

1 with our recommendations what they choose to do, and we can
2 fuss.

3 DR. ROSENTHAL: And you are.

4 DR. McCULLEY: But it doesn't do a hell of a lot
5 of good.

6 Dr. Coleman.

7 DR. COLEMAN: I would like to make a
8 recommendation that at least with these phakic intraocular
9 lens implants, that you also follow angle width, because
10 there have been reports on at least increased pigment
11 deposition and the development of elevated intraocular
12 pressures in patients with these phakic IOLs in France, and
13 so I think that that is at least something that should be
14 followed as an adverse event.

15 In addition to following on intraocular pressure
16 changes, I think it is important, if someone has to go on
17 glaucoma medications for intraocular pressure control, that
18 that is also an adverse event.

19 DR. STARK: Did you say width? That makes me
20 think an additional thing that could be easily done, would
21 be standardized photographs, just a photograph of the angle,
22 because that would pick up whether or not these angles are
23 getting more and more pigment from liberation to pigment.

24 DR. COLEMAN: I would recommend that if there were
25 good photographic documentation of angles, but that is very

1 debatable whether or not you even have the technology now,
2 so I think you would have to rely on clinician grading of
3 the angle.

4 DR. McCULLEY: Dr. Pulido.

5 DR. PULIDO: Would a proxy for that be infrared
6 transillumination of the iris, because whatever is removed
7 from the iris is what is going to be going into the angle,
8 is that a good way of documenting it?

9 DR. COLEMAN: In terms of those are talking about
10 transillumination defects, and those might be able to look
11 at the pigment deposition, but I am also concerned in terms
12 of especially with the hyperopes that you are going to have
13 some narrowing of the angle, and so you actually are going
14 to have to deal with gonioscopic examination, and not just
15 doing it for an exclusion criteria, but also in terms of
16 following patients for an adverse event, of their angles
17 getting more narrow, their developing peripheral anterior
18 synechiae.

19 MS. BOULWARE: Gonioscopy is one of the
20 evaluations to be performed on all the subjects.

21 DR. COLEMAN: Before and after?

22 MS. BOULWARE: Yes.

23 DR. COLEMAN: And reported on?

24 MS. BOULWARE: Yes.

25 DR. FERRIS: Clinical assessment 1, 2, 3-plus?

1 MS. BOULWARE: Yes.

2 DR. McCULLEY: Other comments? Dr. Sugar.

3 DR. SUGAR: If we were just looking at other
4 things in this document, under exclusion criteria, you have
5 subject has an ocular condition, and then you list pre-
6 keratoconus, keratoconus, recurrent erosion syndrome, or
7 corneal dystrophy.

8 I think recurrent erosion syndrome should not be
9 an excluder for--or epithelial-based membrane--should not be
10 an excluder for intraocular implants, but maybe should be
11 intracorneal implants. I don't really know about
12 keratoconus or pre-keratoconus for intraocular implants.

13 MS. BOULWARE: Trying to avoid confounding visual
14 acuity measurements if it is developing keratoconus,
15 difficulty in correcting and getting good VA.

16 DR. McCULLEY: Dr. Pulido.

17 DR. PULIDO: If we are going to get into that, as
18 far as exclusion criteria, again, pigment dispersion, you
19 might not necessarily have glaucoma, but you could be
20 predisposed. There are high myopes, and they can have
21 pigment dispersion way before they have glaucoma. You don't
22 want those patients in there.

23 If we are going to continue to talk about that, on
24 the following page where you talk about what needs to be
25 measured, 7B, you know, we had talked about gonioscopic

1 exam, but we do not talk about--and slit-lamp examination--
2 we do not talk about retroillumination of the iris.

3 Again, I bring up the question do we want infrared
4 transillumination studies, and dilated fundus exam, and I
5 would like Dr. Ferris' opinion about this. "Should include
6 exam for the presence of retinal tears."

7 Well, gosh, there is a lot of other pathology that
8 I think is important to look for, as well, other pathology
9 that predisposes to retinal detachments, including lattice
10 degeneration.

