT: Michael Grimmett, Assistant
2 Professor, Bascom Palmer Eye Institute, University of Miami.

3 DR. MATOBA: Alice Matoba, Associate Professor of
4 Ophthalmology, Baylor College of Medicine.

5 DR. FERRIS: Frederick Ferris. I am the Director
6 of the Division of Biometry and Epidemiology at the National
7 Eye Institute, NIH.

8 DR. PULIDO: Jose Pulido, Professor and Head of
9 the Department of Ophthalmology, University of Illinois,
10 Chicago.

11 DR. JURKUS: Jan Jurkus, Professor of Optometry,
12 Illinois College of Optometry.

13 DR. McCULLEY: Jim McCulley, Professor and
14 Chairman, Department of Ophthalmology, University of Texas,
15 Southwestern Medical School in Dallas.

16 DR. BULLIMORE: Mark Bullimore, the Ohio State
17 University College of Optometry.

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

20 DR. MAGUIRE: Leo Maguire, Associate Professor of
21 Ophthalmology, Mayo Clinic.

22 DR. WEISS: Jayne Weiss, Professor of
23 Ophthalmology at Kresge Eye Institute, Wayne State
24 University, Detroit.

25 DR. STARK: Walter Stark, Professor of

1 Ophthalmology, Johns Hopkins University School of Medicine.

2 DR. ROSENTHAL: Ralph Rosenthal, Director of the
3 Division of Ophthalmic and ENT Devices.

4 MS. THORNTON: Thank you very much.

5 **Conflict of Interest Statement**

6 MS. THORNTON: I would now like to read into the
7 record the conflict of interest statement for today's
8 session. The following announcement addresses conflict of
9 interest issues associated with this meeting and is made
10 part of the record to preclude even the appearance of an
11 impropriety.

12 To determine if any conflict existed, the agency
13 reviewed the submitted agenda for this meeting and all
14 financial interests reported by the committee participants.
15 The conflict of interest statutes prohibit special
16 government employees from participating in matters that
17 could affect their or their employer's financial interests.
18 However, the agency has determined that participation of
19 certain members and consultants, the need for whose services
20 outweigh the potential conflict of interest involved, is in
21 the best interest of the government.

22 A financial interest waiver has been granted to
23 Dr. Frederick Ferris for his interest in a firm that could
24 potentially be affected by the panel's recommendations. The
25 panel allows him to participate fully in today's

1 deliberations. Copies of his waiver may be obtained from
2 the agency's Freedom of Information Office, Room 12A15 of
3 the Parklawn Building.

4 We would like to note for the record that the
5 agency took into consideration other matters regarding Drs.
6 James McCulley, Jose Pulido, Anne Coleman, Frederick Ferris
7 and Walter Stark. Each of these panelists reported interest
8 in firms at issue but in matters that are not related to
9 today's agenda.

10 The agency has determined, therefore, that they
11 may participate fully in all discussions. In the event that
12 the discussions involve any other products or firms not
13 already on the agenda for which an FDA participant has a
14 financial interest, the participant should excuse him or
15 herself from such involvement and the exclusion will be
16 noted for the record.

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

22 Thank you, Dr. McCulley.

23 **Open Public Hearing**

24 DR. McCULLEY: We will now begin the open public
25 hearing session. We have thirty minutes. We have had one

1 person indicate that they wish to speak. We have thirty
2 minutes allotted for this time.

3 We will begin with the person who has submitted,
4 Dr. David Spalton. We ask that people limit the length of
5 their comments as we only have a total of thirty minutes.

6 DR. SPALTON: Mr. Chairman, ladies and gentlemen.

7 [Slide.]

8 I am David Spalton. I work at St. Thomas'
9 Hospital in London and I have a special interest in
10 intraocular lens biocompatibility posterior capsule
11 opacification. The references in your documentation that
12 you see from Pande, Ursell, Hollick, Mecock, Boyce
13 Papolinski and Barman are all colleagues of mine who work
14 with me on my research projects. I am also a paid
15 consultant to Alcon.

16 [Slide.]

17 We are all very well aware of what the pathology
18 of PCO is, the proliferation of the lens epithelial cells,
19 metaplasia to myofibroblasts and fibrosis from collagen
20 secretion. That is a point that I would like to make, and
21 that is that some ophthalmologists feel that there are two
22 processes. There is Elshnig pearl formation and fibrosis.
23 But, in my view, these two processes are intimately related
24 and are not separate things. I think this is an important
25 point in the assessment of PCO.

1 [Slide.]

2 This slide summarizes the current methods of
3 measuring PCO. There are two parameters that we are really
4 interested in. One is how much PCO there is and the other
5 is how bad it is. Intuitively, the ophthalmologist makes
6 these suggestions subjectively at the slit lamp of patients.
7 YAG rates are really a subjective assessment of the severity
8 of the amount of PCO and the other systems, the EPCO, the
9 Friedman, our system at St. Thomas and the Nidek system, are
10 attempts to quantify this rather better.

11 [Slide.]

12 I think one of the questions is what should be the
13 endpoint for PCO measurement. There are a lot of people who
14 consider that one should measure the central three
15 millimeters for ambient visual function. But I think it is
16 important to draw the panel's attention to the problems of
17 younger patients who have larger pupils, patients who do
18 night driving where pupils are going to be larger, and also
19 the problems of the vitreoretinal surgeon and the medical-
20 retinal specialist who want to look at peripheral retinal
21 pathology.

22 I think it is a particularly important problem in
23 a lot of our patients. I personally feel that our goal for
24 the endpoint should be a totally clear capsule rather than a
25 central donut.

1 [Slide.]

2 Briefly, to review the methods, the EPCO system is
3 a European system which is very popular. It has got the
4 advantages of being simple and inexpensive and it basically
5 consists of a computer graphics system to manually draw the
6 areas of PCO on a red reflex photograph.

7 It has some problems. It is heavily dependent on
8 the quality and the way the photographs are taken and we
9 feel is a bit subjective.

10 [Slide.]

11 If you are going to go into image analysis, one
12 has to consider how you should analyze the images. There
13 are basically two methods being used at the moment. The
14 first is intensity thresholding. This is the
15 straightforward simple technique where one assigns
16 brightness intensity to each pixel.

17 The bright pixels are then binarised to being
18 clear, the dark ones to be opaque. The problem is, as I
19 will show you, there are fundamental problems in this. It
20 is very dependent on the background illumination, but the
21 fundamental problem is that it cannot pick up lens
22 epithelial-cell plaques of the same intensity as background.

23 [Slide.]

24 Here we have the retroillumination photograph
25 taken with our own systems. You see this area here which is

1 enlarged. This area here is clear. This is opaque. But
2 the intensity of these pixels in the opaque area is really
3 very much the same intensity as the clear. Therefore,
4 intensity thresholding will not pick up this opaque area.

5 Conversely, there is an opaque area down here
6 where the pixels are brighter in the opaque area than in the
7 clear area. Obviously, you would get artifacts if you used
8 intensity thresholding in that situation.

9 We have, therefore, gone on to a more complex
10 technique which is texture segmentation which is, in fact,
11 based on the relationship of the pixel-intensity to each
12 other rather than the absolute value of pixel intensities.

13 This has got the advantage of being much more
14 independent of background illumination. It also allows you
15 to study patterns of pixel clumping in the image. There are
16 very well-defined algorithms for this. The down side is
17 that the software is very complex and highly mathematical.

18 [Slide.]

19 Our system, which we call the POCO system--there
20 are now six systems in use worldwide, probably two more to
21 be installed. Basically, what we do is the ophthalmologist
22 acquires the image locally and then it is internetted to
23 London where we have a central reading center. That gives
24 us an element of quality control for our studies.

25 [Slide.]

1 The capture system is based on a Zeiss anterior
2 segment slit lamp with a digital camera. This is the Kodak
3 420 camera. It is extremely high resolution. The
4 resolution system being down to about 20 microns. And a
5 fiberoptic retroillumination system.

6 [Slide.]

7 This shows an example. Here is a patient with a
8 PMMA lens. You can see here is the lens. There is quite a
9 lot of fibrosis in the capsule against the red reflex.

10 [Slide.]

11 Here is a specular reflex. You see it again. If
12 you look here, you can just make a little band across the
13 top here.

14 [Slide.]

15 This is what we see with our own camera with the
16 retroillumination image which we then analyze. You can see,
17 we get very good detail and we pick up these. We have got
18 nice even illumination. We have a problem at present with
19 the Purkinje reflexes.

20 [Slide.]

21 This is how the computer sees that image that I
22 have just showed you. Basically, we have binarised this
23 image then. What is white is clear. What is black is
24 opaque, giving a percentage area of PCO not a severity
25 measurement.

1 [Slide.]

2 Briefly, our segmentation progress, the initial
3 program is actually based on a military software program for
4 identifying aircraft targets on a cloudy night. We draw a
5 mask to outline the posterior capsule. There is an
6 intensity segmentation which removes the Purkinje light
7 reflexes and identifies the smooth, dark areas.

8 It then goes through a process of local contrast
9 enhancement. There is a filtering process which enhances
10 the clumping of pixels in the smooth areas and then it goes
11 through a complex mathematical technique known as a co-
12 occurrence matrix which segments out groups of pixels. And
13 then, the final stage is interactive matching of this
14 segmentation to the raw image. And we calculate a
15 percentage of PCO.

16 The paper describing this, by the way, is in the
17 process of review for IOVS.

18 [Slide.]

19 One of the questions that we have to answer is
20 what is the area of interest. I have already said that I
21 believe I am interested in completely clear capsules. So
22 we, with our program, can measure any area but we have
23 chosen to define the area of interest as the area within the
24 capsulorhexis of, if the capsulorhexis is off the
25 intraocular lens, we take the intraocular lens edge as the

1 boundary.

2 [Slide.]

3 This next slide shows this. This is the slide I
4 showed you originally. You can see, once again, a PMMA
5 lens. Here is the outline of the capsulorhexis. Here is
6 the outline of the implant. It is off here. So we draw
7 manually with a computer, mask this boundary here and
8 analyze the image within that area.

9 [Slide.]

10 This shows you what the computer sees in that
11 case, giving a value of 64 percent for area.

12 [Slide.]

13 Our system has got, as one might expect from the
14 computer system, very high inter- and intraoperator
15 reproducibility. We have a clinical reproducibility of
16 slightly better than 10 percent on images taken a week apart
17 and I think the reason for that is what Dr. Bullimore
18 mentioned in his statement that there is some variability in
19 actual capture of the images and things like pupil
20 dilatation.

21 [Slide.]

22 We have also had the opportunity to use the Nidek
23 system and, in particular, the protocol which was described
24 by Dr. Hyashi. I would just like to briefly review that.
25 This system is very different. It measures back scattering

1 of light from the central three millimeters of the posterior
2 capsule as I have outlined here from a scheimflug image.

3 It has the advantages that you get less artifacts
4 from the anterior vitreous and the cornea. Potentially you
5 may get more artifacts from the intraocular lens, but Dr.
6 Hyashi deals with that in his protocol.

7 The problems with this technique is that you are
8 basically doing a central sampling and it is also weighted
9 to the central pixels. Because it is scheimflug, it is
10 partial sampling and, at present, the system is actually
11 rather cumbersome and slow to use.

12 This shows you one of our retroillumination images
13 superimposed with the four meridians that Dr. Hyashi
14 described in his technique. You can see basically that it
15 does not mention the peripheral part of the lens. There is
16 a partial sampling in the central part and it is also
17 weighted in that you are measuring more pixels right in the
18 center of the lens here.

19 I think this is why there has been some confusion
20 using this system and comparing with our own in comparable
21 PCO rates with different intraocular lenses.

22 This shows basically the results comparing the two
23 systems. We, obviously, are picking up higher values when
24 the Nidek system picks up low values because we pick up the
25 peripheral PCO. Obviously, both systems have a good

1 correlation when there is no PCO or when there is
2 100 percent PCO.

3 Interestingly, the Nidek will also have some
4 outliers like this where it picks up high PCO and we pick up
5 low PCO. I will show you why this is the case.

6 [Slide.]

7 This is that image that I have shown you where
8 there is a central fibrotic plaque I think left over from
9 surgery or probably some of the posterior subcapsular
10 cataract. But this is going to be picked up by the Hyashi
11 system as a very high rate of PCO whereas our system, which
12 is measuring the whole area, will give a much lower value.

13 I think this explains why there have been
14 conflicting results in some of the comparison PCO rates with
15 different intraocular lens studies. The basis is the way
16 the technique is used.

17 [Slide.]

18 Finally, just a couple of other points. Our
19 system, because we have got very high resolution and also
20 because we can enhance the contrast, and the contrast
21 enhancement in our software is a fairly complex process but
22 a very good process, we can pick up very early lens
23 epithelial-cell changes.

24 This can shorten the length of time we need to
25 follow up patients to decide whether an intraocular lens has

1 a good PCO rate or not. Our six-month results, as I will
2 show you, predict the three-year PCO rate pretty accurately.

3 I think, pathologically, what we are seeing is
4 that there is an early infiltration of lens epithelial cells
5 onto the posterior capsule into an area and then they tend
6 to thicken up with time rather than increase in area with
7 time. So it is a migration and a thickening process rather
8 than a continuing infiltration. When it gets worse, we are
9 seeing that thickening process.