11 So, this document needs to be obviously improved.

12 DR. McCULLEY: Do you have other comments that you
13 would make? It sounds like you have extensively critiqued
14 this. Possibly you could provide directly to Ashley and the
15 FDA your recommendations for some of the fine-tuning.

16 DR. PULIDO: Okay.

17 DR. McCULLEY: And then if you have issues with
18 that, you could send that to some of the rest of us as a
19 homework assignment.

20 MS. BOULWARE: Thank you.

21 DR. McCULLEY: Any other comments on these
22 questions?

23 DR. STARK: In addition to Jose doing that, I
24 would certainly put a detailed examination of the vitreous,
25 because I think as the vitreous detaches in younger people,

1 it may be a problem, but I would like to see Anne work on a
2 detailed description of gonioscopy, because we are going to
3 pick up some changes there with changes in pigment and
4 anterior synechia, so if you would volunteer to do that.

5 DR. McCULLEY: Anne just volunteered to do that.
6 Rick.

7 DR. FERRIS: Well, you can have these clinical
8 assessments for what they are worth, and I will now give you
9 my opinion of what they are worth, and that is, we, for
10 example, in the early treatment diabetic retinopathy study,
11 we have retina people trying to assess vitreous detachments
12 in people with diabetes, where it had clear relevance.

13 "These vitreous detachments came and went with
14 alarming frequency, suggesting to us that the data was close
15 to useless."

16 I don't know about these anterior segment surgeons
17 who are doing this, and whether they can assess the vitreous
18 or not, but I could guess.

19 DR. McCULLEY: We will pay much more attention
20 because we will be much less secure in what we think we are
21 seeing.

22 DR. FERRIS: Okay.

23 DR. STARK: You mean if the retina surgeons cannot
24 do it--

25 DR. McCULLEY: We won't be able to do it.

1 DR. FERRIS: I am suggesting that--it is
2 difficult, and it is astounding to me how poorly the
3 clinical exams match up with the photographic assessments
4 whenever we do them, and whatever we have done, so if it is
5 important, then, maybe an attempt even in a subgroup to look
6 carefully with a standardized approach is worthwhile, and
7 you have to decide what is important and what isn't.

8 DR. McCULLEY: Any other comments about what we
9 have just been talking about in this final question?

10 Ashley, do you need anymore on this?

11 MS. BOULWARE: No, thank you.

12 DR. McCULLEY: Dr. Rosenthal has asked that we go
13 back to the clear lens extraction and implant. What I would
14 suggest is that we can do that, but what we need to do, at
15 the risk of getting nowhere, is if we open-end this, if you
16 guys can come up with specific questions that we can provide
17 a specific answer to, I think we can do this effectively.

18 DR. ROSENTHAL: Can we take a short break and do
19 that?

20 DR. McCULLEY: Yes, we can. But if you can't do
21 that, I don't think we can do our side. So, we need
22 specific questions from you, not what do you think about the
23 world of the retina, we need specific questions, and we can
24 provide specific answers. If you don't do that, then, we
25 start getting open-ended, and it spreads to cover the whole

1 room.

2 MS. BOULWARE: Given a break, we would love to
3 attempt to do that.

4 DR. McCULLEY: And there is a pony in there
5 somewhere. Never mind if you don't know the joke.

6 Let's take a five-minute break.

7 [Recess.]

8 DR. McCULLEY: Ashley, do you have your specific
9 questions ready for us?

10 MS. BOULWARE: Yes.

11 DR. McCULLEY: We are going to now for about the
12 next 30 minutes or so entertain questions from the FDA
13 specifically about clear lens extraction and intraocular
14 lens implantation.

15 MS. BOULWARE: Yes.

16 DR. McCULLEY: Okay. First question.

17 MS. BOULWARE: Keeping in mind now that this is
18 just for IOLs for clear lens exchange.

19 DR. McCULLEY: Can you speak more into the mike,
20 Ashley.

21 MS. BOULWARE: Looking at the safety endpoints
22 that we had previously established--and I will review them
23 very quickly--the maintenance of endothelial cell counts,
24 maintenance of best corrected acuity, induced cylinder and
25 adverse event rates, and then the efficacy endpoints of

1 predictability, uncorrected VA, are there additional or
2 different safety and efficacy endpoints that should be added
3 for this indication?

4 DR. McCULLEY: Go back to your first. Dr. Weiss.

5 DR. WEISS: Dr. Grimmett had mentioned that it is
6 a 2.5 percent cell loss per year after cataract extraction,
7 and although this is a clear lens extraction, it is still a
8 lens extraction, so I think you would have to increase the
9 endothelial cell loss rate to be consistent with that is
10 known to occur after lens extraction.

11 MS. BOULWARE: This is not a target value, this is
12 simply to power the study to be able to detect a rate as low
13 as 1.5 percent, so it would be up to the panel to recommend
14 whether a rate of, say, 2.0 or 2.5 percent would be
15 acceptable at the time the PMA were submitted.

16 DR. McCULLEY: You just indicated to us a minute
17 ago that if it was 2.5 percent, and a person had this done
18 in their 20's, that they would be out of cells by 60.

19 MS. BOULWARE: They would be at 1,000 cells by 60,
20 so you would have to be a very careful cataract surgeon if
21 they had a cataract at age 65, not to have them
22 decompensate. That has been kind of our baseline, and our
23 personal opinion based on our estimations, is that 2.5
24 percent is too high for a patient that is of that age.

25 Now, if you are 45, 2.5 percent might not be a

1 problem.

2 DR. McCULLEY: Well, it is going to be age and
3 that patient's individual cell density.

4 MS. BOULWARE: Correct.

5 DR. McCULLEY: Because they are scattered.

6 Dr. Ferris.

7 DR. FERRIS: That is actually the reason--and I
8 know people thought I was being facetious when I said that I
9 would rather see this done first in older people--I mean
10 there was an issue with intraocular lenses when they first
11 started out, and you were at risk for endothelial loss and
12 eventual epidemic of blindness.

13 So, if you could show that it was stable in older
14 people, then, maybe you can move to younger people, but I am
15 actually very concerned about doing this at the beginning in
16 people who are 20. My daughter is 18. She wouldn't have a
17 clue if you told her that 40 years from now you might have
18 to have a penetrating keratoplasty.

19 DR. McCULLEY: So, the answer to this is there are
20 increased concerns about endothelial cell loss in this
21 patient population.

22 MS. BOULWARE: But the endpoint is still a valid
23 endpoint to look at.

24 DR. ROSENTHAL: But the age inclusion criteria
25 certainly has to be very seriously considered.

1 DR. McCULLEY: Age inclusion criteria and
2 beginning endothelial cell density.

3 DR. ROSENTHAL: Good. Thank you.

4 DR. McCULLEY: Dr. Pulido.

5 DR. PULIDO: And level of myopia. I mean we are
6 now in a different realm, so I don't want that minus 4
7 diopter myope, I would not want to see that 4 diopter myope
8 having a clear lens extraction.

9 DR. McCULLEY: Now that we have another shot at
10 getting our philosophical opinion into this, with setting
11 lower limits, would you like to suggest a lower limit that
12 maybe will be listened to?

13 DR. BULLIMORE: By whom?

14 DR. PULIDO: I would like the panel at this point,
15 where we are allowed to make lower limits, to try to develop
16 a rational lower limit for this kind of study that would be
17 reasonable and allow safety for--what we think is a safe
18 situation for our patients, and I would like to open it up
19 to the rest of the panel.

20 DR. McCULLEY: Who would like to suggest a number?
21 Dr. Stark.

22 DR. STARK: Are we talking about clear lens
23 extraction?

24 DR. McCULLEY: We are talking about clear lens
25 extraction with IOL insertion for optical purposes.

1 DR. STARK: Lower limit would be minus 11.

2 DR. McCULLEY: Minus 11.

3 DR. FERRIS: I will take the opposite concern. I
4 was talking to Leo, and he may have some numbers for us, but
5 I think if you take these high myopes, take their lens out,
6 that their 10- to 20-year incidence of retinal detachment is
7 so high that maybe you ought to buckle them now.

8 DR. McCULLEY: Maybe you ought to do what to them?
9 Oh, buckle them.

10 DR. FERRIS: I would guess that their rate may be
11 as high as 50 percent in 20 years. At least I would be
12 concerned that there would be a very high retinal detachment
13 rate in this group 20 years down the road.