10 [Slide.]

11 This is just to emphasize that point. This takes
12 a group of patients with three different types of
13 intraocular lenses. We have plotted the six-month PCO value
14 against the three-year PCO value with a r-squared value, I
15 believe, of 0.7 percent showing a very good correlation and
16 an early predictability of the eventual outcome using our
17 software.

18 This is important because it actually considerably
19 shortens the length of time we need to follow up patients to
20 get an idea of how good a lens is going to be.

21 [Slide.]

22 Finally, I want to say just a word about the two
23 parameters that we have talked about. As I say, we measure
24 the area of PCO. Many people have tried to make a severity
25 grading of PCO. I think, in my mind, a severity--this is

1 how bad it is--is actually meaningless unless you correlate
2 that with visual function.

3 The reason is that, in an image like this, one
4 might say a dark area has more severe PCO than a light area.
5 But you could equally argue that dark areas will attenuate
6 light reaching the retina producing less image degradation
7 whereas areas like this, which seem better, have much more
8 edges and scattered light forward causing much more image
9 degradation.

10 So I think that the point that I would like to
11 make is that any grading of severity really has to be
12 correlated with visual function, in my view, to have any
13 meaning. And just a sort of visual interpretation of images
14 can be flawed.

15 [Slide.]

16 The way that we are approaching this, I think, in
17 my second slide, I showed you that no one has an objective
18 measurement in my view yet of measuring severity. We have
19 spent a lot of time taking the central three millimeters and
20 correlating it with psychophysical tests and we found no
21 correlation with the area of PCO, which is not surprising,
22 because you can get very fine, smooth areas which don't
23 affect the vision.

24 What we are now working on is a sort of
25 computerized measurement of edge strength of PCO in the

1 central three millimeters which is the amount of edge and
2 how strong that edge is.

3 [Slide.]

4 If we plot that--this is the edge strength plotted
5 against low contrast visual acuity with the LogMAR chart--we
6 are sort of getting some correlation although this is early
7 work and we obviously need far more cases on the right-hand
8 side to make that correlation line actually real. We need
9 more severe cases.

10 [Slide.]

11 So, in summary, Mr. Chairman, I would like to say
12 I think that there is no perfect system for PCO measurement
13 in the world at the moment. I think that many of the
14 systems have different pros and cons. As far as our own
15 system is concerned, we have high resolution, good
16 reproducibility and the ability to predict early posterior
17 capsular pacification rates.

18 Thank you for your attention.

19 DR. McCULLEY: Thank you. Before you leave the
20 podium, are there any questions from panel? Dr. Maguire?

21 DR. MAGUIRE: Dr. Spalton, you are familiar with
22 Shack-Hartman analysis, aren't you?

23 DR. SPALTON: I know the concept, but I would not
24 say that I understand the physics of it in any way at all.

25 DR. MAGUIRE: If one separated the area over the

1 pupil into an array of small dots the way that Shack-Hartman
2 does, and then you looked at the point-spread functions of
3 each individual dot, wouldn't that give you--

4 DR. SPALTON: I think you are absolutely right. I
5 think that we have really found--I think the basic problem
6 is that elderly patients are very bad at doing
7 psychophysical tests, as I am sure many of the members of
8 the panel are aware. We are moving in that direction,
9 either measuring MTF in vivo--there is some apparatus for
10 doing that now. I think the wave-front analysis is also a
11 potential.

12 I think there are other barometers around. I
13 think those all have great potential for giving a more
14 objective assessment to visual function. I am sure that you
15 are right.

16 DR. MAGUIRE: At ARVO, Ray Applegate's group
17 presented that as a method for looking at non-corneal
18 aberrations.

19 DR. SPALTON: I think, in theory, it should work.

20 DR. MAGUIRE: They have a very nice description of
21 variation in point-spread function of each individual point
22 over the entire pupillary area. The lens sets in the Shack-
23 Hartman machines are getting more concentrated. There are
24 some machines coming out that have a thousand lensettes over
25 the surface. That seems like something that would take care

1 of some of the deficiencies that you noted--

2 DR. SPALTON: I would agree.

3 DR. BULLIMORE: I have a couple of questions. You
4 mention your relationship with Alcon. Do you have any
5 financial interest in any of technology presented here?

6 DR. SPALTON: No.

7 DR. BULLIMORE: You mentioned clinical
8 reproducibility was plus or minus 9.8 percent. Is that a
9 standard deviation or the 95 percent limits of agreement?

10 DR. SPALTON: That is 95 percent limits of
11 agreement using the Bland Altman technique.

12 DR. McCULLEY: Anyone else?

13 DR. PULIDO: Dr. Spalton, I am a little confused.
14 I looked at that picture clinically, the picture of the
15 posterior capsule that had the central thick fibrosis. Your
16 system undercalled that while the Nidek system overcalled
17 that.

18 DR. SPALTON: No; I think both systems were
19 actually right but for different reasons.

20 DR. PULIDO: To me, that is a much more clinically
21 significant posterior capsular opacification than
22 opacification that occurs at the edges of an implant, don't
23 you think?

24 DR. SPALTON: Yes. I think what you are saying--I
25 mean, both systems are right. The reason that we get an

1 undermeasurement there is that we measure a much larger
2 area. So, as a percentage, that is going to be a smaller
3 area. The Nidek is measuring the central part. You can
4 argue that that is the most important part from visual
5 function.

6 The point that I was making earlier on I think is
7 that my own personal goal as an ophthalmologist is to have a
8 totally clear capsule. The advantage of measuring
9 peripheral change in PCO is that you pick up those changes
10 earlier than you pick up the central changes.

11 So if you are going to have to wait to pick up
12 central changes, you are probably going to have to wait
13 probably two or three years, or a long time to pick those
14 sorts of changes up.

15 DR. PULIDO: But, in this case, there was central
16 opacification and peripherally it was clear.

17 DR. SPALTON: Yes.

18 DR. PULIDO: So your hypothesis that it starts
19 peripherally and it goes centrally might--

20 DR. SPALTON: No; I think that that is not the
21 case. I think what we are seeing in this patient here was
22 probably someone who has got a fibrotic plaque left on the
23 posterior capsule after surgery from, I suspect, a posterior
24 subcapsular cataract where the surgeon had not really
25 polished off that.

1 I mean, obviously anything on a retroillumination
2 image contributes to that image. I think it depends on what
3 you mean by PCO. That patient has an opaque capsule. He
4 certainly needs a laser capsulotomy. Why is that there? I
5 suspect that is a remnant from security rather than--it is
6 hard to imagine how cells would get into the center on their
7 own without migrating in from the outside.

8 PCO tends to migrate in centripetally. Do you see
9 what I mean?

10 DR. PULIDO: Thank you.

11 DR. COLEMAN: Mine kind of relates to your comment
12 that you prefer to have a clear capsule versus just clarity
13 in the three millimeters centrally. Have there been any
14 functional or quality-of-life studies supporting that claim?

15 DR. SPALTON: No. There haven't at all. I think
16 it is purely clinical appreciation.

17 DR. WEISS: Is there a way to make an adjustment
18 in your system so that you can get two measurements, one
19 that you are presently getting in terms of the percentage of
20 the capsule that is opacified and another one just looking
21 at, for example, the central three millimeters?

22 DR. SPALTON: Yes. We have actually done that a
23 lot. As I alluded to in the last slide, when we are looking
24 at correlating psychophysical-visual tests against the
25 central three millimeters, we have been measuring the area

1 measurements of the center there. But that gives a very
2 poor correlation just in a straightforward way.

3 But we can measure the central three millimeters.
4 We can measure any area that you want. It is just a
5 question of setting the computer parameters.

6 DR. WEISS: So, if you did that, would it then
7 correlate more with the Nidek?

8 DR. SPALTON: Yes; I think you could argue that
9 that may correlate better with the Nidek system. It depends
10 on what you want to correlate. I think they are both
11 measuring different things.

12 The Nidek system gives you a composite measurement
13 of area and severity. It measures it in what is called, I
14 think, computer-compatible tapes, units which I am not sure
15 what they are, but it is a sort of composite unit, really,
16 that the Nidek gives you.

17 DR. McCULLEY: Other questions or comments?

18 DR. FERRIS: I just had a comment and that is
19 statistics and instruments like this that try to give us
20 standardized measurements are the extreme in data reduction.
21 We are trying to get one number to summarize something
22 which, as Jayne just pointed out, maybe can't be summarized
23 in one number.

24 It seems to me, from your presentation, that there
25 truly are at least two important issues. One is how much

1 involvement is there centrally and the second is how much
2 involvement is there in the total area. That one is a more
3 difficult one because, as you point out, it is kind of
4 floating denominator. You have to circle the area. It is
5 not so simple as taking, well, the central five millimeters
6 and the central seven millimeters.

7 It seems to me that both numbers are interesting
8 and important and might be worth calculating on everyone.

9 DR. SPALTON: I would agree with you. I think
10 that they are both useful datasets to have. It is a
11 philosophical decision of what you are interested in, which
12 you measure, really.

13 DR. FERRIS: It may not be totally philosophical
14 because you pointed out that you can, then, look to see
15 which one of these predicts visual function now at the same
16 time but, also, in the future. It would be very interesting
17 to see whether your statement that these peripheral lesions
18 predict eventual central involvement, both by looking
19 sequentially to see whether they, indeed, do predict central
20 involvement and whether they predict functional involvement.

21 These are surrogate outcomes. Linking them to
22 function would be very helpful indeed, I would think.

23 DR. SPALTON: I am sure that is actually right. I
24 think this business of central function--I think the analogy
25 is if someone came out with a 3-millimeter intraocular lens,

1 no one would use it. I mean, I think that there is more to
2 the eye than the central three millimeters. But I think it
3 is difficult to quantify that.

4 DR. MATOBA: I might be confused, but I am not
5 clear, have you or have you not correlated either your
6 larger area or the smaller area analysis with clinical
7 parameters such as visual acuity?

8 DR. SPALTON: Yes. We have done a lot of work on
9 that. The correlation between LogMAR visual acuity and the
10 central area PCO is very low--between forward-light scatter,
11 using the Vandenberg straight-light meter, is very low
12 correlating it between low contrast acuity LogMAR and Petty
13 Robson.

14 If you do those four tests, you get, in their own,
15 a very poor correlation with what the patient has--

16 DR. MATOBA: But, for the central three
17 millimeters, if you--

18 DR. SPALTON: Yes; with the central three
19 millimeters, you get a very poor correlation.

20 DR. MATOBA: It is low.

21 DR. SPALTON: Yes; it is something like 0.2. It
22 is actually useless which is why we are moving on to other
23 ways of trying to assess the severity of PCO.

24 DR. MATOBA: When you say that the early studies
25 correlate with 36-month opacification, what, exactly--

1 DR. SPALTON: What I am saying is if we take our
2 protocol and we measure the percentage PCO, because we are
3 measuring area, and I think we have to emphasize this, that
4 in our protocol, we measure area of PCO and not the severity
5 of it.

6 At six months, we pick up the same area as we are
7 picking up at three years. The severity in that period of
8 time tends to get worse because it tends to thicken up.
9 But, if you look at the images, and you can put one up
10 beside the other, you see the area is very much the same.
11 It is just that it has tended to thicken up in that time.

12 DR. MATOBA: Is there any indication that severity
13 or larger area involvement early on predicts decrease in
14 vision at three years?

15 DR. SPALTON: Yes. I am not sure that I have the
16 figures to prove that, but I am sure that you are actually
17 right and it does predict. If you have got a lens with a--
18 there is one lens on the European market where, at six
19 months, you get 60 or 70 percent of PCO, if you look at
20 those patients at three years, they have all had YAG rates.

21 DR. WEISS: Do any of the systems that you
22 mentioned correlate with visual acuity?

23 DR. SPALTON: No. As far as I am aware, nobody
24 has a system yet of correlating a physical measurement of
25 the capsule with visual function.

1 DR. MAGUIRE: Wouldn't you say that that is
2 because most measures of visual function are not designed to
3 pick this stuff up, that they are very gross measures. The
4 standard measures of visual function we use are gross
5 measure of function.

6 DR. SPALTON: Yes. I think this is not a
7 surprising thing because this accounts for the diversity of
8 YAG capsulotomy rates, I think, in patients. You look at
9 surgeons' YAG different numbers because we do it on sort of
10 symptoms of the patient and have an intuitive feel for it.

11 Testing visual function in elderly patients, as I
12 say, we spend a lot of time. It is very difficult. It
13 often tells you more about their reticular activating system
14 in their brain stem than the optics of the eye.

15 DR. McCULLEY: I think that is important to
16 recognize, that there are wide differences in cortical
17 function in the elderly and perception and all those things.
18 So we wouldn't expect it to correlate.

19 DR. SPALTON: I think the thing is a lot of these
20 psychophysical tests have been done on twenty-one-year-old
21 Ph.D. students who are highly attuned to it. That is quite
22 a different matter to a seventy-five-year-old lady who is
23 rather bored and wants to go home.

24 DR. MAGUIRE: Then I guess the other point that
25 brings up is if it is difficult to correlate these things

1 with visual function, then how much attention should we be
2 giving to posterior capsular opacity anyway.

3 DR. SPALTON: Well, it covers probably all
4 cataract surgery at the moment. I mean, I think the fact
5 that it is difficult to correlate it doesn't mean that one
6 shouldn't attempt to do it and come out. I personally think
7 that your suggestion of wave-front analysis and MTF is the
8 way that we are going to be going with that, with more
9 sophisticated software. But we will wait and see.

10 DR. MAGUIRE: I agree with you. I just bring up
11 the questions rhetorically just because they show important
12 issues. Basically, the visual function is the product of
13 optics plus cortical processing and it is very subjective.
14 So what you are looking for is a good objective measure of
15 the optical component of it that you can see change over
16 time.

17 DR. SPALTON: That's right. One of the
18 confounding factors, of course, is in this age group, a lot
19 of them will have macular problems as well which can be a
20 confounding factor. A few drusen at the macula can be--

21 DR. McCULLEY: Thank you, Dr. Spalton.

22 Is there anyone else in the audience that wishes
23 to speak during this open public hearing section? Seeing
24 none, the open public hearing section is closed.

25 We will now begin the open committee discussions.

1 We are going to discuss our first topic, which is Posterior
2 Capsule Opacification. Ms. Lochner is going to introduce
3 the topic.

4 **TOPIC A: POSTERIOR CAPSULE OPACIFICATION**

5 **Introduction of the Topic**

6 MS. LOCHNER: Thank you and good morning.

7 I would like to begin by thanking Dr. Berman and
8 Joel Glover who have carried the day on this discussion,
9 particularly since I have been away from the division. I
10 would also like to thank Dr. Spalton for his time, and we
11 certainly do appreciate his perspective.

12 I would like to provide you a brief introduction
13 to your discussion of clinical study requirements for IOL
14 claims related to a reduction in posterior capsule
15 opacification. The goal of this discussion is to obtain
16 clinical study design recommendations from you so that we
17 may develop guidance to the industry in this area.

18 The need for guidance and some amount of
19 standardization in the PCO area became increasingly apparent
20 as we began to review data that sponsors submitted in order
21 to support various claims related to PCO.

22 To date, we have approved claims related to PCO
23 for two lens models, from two companies, and we have
24 informally discussed PCO substudy proposals with other
25 sponsors. Our review of these data created numerous

1 questions internally, centered mostly around the clinical
2 significance of the claims made. However, we attempted to
3 objectively convey the data related to PCO in the approved
4 PMA labeling.

5 Another factor that has added complexity to the
6 PCO issue is the fact that HCFA has been charged with
7 providing greater reimbursement for so-called New Technology
8 IOLs or NT IOLs. An IOL is an NT IOL if FDA has approved
9 specific claims of clinical advantages or superiority
10 compared to existing IOLs.

11 Because the FDA has statutory authority for review
12 of claims of clinical advantages or superiority, we, and
13 sometimes also the panel, are required to assess these
14 claims whether or not the company chooses to pursue NT IOL
15 designation through HCFA.

16 HCFA has informally advised us that they interpret
17 this to mean that NT IOL must be superior to all existing
18 IOLs. Allow me to briefly explain FDA's role in the NT IOL
19 process, and that is that FDA acts in an advisory or
20 consultative capacity to HCFA.

21 To date, HCFA has received one group of
22 applications for review in their first review deadline. FDA
23 provided information to HCFA about the FDA approval status
24 of the clinical claims made by the sponsors, and we provided
25 our opinion on whether the sponsors had demonstrated

1 clinical superiority of their lenses over existing IOLs.

2 In most instances, this can be a fairly
3 straightforward exercise. For example, if a sponsor
4 demonstrates that their multifocal IOL has specific
5 advantages, such as improved near visual acuity, as compared
6 to a control monofocal IOL, one can easily say then that
7 this multifocal IOL is superior to all existing monofocal
8 IOLs.

9 Similarly, if a sponsor were to demonstrate
10 statistically significant improvement in inflammation rates
11 of their lens, as compared to the FDA historical grid, one
12 may also presume that they have demonstrated clinical
13 superiority to all existing lenses.

14 In the PCO area, however, a comparison to one
15 control lens may not necessarily ensure that a sponsor's
16 lens is superior to all IOLs due to the many lens variables
17 that have been shown to impact upon PCO.

18 While we believe that many sponsors will want to
19 perform one clinical study that would both support FDA
20 labeling claims and allow for NT IOL designation, the
21 sponsors are not obliged to do this and FDA cannot require
22 that their study address NT IOL issues.

23 I have provided this introduction into the HCFA NT
24 IOL process as background information, so that you
25 understand the various issues that impact PCO studies. We

1 are not asking that you specifically address the HCFA NT IOL
2 process in your recommendations.

3 Dr. Berman will introduce the specific clinical
4 issues to you, but let me say that the interpretation of
5 different measures of PCO and then the clinical utility or
6 significance is the area that gives us the most difficulty.

7 While most would recognize that reduced PCO would
8 certainly be a clinical advantage, the significance of the
9 PCO claim can be problematic if the sponsor has not chosen a
10 definitive endpoint.

11 This issue of endpoints or "what is reduced PCO"
12 is captured in our questions to the panel. One approach is
13 to simply factually describe the results of each sponsor's
14 studies in their labeling, however, we believe that without
15 some amount of standardization in the conduct of the
16 clinical study, the interpretation of various claims related
17 to PCO will be confounded.

18 This concludes my introductory comments, and now I
19 would like to introduce Dr. Sherri Berman, who will provide
20 a clinical introduction and the questions to the panel.

21 DR. McCULLEY: Donna, before you go ahead, you
22 said you were not specifically asking the panel to address
23 this relative to NT IOLs. I think that is close to your
24 words?

25 MS. LOCHNER: That is correct.

1 DR. McCULLEY: Are we to leave out--you know, I
2 can see how it could be difficult for these two issues to
3 come in--should we specifically try to avoid the issue of
4 the NT IOL situation or that is just a float?

5 MS. LOCHNER: I think you should discuss it in the
6 context of if a sponsor wanted to show that their lens was
7 superior to all existing IOLs, so if that were the context
8 the sponsor was presenting, I think we have actually asked a
9 question and wants your input on how a sponsor could show
10 they are better in the PCO area to all existing IOLs.

11 However, I guess what I am trying to say is I
12 don't think your recommendation should hinge upon that one
13 requirement. So, in other words, if a sponsor were to want
14 to show they were superior to just one IOL, we don't want to
15 rule that possibility out.

16 DR. McCULLEY: Which would not relate then, would
17 not necessarily translate to HCFA being able to assess NT
18 IOL status.

19 MS. LOCHNER: Right. So, from that perspective,
20 we don't want you to be concerned that if you made a
21 recommendation for clinical study requirements that just
22 related to showing superior to one particular IOL, we don't
23 want you to then be concerned that they would not get HCFA
24 NT IOL designation.

25 On the other hand, we also do want some advice on

1 how could a sponsor show they are better than all existing
2 IOLs, so that if they wanted to use that study to get HCFA
3 NT IOL designation, they could.

4 So, I guess I don't want to distance you
5 completely from the HCFA NT IOL process, because we believe
6 most sponsors will want to have one study that meets both
7 requirements, FDA's and HCFA's, however, you know, this
8 panel is not charged with the HCFA process.

9 DR. McCULLEY: You are saying we may not solve
10 HCFA's problem.

11 MS. LOCHNER: Exactly.

12 DR. McCULLEY: Or industry's problem relative to
13 HCFA and NT IOL.

14 MS. LOCHNER: Right, and so we did try to have one
15 focused question that spoke to HCFA's issues, which is
16 showing superiority to all lenses.

17 DR. McCULLEY: In reading through the material you
18 gave us, you were asking about a, quote, "gold standard."
19 The gold standard might not represent a single lens that
20 would represent superiority over all. It would be
21 potentially a baseline gold standard that might have some
22 platinums and some super platinums already out there.

23 MS. LOCHNER: Yes. That is one of the central
24 issues, and I think, as we talk about controls, that is one
25 of the central issues, of, you know, is there a gold

1 standard, and if so, what is it; if not, what is the
2 appropriate control.

3 DR. McCULLEY: And what it represents.

4 MS. LOCHNER: Exactly. All of the questions, you
5 know, as you have probably seen, are somewhat interrelated.
6 What it represents, what the endpoint is, what the standard
7 is, what you are comparing, I mean they are all
8 interrelated. It is a very difficult set of questions taken
9 in total.

10 DR. McCULLEY: Okay. Proceed, please.

11 **Overview of Discussion**

12 DR. BERMAN: Good morning. I am Sherri Berman. I
13 would like to provide you with a brief overview of the goal
14 and scope of today's discussion.

15 As you are all aware, posterior capsule
16 opacification, or PCO, is one of the most common
17 complications of modern cataract surgery.

18 Reported rates of PCO vary widely, in part due to
19 the lack of standardized methodology for objective
20 assessment of the posterior capsule. As part of today's
21 discussion, you all will be asked to comment on the current
22 methods of PCO analysis for use in studies to support claims
23 of reduced incidence of PCO.

24 Differences in surgical technique and patient
25 populations also likely contribute to the wide variability

1 in reported incidence of PCO. Part of today's discussion
2 will attempt to delineate what the panel members consider
3 critical elements of a PCO study protocol that would require
4 standardization.

5 More recently, differences in intraocular lens
6 design, such as lens material and edge shape, have been
7 implicated in the development of PCO.

8 Due to difficulties objectively quantifying PCO,
9 many previous studies often used neodymium YAG capsulotomy
10 rate as a surrogate for PCO incidence. Unfortunately, these
11 studies are confounded by variability in the clinical
12 criteria for the timing of performance of capsulotomy,
13 making it very difficult to compare data on PCO incidence
14 between various IOLs.

15 While acceptable methods for objective measurement
16 of PCO exist that assess both density and distribution of a
17 capsular opacity, should this be the sole endpoint for an
18 IOL study to support claims of reduced PCO?

19 Today, you will be asked to discuss whether the
20 impact on the patient's visual function should have a
21 critical role as a study endpoint, and if so, just what that
22 should be.

23 As IOLs have become more refined, manufacturers
24 wish to gain FDA approval for claims of superiority with
25 respect to many clinical areas, including reduced PCO

1 incidence, delayed PCO incidence, reduced YAG capsulotomy
2 rate, reduced PCO severity grading, et cetera. Today, you
3 will be asked to discuss the clinical relevance and
4 acceptability of any or all of these claims.

5 It is with these issues in mind that you have been
6 asked to provide your clinical input for the development of
7 FDA guidance on the design of clinical protocols to evaluate
8 incidence of PCO.

9 As a framework for such a guidance, and to
10 facilitate today's discussion, we have prepared a
11 preliminary discussion paper that you can find in Tab 1 of
12 your handout, which you have previously had the opportunity
13 to review. FDA's final question for panel members today
14 will ask for your comments regarding the content of this
15 discussion paper.

16 At this time, I will proceed to the panel
17 questions. Each of the four primary reviewers was assigned
18 several questions.

19 Dr. McCulley, if it is okay with you, I will read
20 the panel questions one set at a time, after which the
21 primary reviewer will present his or her comments, and then
22 the panel can complete its discussion on that set of
23 questions before we will proceed to the next reviewer's set
24 of questions. Then, if you want to go back to any areas at
25 the end, we can do that.

1 DR. McCULLEY: This is your show. That sounds
2 reasonable. We may find the need to adjust the approach as
3 we go through, but that sounds like a good place to start.

4 **Primary Panel Reviews**

5 **Clinical Endpoints**

6 DR. BERMAN: We will start with clinical endpoints
7 that was reviewed by Dr. Sugar.

8 DR. McCULLEY: These are under Tab 7, the written
9 reviews.

10 DR. BERMAN: Right. They are in Tab 7 of your
11 notebook.

12 DR. McCULLEY: I think Joel actually addressed all
13 of the questions, didn't you?

14 DR. SUGAR: I will just talk about the first
15 section. Sherri, are you going to ask the questions?

16 DR. BERMAN: I will go ahead and read all three of
17 your questions, and then we can go back and keep the slides
18 up as you present your comments.

19 The first question: Since not all measurable PCOs
20 are associated with clinically significant effects on a
21 subject's visual function, do you believe that demonstration
22 of decline in measures of visual function, for example, best
23 corrected acuity, glare testing, contrast sensitivity, et
24 cetera, should be a required endpoint for a PCO study? If
25 so, what degree of visual impact, for example, more than 2

1 lines of decline, do you recommend? If not, what
2 quantitative measurement of PCO grade do you recommend as an
3 appropriate endpoint?

4 The second question: Is a claim of delay in onset
5 of visually significant PCO within the duration of the study
6 clinically relevant? If so, what period of time do you
7 consider a clinically significant delay?

8 The final question: What minimum difference in
9 PCO rate between 2 IOLs do you consider clinically
10 significant, for which a claim of superiority should be
11 considered? For your consideration, a sample size analysis
12 table has been provided below for various deltas. Do you
13 suggest a minimum number of subjects allowable for such a
14 study?