14 DR. McCULLEY: Leo.

15 DR. MAGUIRE: I wouldn't just pick a number out of
16 the air unless I knew for sure. We have some epidemiologic
17 studies based on our work at Mayo, and I am sure Dr. Stark
18 has at their place, too, and I think that is information
19 that can be brought before the group.

20 DR. FERRIS: And it surely should go in the
21 informed consent that there is this serious risk of retinal
22 detachment if you have this procedure.

23 DR. McCULLEY: Dr. Yaross.

24 DR. YAROSS: I think we probably want to see that
25 the data that Ashley has alluded to, that are going to be

1 used shortly to expand the indication for standard posterior
2 chamber IOLs, down to 21 years of age for a very broad power
3 indication.

4 Presumably, there is now data that supports that
5 at least with a cataract, the risk-benefit is considered
6 acceptable in these age groups, and I think it would be very
7 helpful to see that before a firm recommendation is made on
8 what would be appropriate for another indication for the
9 same device.

10 DR. McCULLEY: I may be missing something here,
11 but if you have a patient with a visually significant
12 cataract, the risk-benefit ratio is so different in the
13 situation, so different from what we are talking about, I am
14 just--maybe I have got my head somewhere wrong.

15 DR. YAROSS: But the long-term health of the
16 cornea will be the same in the presence of that IOL for 40,
17 50 years.

18 DR. McCULLEY: And it would be great to have that
19 data. Do you have the data on those lenses if an implant is
20 placed in a 25-year-old, what the endothelial cell loss is
21 from the studies that have been done, that are going to lead
22 you to feeling comfortable dropping the indication to 21?

23 MS. BOULWARE: There is some data. I don't have
24 it here to present to you, but we have a collection of data,
25 not only on cell loss, but on a number of other issues.

1 DR. McCULLEY: Dr. Matoba.

2 DR. MATOBA: I don't think that that is a
3 comparable situation necessarily, because I mean why does a
4 21-year-old have a cataract? Trauma, uveitis, something in
5 previous surgery. So, that cornea might not be really the
6 same as the patient who just is going to have a clear lens
7 extraction.

8 DR. STARK: The other thing, that it may not be
9 comparable for the retina, why do people, after vitrectomy,
10 get a nuclear cataract? In part, it is speculated that
11 there is a big vitreous cavity, the nutrient for the lens
12 now is spread out all over the eye. Maybe people who are 30
13 and get a nuclear cataract have a large vitreous detachment,
14 and all the nutrient goes back. So, they are not comparable
15 eyes, and you can't draw the same conclusion. There is a
16 phakic normal eye versus a phakic eye with a cataract.

17 DR. McCULLEY: So, we have major concerns about
18 the endothelium.

19 DR. GRIMMETT: I think I just heard that the FDA
20 has data, or has reviewed data regarding IOLs in younger
21 patients, allowing them to decrease the range to 21. Do you
22 know, then, what the rate of cell loss is per year for those
23 younger patients that are pseudophakic?

24 MS. BOULWARE: There is unfortunately not great
25 data on younger patients with cataracts with long-term

1 follow-up, who have had cataract extraction under modern
2 techniques, because they haven't been done that long.

3 Most of the data that is out there, the Bourne and
4 Edelhouser articles that you are probably aware of, some of
5 those are in older populations, some in younger, but a lot
6 of those with older techniques, unfortunately, there is just
7 not 20 years of follow-up on younger patients who have had
8 phaco on a PC IOL.

9 DR. McCULLEY: Back to the loss of BSCVA,
10 specifically, what is your question relative to this?

11 MS. BOULWARE: My question is should this endpoint
12 be any different for IOL for clear lens extraction.

13 DR. McCULLEY: No.

14 MS. BOULWARE: Okay.

15 DR. McCULLEY: Next.

16 MS. BOULWARE: Should these be any different? We
17 have not set except for rates on adverse events.

18 DR. McCULLEY: I would like for you not to say
19 "these." I would like for you to ask us a specific
20 question.

21 MS. BOULWARE: Certainly. Is the endpoint for
22 induced manifest refraction cylinder, that is, less than 1
23 percent of eyes, should have an induced manifest refractive
24 stigmatism of greater than 2 diopters of absolute cylinder
25 appropriate for IOL clear lens exchange?