15 DR. McCULLEY: Let's go back and take these one at
16 a time, and just start with the first.

17 DR. SUGAR: So, you want me to comment on the
18 first question and then we discuss it?

19 DR. McCULLEY: I think so. I think that these
20 individual questions stand enough alone. So, let's comment
21 on each of your three questions in order.

22 DR. SUGAR: I have two comments as a preamble.
23 One is that on May 3rd, HCFA released decisions in the
24 Federal Register on intraocular lenses including a lens that
25 demonstrably reduces PCO and found it not to be new

1 technology. That is a lens that reduces posterior capsular
2 opacification sufficiently that if that becomes the gold
3 standard, the rest of this becomes meaningless, because it
4 is very hard to get lower than a 4 percent capsular
5 opacification rate.

6 DR. McCULLEY: Joel, update us on that. You say
7 May 6th?

8 DR. SUGAR: May 3rd.

9 DR. McCULLEY: May 3rd.

10 DR. SUGAR: HCFA released, they determined two
11 lenses to be new technology. You don't want us to do this.

12 DR. McCULLEY: Right, but neither related to PCO
13 opacity, did they?

14 MS. LOCHNER: That is correct.

15 DR. SUGAR: I don't know what the claims were for
16 the MA60BM lens, which was determined not to be new
17 technology.

18 MS. LOCHNER: I think I can summarize in a
19 nutshell. HCFA did decide that two lenses met the criteria
20 for NT IOL, and those were a multifocal IOL by Allergan and
21 a toric IOL by Staar. HCFA denied NT IOL designation on
22 several of the applications, two of which were related to
23 PCO.

24 It is my understanding that this denial was based
25 upon this issue of showing superiority to all IOLs. In the

1 one sponsor's application, they had compared it to one lens,
2 and--well, they had actually compared it to two lenses, a
3 silicone and a PMMA, and were able to show superiority only
4 to the PMMA lens, and not show superiority to the silicone
5 lens.

6 Likewise, the silicone application was able to
7 show superiority to one particular PMMA lens, and not to the
8 acrylic lens. The are sub-issues of the method used, et
9 cetera, and exactly what was measured in both of those, but
10 if we just, for sake of discussion, say both measured PCO
11 even though they measured different things, you know, there
12 was also that issue.

13 In the one application, the sponsor actually was
14 requesting the NT IOL designation for a model that they did
15 not study, so again, this again gets to some of the control
16 questions that will come later on, but what has to be shown
17 to show superiority.

18 DR. McCULLEY: As I understand it the first lens N
19 has to show superiority to all, and if they get designation,
20 then, they have a five-year clock running.

21 MS. LOCHNER: Right.

22 DR. McCULLEY: That sets the clock for everyone.
23 If someone else comes in, they presumably would have to show
24 superiority to the already approved NT IOL.

25 MS. LOCHNER: Exactly.

1 DR. McCULLEY: That wouldn't bump that one off the
2 wagon, but the other one would have the clock limit set by
3 the first one that came on.

4 MS. LOCHNER: Right, with an additional proviso
5 that during that five-year period, if another company comes
6 in, in the same class, they get the remainder time period
7 for NT IOL. So, now that a multifocal has been designated
8 as NT IOL, it will be reimbursed for five years.

9 If next year another multifocal lens gets an NT
10 IOL designation, it will be a remainder of four years on
11 that span.

12 DR. McCULLEY: And that second multifocal IOL that
13 comes in does not have to show any superiority to the
14 already approved multifocal, just substantial equivalence?

15 MS. LOCHNER: Right, not within that first five-
16 year category. Of course, if it comes in, in year four, it
17 only has one more year left, so it might want to show some
18 additional superiority in some other aspects that hadn't
19 been reviewed.

20 DR. McCULLEY: What Joel was saying is that one of
21 the lenses approved claims a 4 percent PCO rate?

22 DR. SUGAR: I don't know what their claim was.

23 MS. LOCHNER: That was denied. That NT IOL
24 designation was denied.

25 DR. SUGAR: All I am saying is that this creates a

1 threshold that is very difficult.

2 MS. LOCHNER: No, I don't think so. I don't think
3 it was denied because the threshold was deemed to be not
4 superior, that 4 percent was deemed to be an inferior rate
5 of PCO, I don't think that was the basis. I believe the
6 basis was showing superiority to all IOLs, when they had
7 only shown superiority to PMMA.

8 DR. McCULLEY: What 4 percent rate are you
9 referring to? That is where you lost me.

10 DR. SUGAR: That is just sort of the general, in
11 my experience, general opacification rate with the Acrysoft
12 lens, and the MA60BM is the Acrysoft lens, and that lens was
13 denied, and I just think that part of what we are doing, I
14 think we should just end the discussion of the NT IOL issue
15 and discuss what FDA has to do for labeling claims, but I
16 think that they have created a very difficult threshold for
17 future IOLs in that regard.

18 MS. LOCHNER: But bear in mind that, because there
19 is an aspect of this that applies to FDA, and has nothing to
20 do with NT IOL, and that is that, you know, what has shown
21 superiority, it is your feeling that this 4 percent, and
22 most people would say that is certainly a superior rate of
23 PCO, however, in the study that was done, there was not
24 shown a difference between that lens and silicone.

25 So, in some of the discussion points, it is very

1 critical to say what showed superiority. Maybe the
2 threshold was too high in that instance. So, bear in mind
3 that we are asking for clinical study guidance, so that what
4 you believe to be true clinically, we can show in a study.

5 DR. SUGAR: I understand.

6 I have two points. The other point was the one
7 that Marcia Yaross made yesterday, that we should not tell
8 industry what tests to do, if they do a test that is
9 demonstrably scientifically valid.

10 MS. LOCHNER: Absolutely.

11 DR. SUGAR: And you said that apropos of
12 questionnaires about visual function, but that is true for
13 these, so when we talk about what tests, the point isn't
14 what tests, but do they do a test that works or not.

15 MS. LOCHNER: Absolutely, and please bear in mind,
16 when you provide us recommendations, and we provide guidance
17 to the industry, they are under no obligation to do exactly,
18 you know, point by point, that guidance.

19 They can offer a totally alternative approach that
20 is scientifically valid, and we would review it on its
21 merits. You know, I think practically, your recommendations
22 are always helpful to industry, but on any level, they don't
23 have to accept any of them.

24 DR. McCULLEY: Right, nor do you or we when they
25 come back in with their data.

1 MS. LOCHNER: Exactly.

2 DR. BERMAN: And also, just to comment, we are not
3 necessarily asking, when we get to Dr. Bullimore's section,
4 we are not asking for the panel to tell us which one method
5 of analysis you recommend that all studies use. Maybe there
6 will just be certain aspects that you think are critical,
7 you know, like they all have to be validated, they all have
8 to measure density and area, of whatever the panel feels are
9 the critical issues.

10 DR. McCULLEY: Dr. Yaross and Dr. Pulido each have
11 a comment.

12 DR. YAROSS: I think part of the difficulty is
13 that while the HCFA regulations define an NT IOL as one that
14 is superior to all existing IOLs, it does not define
15 existing IOLs. I thought it may be helpful to the panel to
16 know what the current existing IOLs are.

17 In 1999, which is the last year for which data are
18 available from a Deloit & Touche database, only 15 percent
19 of IOLs implanted were PMMA IOLs, so it appears that the
20 existing IOLs are predominantly silicone and acrylic IOLs.

21 DR. McCULLEY: That was one of my questions of
22 what is the penetrance of the market with each of the lens
23 designs. So, 15 percent are PMMA?

24 DR. YAROSS: The way the data are broken out are
25 foldable and non-foldable. So, PMMA represent 15 percent in

1 this database, and foldable silicone and acrylic lenses are
2 about 85 percent.

3 DR. McCULLEY: And there is not a breakdown
4 between those two?

5 DR. YAROSS: Not in the data that have been
6 available to me.

7 DR. McCULLEY: And you don't know that from other
8 databases, that you can share with us.

9 DR. YAROSS: Not that I know that are verified.

10 DR. McCULLEY: Dr. Pulido.

11 DR. PULIDO: That was exactly my point,
12 considering what Joel had said about the May 3rd. Now, what
13 Dr. Yaross has said, it appears that when we talk later on
14 about the control, the control is not the PMMA, but rather
15 PMMA, silicone, and acrylic lenses, is that correct?

16 DR. McCULLEY: Right, but then we also have issues
17 of not just materials, but design and edge design, and so
18 on, and so forth.

19 MS. LOCHNER: Yes. That will be further discussed
20 when we get to that question.

21 DR. McCULLEY: I think we will get more crisp and
22 to the point as we go on, as we start to get a better feel
23 for what the background issues are.

24 Joel.

25 DR. SUGAR: The first question is: Do you believe

1 that the demonstration of decline in measures of visual
2 function should be a required endpoint for a PCO study?

3 To quote Dr. Spalton, "severity is meaningless
4 unless correlated with visual function." There is no
5 question that visual function has to be part of a PCO study
6 at the same time visual function, in and of itself, is
7 sometimes insufficient.

8 On Tuesday, I took a cataract out of a 47-year-old
9 man who had 20/20 acuity. By all measures, the worst I
10 could get him to be was drop 1 line with glare testing, and
11 on Wednesday, after his cataract was removed, he said he
12 couldn't understand why he hadn't had it removed years
13 earlier. He had a posterior subcapsular cataract, which is
14 functionally the same as what we are talking about, and at
15 this slit lamp he shouldn't have seen as well as he did.

16 So, both things don't correlate. People sometimes
17 have a lot of opacification and good vision, but poor
18 function that we don't test, and that was Leo's point, and
19 some people have very high opacification and very good
20 function. So, I think both have to be measured.

21 I sort of went along with the wording in Dr.
22 Berman's paper that we need to set a threshold, and I said 2
23 lines or more under standard testing decline in acuity, but
24 I think that there should be, you know, you can't use that
25 as a single measure.

1 Likewise, decreases in contrast sensitivity,
2 straylightmeter, Scheimflug testing, any other validated
3 measure could be meaningful. So, I don't think that we can
4 come out with a single measure, but visual acuity should be
5 one of the measures.

6 I think that is Question 1. Should we discuss
7 that?

8 DR. McCULLEY: Are there any other comments on
9 Joel's assessment of Question 1? Walter.

10 DR. STARK: Just as one who sees a large number of
11 these patients, just to emphasize again, there is often poor
12 correlation to what you see, and clinically, I see patients
13 with a fibrotic change that it looks worse than their
14 cataract was before we took it out, and their vision is
15 20/20 and they have no symptoms.

16 Then, you see patients with small lens epithelial
17 proliferation that you can only see by retro-illumination,
18 you can't see it by direct illumination, and there is vision
19 down by 2 or more lines, and 2 or more lines may not be the
20 magical number, as Joel indicated, because each line is a 20
21 percent reduction in resolving power, so that is a 40
22 percent reduction or 36 to 40 percent reduction in visual
23 acuity, so it does depend a lot on the needs or awareness of
24 the patient.

25 Now that we understand for the new technology, of

1 companies are trying to apply for that, to be superior to
2 every other lens, that is going to be very difficult to
3 prove I think for HCFA, and I didn't realize it was that
4 complex.

5 It is obvious that they would probably like to put
6 it in their labeling, though, and do a controlled study in
7 that manner, and I think the final endpoint is going to have
8 to be, probably in a large group of patients, the YAG laser
9 capsulotomy rate, and it would probably have to be a
10 controlled study.

11 The only bias would be that if an investigator
12 wanted to do more YAG lasers in the non-new lens, in the old
13 lens, and you would hope that that wouldn't happen. Rick
14 Ferris is probably the one that could answer the question of
15 how many people it is going to take in a large study to look
16 a capsulotomy rates, because we could get that information
17 in billing.

18 DR. McCULLEY: Walter, we are going to come to the
19 issue of YAG rates I think down the line and study design,
20 but you are right about those issues. I think they are
21 parts of the planned questions, right, Dr. Berman? I caught
22 you talking.

23 DR. BERMAN: You did, but it is relevant, and I
24 just want to say again, because it keeps coming up, that
25 there really are almost two issues going on here at the same

1 time, and I think that is what is so confusing. You are
2 grappling with the issue of how do you demonstrate superior
3 to all lenses, but we, at FDA, are also looking at labeling
4 claims coming in for approval, just, you know, different
5 lens manufacturers wanting to demonstrate one type of PCO
6 claim and have it in their labeling just based on a simple
7 study that they did. It doesn't necessarily mean they are
8 ever going in and request that HCFA designation.

9 So, in your deliberations today, I know it is
10 hard, but please try to keep both of these issues in mind.

11 DR. McCULLEY: This is going to be a tough day.
12 If you have got an issue, if you can try to, you know, just
13 jot it down, because you missed important things that Dr.
14 Stark was saying, so you can't respond to what I was asking
15 you to respond to, because you were discussing an issue that
16 had come up that was important to you. Try to wait until a
17 break, so that we can all stay on the same page at the same
18 time. It would make it a lot easier.

19 In our questions that we have coming to us, do we
20 not have coming up--Dr. Stark was addressing YAG rate and
21 study design, we have specific questions coming up that are
22 going to address that, so we will wait on that part. You
23 are absolutely right, Walter, and we will get to those.

24 Any other issues with Joel's? Rick.

25 DR. FERRIS: Just a quick comment, I hope quick

1 comment, regarding visual function. It seems to me that one
2 of the problems we have here is we don't know what the
3 baseline is for function. Some people, the best they are
4 ever going to do is 20/20, but for most patients, 20/20 is
5 not the best they are going to be able to do, and I suspect
6 Joel's patient that he discussed, one of the reasons he was
7 unhappy with his 20/20 is because, indeed, he does function
8 better, and I wonder whether there should be some
9 consideration given the concerns that Donna mentioned
10 earlier, I think they are valid concerns, that capsulotomy
11 rates are going to depend on who is doing them.

12 I think I could elicit whatever symptoms I want
13 from a patient, if I want to elicit appropriate symptoms, so
14 one wonders whether it would be helpful to document that
15 there was a need by doing pre- and post-capsulotomy
16 functional measures to try to document whether some surgeons
17 have consistently improved--I don't know what the measure
18 is, we will talk about that later--but functional measures,
19 whereas, others do capsulotomies and apparently have much
20 lower rates of improvement.

21 DR. SUGAR: So, you are saying that there should
22 be a post facto measure, that the measure is that it made a
23 difference afterwards.

24 DR. FERRIS: Well, because we don't know what the
25 baseline is, if you could document improvement, then, at

1 least you are showing that you are doing this for some
2 functional reason rather than just doing it to do it.

3 DR. McCULLEY: Dr. Coleman.

4 DR. COLEMAN: I was going to recommend just using
5 one of the standardized Quality of Life questionnaires that
6 have been developed possibly for that.

7 DR. McCULLEY: What are the thoughts about that?
8 I don't know. Do you want us to come to conclusion on
9 these, consensus, or do you want just all of our collective
10 opinions for you to digest and deal with later?

11 DR. BERMAN: Well, ideally, we would love to have
12 collective opinions, but that may not be possible for some
13 of these issues, so if you feel like that can't be possible
14 for certain questions, then, maybe just at this point a
15 discussion and input is all we could ask for.

16 DR. McCULLEY: Joel recommended a measure of
17 visual function.

18 DR. SUGAR: Of decrease in 2 lines or greater.

19 DR. McCULLEY: And a measurement of capsular
20 opacity.

21 DR. SUGAR: That gets to quantification in the
22 later question.

23 DR. McCULLEY: Then, the other, I think this would
24 probably, as best I remember all the questions, this would
25 be where if we were going to recommend a Quality of Life

1 questionnaire, that it would be interjected here.

2 What is the opinion about that? Walter.

3 DR. STARK: I think that is a great suggestion
4 from Anne, and there are some being developed by the
5 National Institute and others, because we see people that
6 don't decrease 2 lines. They decrease from 20/20 to 20/25
7 or 20/30. They are symptomatic. Like your patient, you do
8 the YAG, and they say within two minutes, Doctor, this is
9 just amazing, how much better my vision is, I mean as they
10 get up from the YAG laser and look down the hall.

11 So, that is a subjective improvement. They may
12 improve one line, from 20/25 to 20/20, and a subjective
13 test, the Quality of Life test may pick that up, whereas,
14 you haven't made that patient wait until they decrease
15 vision to 20/20 minus or 20/40, in that range. So, there is
16 a big subjective component to this.

17 What is interesting is all these machines. I
18 really enjoyed the presentation by Dr. Spalton because
19 Oliver Schein at our institute has done a similar study with
20 a digital camera, and none of them show any correlation with
21 visual function. I mean they are great pictures, but they
22 just don't correlate with the visual function.

23 DR. McCULLEY: And the machines ain't cheap.

24 DR. STARK: No. And, you know, the aberrometers,
25 that is all a new technology, but I don't think we ought to

1 put our hat in that until it has been demonstrated to have
2 any correlation, because a lot of the fibrosis might show an
3 aberrometer change.

4 DR. McCULLEY: Dr. Jurkus.

5 DR. JURKUS: From someone who might be co-managing
6 these patients, I think the Quality of Life questionnaire
7 would be very important from the standpoint of that is one
8 of the basis of referral for capsulotomy to be performed.

9 DR. McCULLEY: Dr. Pulido.

10 DR. PULIDO: I agree with Dr. Ferris that not
11 necessarily a loss of 2 lines of vision might be indicated,
12 but rather showing after-the-fact improvement would be
13 reasonable also.

14 DR. McCULLEY: Dr. Bullimore.

15 DR. BULLIMORE: I think it is important we keep
16 the discussion of visual function for the moment since that
17 is the question that is being asked, and all the other
18 issues I am sure we will come to in time.

19 I would like to rephrase the FDA's question,
20 though. I think measurement of visual function should be
21 required and it should be one endpoint that a sponsor may
22 use to demonstrate superiority.

23 Since we have got a whole sort of pot pourri of
24 possible outcomes here, visual function is one that they
25 could use to demonstrate superiority, period. Next

1 question.

2 DR. McCULLEY: Visual function can be subjective
3 or objective, and they did ask if--I mean we are going to be
4 overlapping things, and that is a good point, because it
5 said, "If not, what quantitative measurement of PCO," so
6 that was thrown in there, sorry, Mark, but we are saying
7 visual function, yes, so I guess we can ignore that part of
8 the question and we will come back to it. But I think the
9 Quality of Life issue fits in here well, because that is a,
10 quote, "measure of visual function."

11 Dr. Yaross.

12 DR. YAROSS: My comment was on the QOL issue, and
13 that is that we are talking here about not a basic showing
14 of safety and effectiveness, but on optional claims that a
15 sponsor might seek.

16 I think in terms of PCO, we have had a lot of
17 discussion already saying that visual function is the most
18 relevant issue. Regarding QOL, I would say that if a
19 sponsor wishes to make claims about QOL, then, clearly, that
20 is something where we would want to use a validated approach
21 as we have discussed before, but I think that that is a
22 secondary consideration, and if a sponsor can show it with
23 objective measures, then, the QOL may not be necessary.

24 DR. McCULLEY: Well, we are dealing with this
25 somewhat as, quote, "guideline," and with guidelines we make

1 recommendations, so I think making a recommendation about
2 Quality of Life is reasonable for us to make. The sponsor
3 can ignore it or not.

4 Dr. Ferris.

5 DR. FERRIS: I actually feel fairly strongly that
6 we don't have any probably good objective measures of visual
7 function. They all have subjective components, and I have
8 patients all the time, since I do retina work, who I know I
9 have made worse, who tell me how much better they are after
10 the laser treatment.

11 We have to be sure we have a control group, and I
12 think the subjective assessment is very important here,
13 because in a way it is like LASIK. They are coming in with
14 a problem which they may still have 20/20 vision, but they
15 have a problem that they perceive, and it seems to me that
16 we at least need to have the subjective assessments of
17 function, whatever they are, but including a Quality of Life
18 type assessment going in the same direction, and if they are
19 going in the same direction, they don't all have to be
20 statistically significant in my opinion, but they need to be
21 going in the same direction.

22 If they are not going in the same direction, the
23 review group needs to have that information because I think
24 it is an important red flag.

25 DR. McCULLEY: Did I miss anyone in the chain?

1 Dr. Weiss.

2 DR. WEISS: I would agree with what you are
3 saying, but I think we have to be careful of the placebo
4 effect, because for the same reason you might be inferring
5 that the patient actually did better than you thought they
6 did, I would draw the conclusion that they weren't, they
7 think the laser worked, but it didn't, so the Quality of
8 Life, although it is important, I think it is ancillary, and
9 we may be eliminating some patients who have benefited from
10 the use of a particular IOL, but certainly if we can
11 document sort of gold standards of a visual acuity drop
12 where maybe other patients benefited from that IOL and
13 couldn't document a visual acuity drop.

14 We certainly know that those who had a drop in
15 visual acuity, and you did the YAG laser, and the visual
16 acuity improved, at least that subpopulation, you understand
17 what you are dealing with.

18 DR. McCULLEY: I think the point, though, is that
19 we want probably not just one thing as a measure would be
20 our recommendation.

21 DR. STARK: Jim, let me just ask you. Are we
22 going to require a prospective randomized clinical trial,
23 because if we do, I mean this is going to be a big expense,
24 time consuming. There are a lot of endpoints that we are
25 not certain about, and what good is it going to do the

1 company when they can't get new technologies.

2 So, I get back to the other question. Should we
3 look at large numbers, Rick, of YAG laser capsulotomy rates?
4 If we had accurate numbers of YAG laser capsulotomy rates
5 out three years with different lenses, would that give us--I
6 know it is not as clean because some doctors may do it, but
7 is that going to give us as good a number at the end when
8 you start to look at large numbers of YAG laser capsulotomy.

9 DR. McCULLEY: The first question I wrote on page
10 1 is, are we discussing a prospective internally controlled
11 study. I am not sure what the FDA's perspective on this is.
12 I mean we can internally control it by one lens in one
13 patient's eye, another lens or the base lens in the other
14 eye, and it all prospective, or do you have any thoughts
15 about that as to what kind of study you would be envisioning
16 the company to do.

17 DR. ROSENTHAL: Donna, may I just interrupt and
18 maybe you will mention the least burdensome approach, but I
19 must continue to interject that in the discussion.

20 I think part of the recommendation you are going
21 to make is what you have just asked Donna. Is that not
22 correct?

23 MS. LOCHNER: Let me say also that FDA really
24 doesn't have, you know, a strong opinion either way. Our
25 recommendation comes from what a sponsor tells us they want

1 to say in their labeling. You know, we don't care whether
2 they say they are better than one particular lens or whether
3 they say they have got the best PCO rate, you know, of any
4 lens out there.

5 Our guidance comes from what they come to us and
6 say they want to claim. From experience, the companies that
7 have gotten some aspect of a PCO claim, what I gather from
8 their advertising is they want to say they are the best lens
9 out there for PCO. However, I think really our guidance is,
10 what we want you to give recommendations is kind of in
11 general.

12 I mean, in general, a company wants to--if it is
13 easier for you to think of it as showing superiority in PCO
14 as compared to one lens, you know, we can deal with that,
15 give your recommendations in that regard, but I realize this
16 is a bit open-ended, but we don't have a set position at
17 FDA. We base it on what claim a company wants to make.

18 DR. McCULLEY: We will come back to the YAG rates
19 again somewhere else.

20 Rick.

21 DR. FERRIS: Perhaps I can just briefly address
22 the question, and that goes to whether you can use
23 observational studies to assess this or whether you can use
24 clinical trials. I hope we could agree that the clinical
25 trial is the gold standard.

1 The issue in assessing whether treatment A is
2 better than treatment B, in my opinion at least, it
3 inevitably comes down to ruling out chance bias and
4 confounding, and the problem with the observational studies
5 is that it is often difficult to rule out uncontrolled
6 confounding, especially when we see YAG rates in--I don't
7 know what the states are--but Rhode Island being highly
8 statistically significantly different than Nebraska.

9 The investigators then need to control for that in
10 some way, and I am not saying you can't do it, I am just
11 saying that it is a hurdle that they are going to have to
12 address in one way or another, and it may be a difficult
13 hurdle.

14 DR. McCULLEY: Dr. Bullimore.

15 DR. BULLIMORE: I want to reiterate what Rick
16 said. I mean I think so much of what we do on this panel is
17 try and assure reasonable safety and effectiveness, and it
18 is okay to do that with a cohort study, which is what we are
19 normally presented with, and in the case of IOLs, we have a
20 historical grid.

21 If a company wants to claim superiority to another
22 lens or a range of lenses, that really has to be done in a
23 randomized clinical trial, and I would be happy to make that
24 recommendation and see whether the panel wants to endorse it
25 and move on, if that is what you want.

1 DR. McCULLEY: You want that now, or do we want to
2 wait subsequently to touch that one? You are getting to one
3 of the bottom lines, I think. I don't disagree with you.
4 To me, the question is are we talking about it or do we
5 mostly want to talk about a prospective internally
6 controlled trial, that would be that cohort controlled--

7 DR. BULLIMORE: Yes, randomized clinical trial,
8 cohort study, and I think it you want to make claims of
9 superiority, whether it is in the context of the regulatory
10 arena or in the context of the standard of care in clinical
11 practice, you have to have a randomized clinical trial.

12 DR. PULIDO: Can we table that question until the
13 end?

14 DR. BULLIMORE: Here is the issue. If a group of
15 people are sitting down to answer a question like this in
16 the context of clinical research, one of the first issues
17 you would address is study design. Then, you might come
18 back and address it at the end, but study design is probably
19 number one on your list, and then you might discuss outcome
20 measures, which is I think what the shank of this discussion
21 is going to come back to.

22 I don't believe that we can ask or a sponsor could
23 reasonably make these claims based on a cohort study.

24 DR. McCULLEY: Ask Dr. Rosenthal to comment again
25 on the least burdensome issue and how that would fit into

1 the ideal that we are talking about. We can give you what
2 we think our ideal is, I don't think there would be a lot of
3 disagreement about that, but the question then would be are
4 there other less burdensome approaches that would be
5 acceptable to the FDA and subsequently, panel, and then back
6 to you, of course.

7 DR. ROSENTHAL: I think it all depends on the
8 claims they want to make, but I think we need a
9 recommendation from the panel as to what they think is the
10 best possible, and then the sponsors have the option to
11 argue their case.