1 DR. McCULLEY: You just read what you had up
2 there. What I was hoping for was a condensed question, but
3 that's okay.

4 What is the opinion on this question?

5 DR. BULLIMORE: This is fine.

6 DR. McCULLEY: Same. Fine.

7 Okay. Adverse events.

8 MS. BOULWARE: We are collecting the rates. We
9 haven't set target rates, so that is nothing that would need
10 to be changed.

11 DR. WEISS: Don't you need a target rate? What if
12 they report a 50 percent rate of retinal detachment? There
13 has to be some target at which point you say that is not
14 acceptable.

15 MS. BOULWARE: Obviously, under the IDE, if we saw
16 a high rate of retinal detachment, we would stop the study.
17 What we have not done is set acceptable rates for the PMA to
18 be approved, because I don't know that we know those rates.
19 For some rates, they can be compared to the grid rates that
20 we have for IOLs after cataract extraction.

21 DR. BULLIMORE: I am nervous, I am hesitant to say
22 it right, I am happy for them to be blank, so I don't get
23 some sponsor in the future hit me over the head with the
24 rates when they have been met, and they are rates that maybe
25 I don't agree with.

1 DR. ROSENTHAL: If you set the rates, you get into
2 the PDP area, where you set all the parameters, and if they
3 meet them, you approve it. So, I think you are better off
4 to leave some of these adverse rates open and see what they
5 actually are and whether they are acceptable, reasonable
6 assurance of safety and efficacy.

7 DR. McCULLEY: What we are trying to do right now
8 is answer questions you want to ask us.

9 MS. BOULWARE: Right.

10 Dr. Pulido.

11 DR. PULIDO: My only concern about leaving rates
12 open is that let's say this study is a non-masked study, but
13 just rather a study, a cohort study where they treated 300
14 patients, and they had an incidence of retinal detachments
15 of 10 percent after two years.

16 They could come back and say, well, we don't think
17 that this number is out of order for myopes, and as a matter
18 of fact, this happened to us when there was one of the
19 excimer laser--one of the original excimer laser studies
20 where we approved excimer laser for hyperopia, and we saw
21 that there was an increase in hyperopia over time, but we
22 didn't know what the natural history was, and we said there
23 is a change, and they said what is the natural history.

24 So, if they came back and they said there is a 10
25 percent incidence, and they say that is probably the natural

1 history for the myopes, we would have no chance of being
2 able to then say that is natural, and we are not going to
3 accept the study.

4 DR. BULLIMORE: I always place the burden of proof
5 on the sponsor.

6 DR. PULIDO: That wasn't the way it was done in
7 the past.

8 MS. BOULWARE: We can recommend a set of controls,
9 you know, age and refraction-matched controls if that would
10 address that concern.

11 DR. McCULLEY: I think we would need some data on
12 natural occurrence for comparison.

13 DR. ROSENTHAL: Which means you believe that a
14 control population should be involved in a study of this
15 type, if I understand what you are saying.

16 DR. McCULLEY: It could be concurrent or if there
17 is good historical data that presumably could be taken from
18 historical data, published data.

19 DR. ROSENTHAL: Based on age?

20 DR. McCULLEY: Based on everything that would need
21 to be included to give a reasonable comparative population.
22 There has to be a reasonable comparative population, and it
23 can be concurrent or it could be from the literature.

24 DR. ROSENTHAL: I am putting you on the spot.
25 Which is advisable?

1 DR. PULIDO: Obviously, a control group would be
2 the most advisable.

3 DR. ROSENTHAL: Current control or historical
4 control?

5 DR. PULIDO: A concurrent control would be the
6 best, but if there is a historical control that is
7 worthwhile, that is fine, but I just don't want a number of
8 10 percent and nothing to be able to--

9 DR. ROSENTHAL: Is there a historical control?
10 You are a retinal specialist. Is there a historical control
11 on retinal detachment frequencies?

12 DR. PULIDO: There is no good long-term natural
13 history study. There are small studies, and maybe you could
14 do a meta-analysis of the multiple small studies, but they
15 have different criteria. So, as far as a good, long-term
16 natural history, big study, no.

17 DR. McCULLEY: What we are saying is that it has
18 got to be there by whatever mechanism, and if it not there
19 in published, historical data, then, it has to be created.
20 If it is there, then, it could be used, but it has got to be
21 decent data.

22 MS. BOULWARE: These are the efficacy endpoints.
23 With regard to predictability of refraction, should these
24 numbers be any different, the percentage of eyes that
25 achieved predictability?

1 DR. BULLIMORE: The fact that we are using the
2 same numbers as we have for laser refractive procedures,
3 were I a sponsor embarking on this study, this would push me
4 to do lower ranges of refractive error rather than high
5 ones. This would push me to doing implants on minus 4's and
6 minus 6's, rather than minus 10's and minus 12's.

7 So, I am a little hesitant to include these.

8 DR. McCULLEY: Dr. Sugar.

9 DR. SUGAR: I don't know what the data is, but I
10 think Jack Holiday and others have data on outcomes of
11 intraocular lens power calculations that probably are a
12 little worse than this, I mean in terms of predictability
13 data or for the extremes, when we get up to the minus 16,
14 18, and certainly clinically, I have found that is
15 definitely the case, so these numbers probably aren't
16 applicable, but what numbers we should suggest, I don't
17 know.

18 DR. McCULLEY: Isn't the data plus or minus 2 is
19 the scatter?

20 DR. GRIMMETT: Dr. Sugar is correct, of course, as
21 we all know, for the higher ranges, the predictability goes
22 down. The rough numbers for the overall spread are
23 generally 80 percent plus or minus 1; 95 percent, plus or
24 minus 2, and they are down right near 50 percent, plus or
25 minus 1/2. Those are the overall, general spread for SRK2

1 and I believe Holiday, but, of course, they go out of whack
2 the farther you go.

3 DR. SUGAR: That is skewed definitely towards the
4 mean population, which is not a minus 18 or 20.

5 DR. GRIMMETT: Absolutely true.

6 DR. McCULLEY: So, can we refer you to that
7 literature for you to evaluate and come up with some
8 numbers?

9 MS. BOULWARE: Yes.

10 DR. MAGUIRE: Just one more suggestion is that
11 with the problems with IOL prediction after refractive
12 surgery, people have gone back and reevaluated the original
13 formula that the Holiday, SRK, and other things are based
14 on, that it turns out that "A" constant is not really
15 constant.

16 It changes based on corneal curvature and some
17 other things, and anterior chamber, and some other variables
18 that have been left out of the calculations, and there is
19 good work that has been done and presented at Arvo that
20 addresses those issues, and that is something that you
21 should look at, too, as far as IOL calculations to do these
22 procedures in the higher myopes.

23 DR. McCULLEY: Do you remember the author so they
24 can find that?

25 DR. MAGUIRE: I know he is at Wash U. in St.

1 Louis, but I would have to look at it when I get home, if
2 you send me an e-mail.

3 DR. McCULLEY: Why don't you send them an e-mail
4 with the first author, so it would be easier for them to
5 find it.

6 Rick.

7 DR. FERRIS: I take the point that if you have a
8 very high level of myopia, you might relax this somewhat,
9 but for--I don't know what the number is--but less than 12
10 or some such number, it seems to me with a procedure that
11 has a higher risk, you can't relax these numbers.

12 The benefit needs to be at least the same, so
13 certainly anybody who theoretically could get LASIK, you
14 surely shouldn't relax these numbers. Now, for the high
15 myopes, I agree that they may get more benefit because they
16 have more need, and they don't have an alternative, and
17 there may be a reason in a subgroup to relax this.

18 DR. ROSENTHAL: What about hyperopia? You are all
19 concentrating on myopia.

20 DR. PULIDO: I had actually increased the
21 stringency criteria by another 5 percent, because this is
22 greater risk, therefore, there should be a higher
23 stringency.

24 DR. SUGAR: Technologically, it is not reasonable.
25 That is, if we can't do that in standard cataract

1 extraction, why should the sponsor be expected to do that in
2 this other population? They shouldn't be expected to do
3 better than they can do already.