12 MS. LOCHNER: You may want to note that both
13 sponsors who have made labeling claims in their labeling did
14 conduct randomized controlled studies.

15 DR. McCULLEY: That did not show a substantial
16 difference.

17 MS. LOCHNER: True, but I am just saying bear in
18 mind that--

19 DR. McCULLEY: We don't guarantee success.

20 MS. LOCHNER: --they either conducted it or they,
21 you know, they found data in which it was conducted in that
22 way.

23 DR. McCULLEY: Dr. Stark.

24 DR. STARK: Let me just ask, in the labeling for
25 Alcon, shows a zero capsular opacification--this is under

1 Tab 3, the second page in--zero capsular opacification for
2 Acrysoft lens. I think this is three years, and silicon, 14
3 percent, and PMMA, 26 percent. Was that a randomized
4 clinical trial?

5 MS. LOCHNER: Yes, first sentence.

6 DR. STARK: It was?

7 MS. LOCHNER: Yes, the first sentence states that
8 it was a prospective randomized study.

9 DR. STARK: I need to strengthen my bifocals.

10 DR. McCULLEY: But maybe not internally
11 controlled.

12 MS. LOCHNER: By "internally controlled," are you
13 saying one eye--

14 DR. McCULLEY: I mean one eye, one lens.

15 MS. LOCHNER: No, I don't believe it was that.

16 DR. McCULLEY: So, that gets rid of multiple
17 potential confounding factors, and masked?

18 DR. BULLIMORE: That is one approach, I mean
19 whether you do one eye, one lens, the other eye, another
20 lens is one issue, or whether you randomize by patients.
21 That is another design issue.

22 DR. McCULLEY: Would any of us disagree that Dr.
23 Bullimore's statement would be the ideal of what we would
24 like to see? Dr. Grimmett.

25 DR. GRIMMETT: I don't disagree that it would be

1 ideal, but in all fairness to sponsors, I do think that, of
2 course, I think we all would agree there are other methods
3 of obtaining valid scientific evidence, and a well-designed
4 observational study that overcomes confounding factors could
5 certainly be helpful.

6 We, here at the panel, have considered valid
7 scientific evidence from other arenas, of course, but, of
8 course, the gold standard would be considered the randomized
9 controlled trial.

10 DR. McCULLEY: Let's leave that at those
11 statements for now. I think they are clear, and we could
12 argue forever about fine-tuning them. You get the gist of
13 it, and I don't know that we need to go any further with
14 that.

15 Joel, would you like to then--

16 DR. SUGAR: Question 2?

17 DR. McCULLEY: Do you need a restatement of the
18 answer to Question 1?

19 MS. LOCHNER: No.

20 DR. McCULLEY: Question 2.

21 DR. SUGAR: Question 2. Is a claim of delay in
22 onset of visually significant PCO within the study
23 clinically relevant? If so, what period of time do you
24 consider a clinically significant delay?

25 If posterior capsular opacification is to occur

ajh

1 and be clinically significant, it probably doesn't matter
2 whether it occurs in the first few months or the first
3 couple of years after surgery, since in either case it would
4 need to be treated. Probably the only clinically
5 significant delay would be beyond the life of the patient.

6 Dr. Spalton makes the point that six months'
7 results predict three-year results, but that is not
8 functional, that is in terms of area of opacification. So,
9 a claim of delay in onset of anatomic findings may be
10 different from a claim of delay in onset of visual findings,
11 but I think that that information is useful, but certainly
12 should never be a single measure.

13 Was that nebulous enough? I am trying to be.

14 DR. McCULLEY: Can you get more specific?

15 DR. SUGAR: No. The point is that a delay in
16 function is meaningful, but if in the life of the patient,
17 they are going to need a capsulotomy anyway or they are
18 going to have decreased function anyway, what counts is
19 whether they have a decrease in function related to capsular
20 opacification.

21 Dr. Spalton suggests that the anatomical findings
22 early predict what the anatomical findings are going to be
23 later, so that early findings are probably the most
24 meaningful, and six months is I think a reasonable time
25 because there are certainly people who don't opacify early,

1 but do within six months, and there are people that you do a
2 YAG on five years later.

3 So, the information should be taken as not primary
4 decisionmaking information, but useful and worthwhile
5 information.

6 DR. McCULLEY: Are there other questions or
7 comments? Rick.

8 DR. FERRIS: I agree with what Joel said. On the
9 other hand, if you do have an outcome variable, I think
10 analyses that look at time to event, like table type
11 analyses, are important analyses and would be useful in
12 interpreting whether lens A versus lens B was slowing the
13 event rate, and slowing the event rate in this population
14 inevitably means reduced YAG capsulotomies, I think.

15 For example, if we slowed the development of
16 cataract by five years, we would reduce the amount of
17 cataract surgery by half.

18 DR. McCULLEY: Dr. Yaross.

19 DR. YAROSS: When I have spoken with some of our
20 customers regarding this issue, they have felt that for a
21 difference to be clinically meaningful to them, a delay of
22 PCO would need to be in the range of two to three years.

23 DR. McCULLEY: Joel, how would you respond to
24 that?

25 DR. SUGAR: I think that that is reasonable,

1 because for cataract patients, Rick probably knows the
2 numbers better, but within two to three years, a substantial
3 portion of the patients will have died.

4 DR. BULLIMORE: I am surprised to hear the company
5 saying we want to show a three-year delay, because a three-
6 year delay then, in my mind, means at least a five-year
7 study, whereas, if you use time to event, which is
8 predicting, it is a surrogate for that, and you could
9 predict from that, then, you would have a shorter study with
10 an implication.

11 I would worry about having anything in the
12 guidance that said you need to show a three-year delay
13 because that means a very long study and a very expensive,
14 probably a more expensive study than would be necessary if
15 you were looking at time to event.

16 DR. McCULLEY: Sally needs to make an
17 announcement.

18 MS. THORNTON: I just want to remind the panel,
19 please, speak into the microphone. The transcriber and the
20 summary writer are having difficulty hearing you, and the
21 sound man can't turn it up any higher because it will start
22 to squeal, so if you could please speak into the microphone
23 and try to speak a little louder than you have been doing, I
24 think that would be helpful. Thank you.

25 DR. McCULLEY: Dr. Matoba, you were about to say

1 something?

2 DR. MATOBA: Just a clarification. I just wanted
3 to clarify that Dr. Spalton had said that the area of
4 opacification early on, he said predicted visual acuity at
5 three years.

6 DR. McCULLEY: No.

7 DR. MATOBA: He said it correlated with YAG
8 capsulotomy. Did you not?

9 DR. McCULLEY: He said no.

10 Other questions, comments? Do you need anything
11 more on that, FDA?

12 MS. LOCHNER: No, I think we heard you.

13 DR. McCULLEY: Next question.

14 DR. SUGAR: What minimal difference in PCO rate
15 between two IOLs do you consider clinically significant, for
16 which a claim of superiority should be considered? Do you
17 suggest a minimal number of subjects allowable for such a
18 study?

19 This gets down to a statistical analysis, and we
20 were given a table. Sherrie has got a table up there now.
21 I think it is difficult to answer the question. Any
22 significant reduction in posterior capsular opacification
23 has both clinical and economic relevance. A claim of
24 superiority based on a 10 percent difference, assuming
25 accurate and reproducible measurements, should be

1 considered. Given that difference, the sample size would be
2 300 or 150 in each group, but it really depends on what
3 reality actually shows the difference to be.

4 The Acrysoft data showed an 11 percent difference
5 between two groups that had a p-value of 0.24 or somewhere
6 in that range, which was not statistically significant, but
7 I am sure is meaningful.

8 DR. McCULLEY: Dr. Bullimore.

9 DR. BULLIMORE: This really once again should be
10 placed, refer to the sponsor. If they really want to make a
11 claim that 5 percent is clinically meaningful, and for a
12 large portion of the population or the large number of
13 people undergoing cataract extraction, that is certainly
14 economically meaningful.

15 They just need to be aware that they are going to
16 need a lot more patients to show a statistically significant
17 difference of 5 percent, and whatever the claim they want to
18 make, they just need to ensure that they have adequate
19 sample size at the outset to demonstrate that claim.

20 DR. McCULLEY: Rick.

21 DR. FERRIS: From the other end of the spectrum,
22 perhaps someone can enlighten me, does the grid currently
23 have some minimum number of patients that need to be
24 submitted?

25 MS. LOCHNER: The grid data are based on studies,

1 some of which had 500, but nowadays, currently, are based
2 upon 300 completely followed subjects. However, I want to
3 remind you that there is no PCO rate in the grid.

4 DR. FERRIS: I understand that. As a benchmark,
5 the grid has worked fairly well in the IOL world, hasn't it?
6 Not being in the world, I don't know, but--

7 MS. LOCHNER: Based upon the complications it is
8 detecting, and the rate of those complications, most of
9 which I would suspect the rates are going to be much smaller
10 than what would be--what I am trying to say is the PCO
11 difference you would accept would probably be much greater
12 than the rates we are detecting in the grid, however, it is
13 a different control, and those issues come up, and that is
14 why we provided this statistical table.

15 DR. FERRIS: Are we talking about new lenses here?
16 Does a new lens sort of have to submit itself to the grid in
17 any event?

18 MS. LOCHNER: For basic safety and effectiveness,
19 most companies use the grid for their control. They use the
20 grid as a historical control and enroll 300 subjects to show
21 their basic safety and effectiveness.

22 DR. FERRIS: That is where I am leading to. So,
23 in essence, there is a floor of 300 total that has been
24 historically used. I guess this is a guideline, and you
25 could use fewer, but maybe you need to justify why you were

1 using fewer patients.

2 MS. LOCHNER: I think we are talking about--

3 DR. McCULLEY: Two different things.

4 MS. LOCHNER: Yes.

5 DR. McCULLEY: We are talking about PCO claim
6 here, which isn't part of the grid. So, it would be
7 existing or new lenses. If new lenses wanted to make a
8 claim, our recommendation for demonstration of what is
9 required for a PCO claim might go beyond in time what would
10 be required to meet grid requirements.

11 DR. ROSENTHAL: I think Dr. Ferris' point is if a
12 company is coming in with a new lens, and they are using the
13 grid, they have got to use 300 eyes. To do 300 eyes, it
14 looks like you can get a 10 percent difference. Isn't that
15 your point?

16 DR. FERRIS: Exactly.

17 DR. SUGAR: Actually, 150 eyes in each group would
18 exceed the statistics. That is what I am saying, 150 per
19 group. The 300 eyes is all in the treated group, the IOL
20 group, so you are talking about 300 plus a control group.

21 DR. STARK: I think that just shows again the
22 complexity of making this claim is going to be 300 in one
23 group in a prospective randomized trial, 300 in another
24 group, and you are talking about a low complication rate of
25 capsular opacification at one year, and maybe having to go

1 to three to five years, so I think Mark's comment, if we are
2 going to require a randomized clinical trial, and we have
3 got a low, let's say with current day technology, you know,
4 what you are going to compare it to, maybe a 10 percent
5 capsular opacification rate, maybe 15 percent. It is not
6 the 50 percent that it used to be with more inflammatory
7 reaction after extracapsular cataract extraction.

8 If we are going to require that, we are talking
9 about a minimum of 300 in each group, three to five years
10 follow-up, and if the people can't get new technology
11 reimbursement, and all they are going to do is make a little
12 claim here, I am just wondering, you know, are they going to
13 want to invest \$5 million in that kind of a study.

14 MS. LOCHNER: May I offer a point of clarification
15 about the numbers here?

16 DR. McCULLEY: Yes.

17 MS. LOCHNER: If you think most lenses have, for
18 example, the lowest rate we have there is 15 percent, so if
19 you think most lenses out there have 15 percent, but this
20 new lens with superior PCO rate has 5 percent, you actually
21 only need 138 per arm.

22 I just wanted to make that clarification, because
23 the 300 really comes, per arm, comes from if you think the
24 rate out there for most lenses is 30 percent, and you think
25 your new lens has an improved rate of 20 percent, then, you

1 need to go up to 300.

2 So, before we get too far down the track of, you
3 know, the 300 number, I want you to keep it in the context
4 of what we are really saying.

5 DR. McCULLEY: Rick.

6 DR. FERRIS: There is another context that is
7 important, and notice that that 10 percent difference
8 between 5 and 15 percent is a 3-fold reduction, and that
9 clinically is a very unusual event. I mean a 50 percent
10 reduction is a superb new treatment in most people's minds.

11 So, if you redid those numbers for a 50 percent
12 reduction, I think you will quickly see you will pop right
13 back up to 300. Walter's point is well taken, and one of
14 the issues that I think we should be addressing is whether
15 some of these other surrogates could be used, which wouldn't
16 necessarily require a five-year clinical trial.

17 Dr. Spalton showed us this morning something at
18 six months, which was predictive of a three-year outcome.
19 That kind of information might be very helpful.

20 DR. McCULLEY: Have we given you adequate input on
21 that question?

22 MS. LOCHNER: Yes.

23 DR. McCULLEY: I guess we go on to Dr. Weiss now,
24 who will answer her questions. Joel's answers were very
25 good on all of them.

1 example, their new material was superior, it would be ideal
2 to control all the other variables except the variable to be
3 studied. So, for example, as in the studies that they had
4 with the Acrysoft lens, they had control lenses, which had
5 approximately the same capsular angulation and sharp edges,
6 and the same optic size, so that the variable that was
7 really being looked at was the IOL material.

8 On the other hand, that is not 100 percent
9 necessary if you just want to say IOL X, for whatever
10 reason, shows statistically significant decrease rate.
11 Let's say it had a half percent capsular opacification rate
12 by comparison to anything else that has been looked at.

13 But I think ideally, it would be nice to have the
14 variables that we know impact on PCO incidence being similar
15 in the control lens except for the variable that is going to
16 be changed in the lens to be studied.

17 Would you like me to go on to the other ones?

18 DR. McCULLEY: No, we will discuss this one now.

19 What factors should be considered in choosing an
20 appropriate control IOL? If we put it in the context that
21 there is this hope to make a claim that would have other
22 implications, what would the gold standard, what would that
23 control lens have to be? It depends on claims.

24 I mean if a person wants to make a claim of
25 superiority to PMMA, then, so what? If they want to make a

1 claim of superiority to what is typically being used--and
2 Marcia just shared with us that 85 percent of the lenses are
3 foldable, so either silicone or acrylic--then, what lens
4 should be used?

5 If one wants to consider making a claim that it is
6 better than all, what would it be compared to?

7 DR. WEISS: Well, before, when I reviewed this,
8 that was before the status had been conferred on the two
9 lenses and the Acrysoft had been rejected. So, at that
10 point, I was using the Acrysoft as the better lens to be
11 compared to the PMMA lenses, but if, indeed, now that it has
12 been rejected and the horse is out of the barn, and most
13 lenses being implanted or foldable lenses, I would probably
14 say out there what we have in terms of the lowest PCO rate
15 would be the Acrysoft lens, a foldable IOL with sharp edge
16 and biconvex design, and that is going to set a very
17 difficult standard for anyone to try to show that they are
18 getting a lower PCO rate, because that has a 10 percent PCO
19 rate.

20 DR. McCULLEY: But if the Acrysoft wanted to make
21 a claim--

22 DR. WEISS: Well, it sounds like they made it.
23 They made their claim, and it was rejected.

24 DR. McCULLEY: Because they apparently did not
25 show statistically significant superiority to silicone.

1 Dr. Stark.

2 DR. STARK: Just to add again to the complexity of
3 the issue, now that the lights are turned on, I can read
4 this, and this Acrysoft data, this is an FDA claim or an FDA
5 permitted claim, a prospective, well-controlled, randomized
6 study, and it gives a reference, and the Acrysoft lens
7 utilizing a uniquely developed method of novel computerized
8 digital imaging system. This is what their claim is based
9 on. It must be based on then Dr. Spalton's or somebody
10 else. Then, they go on to say they did 30 Acrysoft, 30
11 PMMA, and 30 silicone lenses. All were implanted in an
12 unfolded state, so they are all done extracapsular, older
13 technology.

14 The important thing at the end of this first
15 sentence is, "There was no statistically significant
16 difference in best corrected visual acuity and contrast
17 sensitivity established between Acrysoft and PMMA and
18 silicone lenses." So, it was all based on the digital
19 imaging, which didn't correlate with visual acuity, and that
20 is the way they made their claim.

21 DR. McCULLEY: They have gone down in flames.

22 DR. STARK: But the other important issue is there
23 are three different Acrysofts now - a 5.5 millimeter, a 6.0,
24 and a 6.5 millimeter. All have a little difference in
25 glare, you know, from the edge, and they are making the

1 change now to a rounded Acrysoft lens.

2 So, it just goes to the complexity of this issue
3 with all the different lenses and the different techniques
4 is going to make the study much more difficult.

5 DR. McCULLEY: So, it sounds like for existing
6 lenses, they would have to show superiority over the other.
7 They have shown superiority over PMMA. They would have to
8 conduct an appropriate study for either Acrysoft or silicone
9 or some variant thereof to show superiority of the others or
10 over the others.

11 A new lens coming along would have to show
12 superiority to an acrylic lens or a silicone lens, and since
13 those two have not been clearly differentiated, superiority
14 to each of those lenses would have to be shown. If those
15 two lens types want to get into a contest, they have got to
16 show superiority one over the other.

17 So, we don't have an established gold standard
18 until somebody comes out of the gate and wins the race, and
19 no one has won it yet, so you have to take at least the two
20 lead horse types of lenses, which would be acrylic and
21 silicone. Sorry, the Kentucky Derby is affecting me.

22 DR. ROSENTHAL: May I pose a question?

23 DR. McCULLEY: Yes, Dr. Rosenthal.

24 DR. ROSENTHAL: What if a company took a lens made
25 out of a superior material with all the negative things Dr.

1 Weiss mentioned, and compared it to another lens from
2 another material that may not be as good, but have all the
3 other configurations--if you know what I am trying to say--

4 DR. STARK: Do you mean the bad ones and the good
5 ones?

6 DR. McCULLEY: You are making an assumption that
7 all of those bad things are bad, and the test conditions--
8 and I think Dr. Ferris hit it in his--we have got to look at
9 complications, so the lens can't be good for PCO and then
10 otherwise trash the eye.

11 DR. WEISS: I understand what Dr. Rosenthal is
12 saying.

13 DR. ROSENTHAL: You do? Thank you.

14 DR. WEISS: Yes, I do, and I think his point is
15 well--

16 DR. ROSENTHAL: It's a setup. You can set up a
17 study to get one better than the other. Yes, she knows what
18 I am saying.

19 DR. WEISS: And your point is well taken, and I
20 agree with you, and that is why I--and maybe I will share
21 with you what I agree with, we seem to be the only ones
22 sharing this conversation--is there are five variables.

23 I wrote down that there are five or four main
24 variables, and I think most people agree that in each
25 variable there is a better way to go. But let's say you

1 have three of the variables which are the worst way to go,
2 and you change one variable which is so much better, it
3 compensates for all the others.

4 I think that is still a valid study, because the
5 bottom line is this is not meant to be just an academic
6 scientific exercise, but the bottom line is if you can show
7 with whatever manipulations you make it is markedly better
8 for PCO, then, you would get the status.

9 So, the bottom line is the difference in the PCO
10 rate.

11 DR. PULIDO: I disagree all that you are doing is
12 showing that for that specific variable. Let's say what you
13 have changed is PMMA in one and Acrysoft with another or
14 acrylic with another. All you have shown is that acrylic is
15 better than PMMA, but you haven't shown superiority over
16 every other lens.

17 DR. WEISS: But it depends on the PCO rate. If at
18 the end, that new lens where you changed the material has a
19 PCO rate of 0.1 percent, then, you have. If it has a PCO
20 rate of 9 percent, then, you haven't. So, it really depends
21 on the bottom line number.

22 DR. McCULLEY: But we have already said you are
23 going to have to show it over. If one of the existing
24 lenses wants to claim, they have to show superiority over
25 existing lenses. A new lens comes in, they are going to

1 have to show superiority over prior existing lenses, and
2 right now it would appear they would have to show
3 superiority over acrylic and silicone.

4 DR. WEISS: I agree.

5 DR. McCULLEY: Rick said in his review that if one
6 creates a lens that has zero PCO, but has significant other
7 complications associated with it, that would have to be
8 taken into account, as well, so that one couldn't just come
9 in with an awful or semi-awful lens that decreases PCO, that
10 has other things that would then qualify it for a better
11 lens, I mean that would be silly, and presumably, our
12 government, in its wisdom, would not allow that kind of
13 silliness to occur, I hope.

14 Rick.

15 DR. FERRIS: I had one other question, and since I
16 am not in this field, it may be a dumb question, but the
17 idea that you would have to show that your new lens is
18 better than all other lenses is an impossible clinical
19 trial.

20 Now, the question is could clinicians say one or
21 two lenses are about as good as we have right now, that this
22 lens of people we are talking about seems to have a
23 comparably, in a clinical assessment, quite a low PCO rate,
24 and if you could show that it was better than that lens,
25 that that would be roughly equivalent to showing that it is

1 better than all lenses since that other trial is virtually
2 impossible to do?

3 I take Walter's point that if you tell a company
4 that the only way you are going to be able to do this is to
5 show it is better than 10 different lenses, and you do the
6 sample size calculation for that, that is a trial that is
7 never going to get done, and if we set that hurdle up, then,
8 what we are doing is saying forget about it, you are never
9 going to do one of these.

10 So, the question is, is it possible to say that
11 one or two, maybe two--I think two might be within what you
12 could do--I think if you get beyond two different lenses,
13 you know, one silicone, one acrylic, compared against those
14 two, and you could show that it was better than either of
15 those two, would that be good enough?

16 DR. McCULLEY: Probably not. I don't know that it
17 would do it either of the two, because those two classes
18 have not yet been differentiated to satisfaction.

19 DR. PULIDO: And the problem is it is a moving
20 target, as well. Like Walter Stark was saying, there is
21 constant changes. Yes, you could have an acrylic lens that
22 is now 5 millimeters, and next year it will be 6.5, and will
23 that be the new target that you are going to use? So, maybe
24 it would have to be whatever is most commonly used in the
25 market.

1 So, for us to come out and say right now this is
2 going to be the standard for which to compare, would not be
3 worthwhile five years from now.

4 DR. FERRIS: My point is once you create the
5 standard, and then once somebody passes that hurdle, then,
6 they become the next control group. So, once you do it,
7 then, the next trial--at least you would know what the next
8 trial is going to require, and what I am suggesting now is
9 if we could at least say here is something that a group of
10 clinicians would accept, if you could show it is better than
11 this lens, we would accept that now as the first one in.

12 DR. STARK: We are not even to that point yet,
13 Rick, and there again, the complexity of this issue, we are
14 not at that point to say that the silicone is better or
15 worse than the Acrysoft, what, 6 millimeters, 6.5, and so
16 what would be nice is to the two main companies, maybe
17 Alcon, and I don't know who the major producer of the
18 silicone is, to have them duke it out with a good clinical
19 trial, and then we know what the opacification rate is at
20 three years, and let that be the standard.

21 The problem is, as I have seen over the years, by
22 then a company comes in and asks for approval, and we are
23 sitting at this table and say, well, gosh, you guys didn't
24 do wave-front analysis, and that is now the gold standard,
25 and that is what we want.

1 It is too bad that your camera or your pictures
2 don't correlate that with the visual acuity, because that
3 would make it simple, at six months you have your answer,
4 but I will get back to if Mark Bullimore, you know, he was
5 saying are we going to require a randomized clinical trial,
6 then, it is going to be impossible to do.

7 DR. McCULLEY: Dr. Yaross.

8 DR. YAROSS: We keep coming back to this issue of
9 what is existing technology, and we have this dilemma about
10 whether or not an existing product can ever be better than,
11 quote, "existing technology."

12 Clearly, we are talking about something that is a
13 tough issue. There are a couple of things we can look at.
14 The legislation for NT IOL was passed in 1994. The final
15 regulation went into effect in 1999. So, that says
16 basically existing technology is probably the products that
17 were around in the mid-nineties, and, you know, exactly
18 where you draw that line, HCFA hasn't done so, so whether or
19 not we are going to do that, probably not.

20 I think I mentioned to you, Dr. McCulley,
21 yesterday that I may surprise you in the discussion today,
22 but I think the issue is that we are talking about a very
23 high standard because the NT IOL regulation is intended to
24 incentivize breakthrough technology, and it is not intended
25 to be a way to necessarily just provide additional rewards

1 to existing technology.

2 Dr. Ferris talked about how a 50 percent reduction
3 in something is an unusual medical event and a very
4 significant event, and would probably be constituting a
5 breakthrough, and so when we are talking about a high
6 standard, this is where we have to differentiate it from the
7 least burdensome aspect of demonstrating safety and
8 effectiveness, and certainly none of these issues should
9 impact on what is the FDA and panel standards for approving
10 a product as safe and effective, but this NT IOL regulation
11 is a very different animal and a very different standard,
12 and it is intended to be for significant breakthrough
13 products.

14 DR. McCULLEY: Thank you.

15 Dr. Sugar.

16 DR. SUGAR: I think my point is related, that we
17 are confusing FDA requirements and NT IOL issues, and the
18 sponsor can choose to compare their lens to whatever lens
19 their study compares to, and their claim would be that this
20 is better than, or worse than, or whatever the lens that
21 they have compared it to, and the global issue is more
22 HCFA's than ours.

23 DR. McCULLEY: As I understand this, HCFA has
24 indicated that they will use FDA data in assessing NT IOL
25 status. If that is correct, then, that puts something back

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1 on us. If they are going to use the data coming here, we
2 need to give some idea of what kind of data we would like to
3 see.

4 MS. LOCHNER: Yes, it is a bit of a circular
5 argument, but, first of all, if a company wants to make
6 claims of superiority, they have to get those claims
7 approved by FDA.

8 Second of all, if they want to claim they are
9 superior to all IOLs, so that they can get HCFA NT IOL
10 designation, they have to bring that both to FDA, because we
11 have to review claims, and to HCFA.

12 So, I think you have to keep them separate in the
13 sense of they don't have to show they are better than all
14 IOLs to get an FDA claim, but they do to get a HCFA claim.

15 DR. McCULLEY: To get a HCFA NT IOL designation.

16 MS. LOCHNER: And they do have to get the claim by
17 FDA, because we have authority over claims. So, we ask you
18 these questions about how would they show superiority to all
19 IOLs because that is something we may have to review at FDA,
20 and then, of course, the extra bonus is the company would
21 probably get their HCFA NT IOL designation.

22 DR. McCULLEY: Your question was is there a gold
23 standard, and then you are telling us there does not appear
24 to be a single gold standard.

25 MS. LOCHNER: Right. We obviously asked that

1 question because it would make the whole NT IOL process a
2 lot simpler. It doesn't mean that we have to get an answer
3 from you that says yes, there is, and here it is, but it is
4 a question we asked because it would be one approach that
5 would make the whole NT IOL process a lot simpler.

6 I think the other thing to bear in mind is we
7 recognize this is a very complex discussion. I gave a few
8 examples in my introductory comments where it was a little
9 bit more clear-cut, and this issue of superiority to all
10 existing IOLs is a lot simpler question, just to point out
11 that it isn't always this complex, and we bring the
12 difficult things to you.

13 DR. McCULLEY: If it were simple, right, you
14 wouldn't be bringing it to us.

15 Dr. Pulido.

16 DR. PULIDO: Just a suggestion. We know what is
17 being used out in the marketplace, and could we then say
18 that if, for instance, there was two that are most commonly
19 used in the marketplace, if you show superiority over those
20 two types of lenses, you have shown superiority over all
21 lenses?

22 DR. McCULLEY: Do you want to respond to that? I
23 don't know the answer to that.

24 MS. LOCHNER: I think that is potentially a
25 possible approach. I think there is a lot of probably ifs,

1 ands, or buts that need to be factored into that, but I
2 potentially showing that this is the realm of what is out
3 there in, you know, X percentage, and I am better than the
4 realm of what is out there, I think that is certainly an
5 approach that HCFA would consider.

6 You know, it is just important to note that HCFA's
7 regulation doesn't say you have to show you are better than
8 every IOL that has been approved. They are really asking
9 that you show what is being used today.

10 So, I think you have raised an approach that is
11 possible, Dr. Pulido, but obviously, there is a lot of ifs,
12 ands, or buts in that.

13 DR. McCULLEY: So, it is what we were saying
14 before, you would have to show it to an acrylic, to a
15 silicone, but then they not all are the same, as Dr. Stark
16 and others have pointed out, so it would be tough to pick
17 which exact one.

18 MS. LOCHNER: Right, you would have to show,
19 right, exactly, and scientifically justify your choices.

20 DR. McCULLEY: Dr. Weiss.

21 DR. WEISS: Just in terms of the studies that have
22 gone on so far with the silicone lenses and the acrylic
23 lenses to try to prove their superiority, most of these
24 studies compared it to an Alcon 6 millimeter PMMA lens.
25 They used that as one of the controls. They used the

1 Acrysoft lens in two of these studies as another comparison,
2 and then they used a silicone lens.

3 One of these studies was using an AMO silicone
4 lens, another one was using an IOLAB silicone lens, so
5 somewhat similar to what you are saying. I don't know how
6 you would decide what company is going to be made the gold
7 standard, and I think that obviously would be very
8 controversial.

9 DR. McCULLEY: I don't think you thought we were
10 going to have a quick, easy answer to this.

11 Dr. Stark.

12 DR. STARK: The National Eye Institute is
13 interested in funding well-designed clinical trials to
14 answer questions like this and to get support from industry,
15 and there are some examples. I think Rick can tell us--I
16 can't remember what the example is--where industry helped
17 support a well-designed trial run by the National Eye
18 Institute, but it seems to me that if somebody is going to
19 want to make this claim for a new technology, not just to
20 FDA, but new technology, what you would have to do is get
21 two or three companies, and we have talked about the
22 companies that maybe have the largest market share, and let
23 them go to the NEI or another group, and have a well-
24 designed clinical trial done that shows, that can look at
25 one-, two-, and three-year posterior capsular opacification,

1 both digital analyzed, maybe wave-front or aberrometer, but
2 also tying that together with clinical function, both visual
3 acuity and subjective reports, and then come out and we will
4 have an answer. We will have an answer as to what the
5 capsular opacification rate is at that time and what it is
6 with the different lenses that are currently being used.

7 That would set the standard, and it may be that
8 one of those companies would come out and show it was much
9 superior to the other. They would pick their best lens.
10 Then, they would come out and show that. They may then be
11 able to apply, not only they would apply to the FDA for that
12 designation, but they would be apply to HCFA for this extra
13 \$50.

14 Then, as they begin to think about that extra \$50,
15 they may decide, if they don't think they can show the
16 difference, that it is going to cost too much, but, Rick,
17 there is an example of where the NIH has used industry
18 support to run the clinical trial, isn't it?

19 DR. McCULLEY: You are talking about methodology
20 where one might approach this issue.

21 Have we answered your question, Dr. Weiss's first
22 question adequately?

23 DR. WEISS: Not totally. There is a third part,
24 is there a gold standard PCO rate that could be designated
25 by the FDA. The rate from--and I summarized the rate in my

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1 report from various studies--but if we go sort of midline,
2 there is Schaumberg and they looked at 22 published studies
3 and put together a PCO rate at one year of 11.8 percent,
4 three years of 20.7 percent, and five years at 28.4 percent,
5 but if you look at the individual studies, the rate varies
6 greatly.

7 I think I would suggest the use of arbitrarily a
8 number of approximately 20 percent at three years, but, of
9 course, it is open to discussion. The one rate that I was
10 most impressed with was the fact that in 1895, there was a
11 rate given of 30 percent PCO rate, and now the five-year
12 rate is reported at 28 percent PCO rate, so nothing has
13 changed in the last hundred years.

14 DR. McCULLEY: I would almost say from what you
15 have said that the answer to that portion of the question is
16 no.

17 DR. WEISS: It would have to be arbitrarily
18 defined, but right, right now there is no gold standard.

19 DR. McCULLEY: Is that okay?

20 MS. LOCHNER: Yes.

21 DR. McCULLEY: I saw Rick's hand first, and then
22 Dr. Pulido.

23 DR. FERRIS: Just one comment on this, and that
24 is, this PCO outcome, as I understand it, depends greatly on
25 what technique you use to measure it. So, setting an

1 arbitrary standard would seem to be very difficult unless
2 you also define how you measured that.

3 That, I think has to be taken into account, that
4 it is 10 percent rate or 20 percent rate measured this way,
5 using this technique, and so on. I am not sure that the
6 methodology is there, maybe some of it is there now, but
7 that would have to be incorporated because differences
8 between techniques probably yield greatly different event
9 rates.

10 DR. McCULLEY: The answer to the question remains
11 no.

12 Let's take about a 10-minute break and then we
13 will reconvene.

14 [Recess.]

15 DR. McCULLEY: We are going to begin with Dr.
16 Weiss's second question. Your second question was: What
17 factors are important to be matched in the trial and control
18 populations (e.g., age)?

19 DR. WEISS: I would say age, the type of cataract.
20 Most studies have excluded traumatic and uveitic cataracts.
21 The exclusion criteria, which I have listed on my form, and
22 also the surgical technique. I am not going to elucidate
23 the exclusion criteria because I think someone else is doing
24 that in their review.

25 DR. McCULLEY: We were provided a nice, long list.

1 I guess that is more the exclusion criteria. Okay.

2 Are there any other comments about variables to be
3 matched? Dr. Bullimore.

4 DR. BULLIMORE: I just want to caution the agency
5 about matching subjects. I think there are confounding
6 variables that any analyses and sample size calculation
7 should control for, but trying to match up patients in a
8 randomized, controlled, clinical trial is perhaps not always
9 the optimal approach, and letting the randomization take
10 control or take account of those variables is maybe another
11 approach.

12 DR. McCULLEY: Other comments? Dr. Yaross.

13 DR. YAROSS: Certainly, as was mentioned before,
14 contralateralized studies are one way of addressing that and
15 should be considered.

16 DR. BULLIMORE: But then, of course, there is the
17 assumption that the cataract is the same in the two eyes,
18 well, that doesn't happen very often, so what do you do
19 then, but contralateral-designed studies should be offered
20 as one alternative.

21 DR. McCULLEY: Other comments?

22 Dr. Weiss, your third question was with regards to
23 HCFA NT IOL designation. What additional considerations
24 must be factored into the choice of a control IOL for the
25 sponsor to demonstrate superiority over all IOLs or over a

1 class of IOLs? Do you believe it is feasible to allow
2 claims of superiority over all IOLs with respect to PCO
3 rate?

4 We have been hitting on that a lot. Do you have
5 any additional comments?

6 DR. WEISS: I think just as regards to this, most
7 of the comments have been stated at different points in
8 time. The discussion about the format of the study, if it
9 could be performed in a blinded fashion as to PCO
10 assessment, that would be helpful. Other study criteria
11 have been already discussed.

12 There must be a significant time period after
13 follow-up surgery, and in terms of superiority over all
14 IOLs, in my opinion, if the PCO rate at a particular time
15 and with a particular way of assessing it, let's say YAK
16 capsulotomy rate for every single IOL on the market was
17 known, and was significantly high, then, if the PCO rate,
18 let's say via YAG capsulotomy, for example, assessing it the
19 same sort of way, which has been assessed with all the
20 existent lenses, you might be able to compare it, but that
21 claim is full of "ifs."

22 At the present time, I don't think it is feasible
23 to allow claims of superiority over all the IOLs, because we
24 are not going to have the same criteria to judge all IOLs.
25 So, most likely you are going to have to have the controls

1 built into the study.

2 DR. McCULLEY: Does that give you what you need?

3 MS. LOCHNER: Yes.

4 DR. McCULLEY: I think as we go through more of
5 these, we can come more to the point, because we will have
6 discussed a lot of the surrounding issues. If, in our
7 enthusiasm for efficiency we start not giving you all you
8 want, then, I am going to rely on you to let me know.

9 **Methodology**

10 We go to Dr. Bullimore. Your first question is:
11 Regarding current methods of PCO analysis, do you consider
12 particular methods acceptable for PCO IOL studies? Are
13 there particular criteria that you consider critical, e.g.,
14 region of posterior capsule evaluated, level of
15 reproducibility, et cetera? Do you consider any of the
16 current methods not valid? Do you think that subjective
17 clinical grading systems should be permitted, e.g.,
18 comparison to standard reference photos?

19 These can be answered individually, I think.

20 DR. BULLIMORE: I am going to take them as a
21 gestalt. I am not going to anoint any particular techniques
22 given the wrist slapping I experienced yesterday with
23 respect to Quality of Life instruments. I am not bitter.

24 As I have said earlier, there is a range of
25 candidate outcome measures that could be considered, and

1 really it is up to the sponsor which they want to consider
2 and which they want to base their claims on.

3 I lump them into four categories: visual
4 measures, clinician grading or subjective grading, if you
5 like, image analysis, and surgical outcomes. I will take
6 each of these in turn.

7 With visual measures, obviously, one of our
8 primary considerations is what the patient actually sees,
9 and if we are going to measure visual acuity, obviously, we
10 should use good methods like LogMAR charts, and if we use
11 well-designed charts, then, we can score by letter and treat
12 visual acuity as a continuous variable and get oodles more
13 statistical power than we would by treating as a categorical
14 variable.

15 I was interested to look at St. Thomas's study
16 that Dr. Spalton mentioned earlier, and we have a number of
17 papers on this. They treated visual acuity as a categorical
18 variable, but looking at their numbers, I suspect had they
19 treated it as a continuous variable and measured it slightly
20 differently, they might have found significant benefit for
21 the Acrysoft lens, or they might not have.

22 Some people have mentioned that visual acuity
23 alone is not a sensitive enough measure, and things like
24 contrast sensitivity and glare could be used. One paper
25 found a greater change in contrast sensitivity than visual

1 acuity when taken in log terms, and there may be useful
2 information to be gained by using supplementary techniques.
3 The more you measure, of course, the greater chance you have
4 of finding a significant variable, and, of course, the FDA
5 has to make sure, when you are using multiple outcome
6 measures, that claims of significance are based on a p-value
7 that is adjusted for these multiple comparisons.

8 The primary disadvantage of visual assessment is
9 we are dealing with an aging population, and on top of lost
10 to follow-up we have other things that can affect vision
11 like at the retinal level. Hopefully, within the randomized
12 clinical trial, the randomization will take care of that,
13 but study design and sample size must be adjusted to take
14 these considerations into account.

15 Do you want to stop and discuss visual measures,
16 Mr. Chairman? It seems appropriate.

17 DR. McCULLEY: Dr. Pulido.

18 DR. PULIDO: Just a question for you, Mark
19 Bullimore, and that is, when it came to the refractive
20 surgery submissions, we kind of avoided the contrast
21 sensitivity data because it was difficult for us to make
22 determinations what it meant.

23 Now, you are suggesting that we use contrast
24 sensitivity data. Why, in this situation, can we use
25 contrast sensitivity data when with the excimer laser