4 DR. McCULLEY: If you take a minus 14 and make
5 them a minus 250, they are a happy camper.

6 DR. BULLIMORE: Mr. Chairman, I think based on the
7 veracity of the comments earlier, I think the primary
8 concern here is safety, and we can move on from efficacy.

9 MS. BOULWARE: I would like a number for
10 hyperopia, if you have one.

11 DR. McCULLEY: You would like what?

12 MS. BOULWARE: A number for hyperopia above which
13 these should be relaxed.

14 DR. McCULLEY: Dr. Grimmett.

15 DR. GRIMMETT: I think earlier we said that in
16 looking at the data on past predictability of IOL formulas,
17 I would simply match whatever the current hyperopia findings
18 show.

19 DR. McCULLEY: Go look it up.

20 DR. GRIMMETT: I looked this data up five, six
21 years ago. It might be in a file that I have.

22 DR. McCULLEY: If you find it, will you send it to
23 the FDA?

24 DR. GRIMMETT: Sure. I pulled about 30 articles
25 or so.

1 MS. BOULWARE: Thank you.

2 DR. STARK: The uncorrected vision, as Jim
3 indicated, in the higher myopes, we shoot for myopia,
4 diopter, and they might be plano, they might be a minus 2.
5 I wouldn't be quite as strict on the uncorrected visual
6 acuity under minus 11 or 12, in that range, I mean when the
7 myopia is greater than that.

8 DR. BULLIMORE: What about hyperopia?

9 DR. STARK: I would pick the cutoff point in both
10 where LASIK is not approved or PRK or LASIK, where we don't
11 have other reasonable alternatives.

12 DR. McCULLEY: But we need a visual acuity. We
13 need a UCVA.

14 DR. STARK: In hyperopes, you are going to have to
15 be careful with the minification, so a contact lens correct
16 visual acuity on them prior to the surgery might be helpful
17 for the sponsor, because it is going to minify the image and
18 give half of the line less best corrected visual acuity for
19 a plus 5 hyperope.

20 DR. McCULLEY: So there are multiple things you
21 are going to have to take into consideration there.

22 MS. BOULEWARE: Okay.

23 DR. McCULLEY: Next question?

24 DR. BULLIMORE: Are there any additional safety or
25 efficacy endpoints that should be added for this indication

1 other than those you just saw?

2 DR. McCULLEY: One is informed consent that they
3 are going to lose their accommodation, most likely.

4 DR. BULLIMORE: This is an endpoint to be measured
5 as safety or efficacy of the product. I did take that down.

6 DR. McCULLEY: It is informed consent.

7 DR. PULIDO: As we talked about before, pigment-
8 dispersion syndrome. It may not be as common in clear-lens
9 extraction as in other cases, but that should be in there,
10 not just glaucoma.

11 DR. McCULLEY: Anything else?

12 DR. SUGAR: Wait. I don't understand what you are
13 asking for. Pigment dispersion may actually be treatable by
14 removing their lens.

15 DR. PULIDO: Right; but if they develop pigment
16 dispersion--

17 DR. SUGAR: So it is something to look--you mean
18 as an adverse--or a complication?

19 DR. PULIDO: Correct.

20 MS. BOULEWARE: We will add that for this and in
21 the other document.

22 DR. McCULLEY: Do you have any other specific
23 questions for us?

24 MS. BOULEWARE: Yes; I had taken down your
25 recommendations in terms of the inclusion criteria that we

1 might want to limit it to an older age group because of the
2 risk of epithelial cell loss, because it might be higher if
3 you are doing phakoemulsification or remove the lens, and to
4 take into account beginning endothelial-cell density and
5 that there would be limits on the range of refractive
6 correction allowed.

7 Are there any other unique inclusion or exclusion
8 criteria that should be applied? I know Dr. Stark mentioned
9 beginning UCVA. 20/40 was considered a bit liberal for this
10 particular procedure. Would you like to suggest a different
11 number as an inclusion criteria?

12 DR. McCULLEY: We came up with a recommendation a
13 minute ago, even though it was somewhat arbitrary, of this
14 procedure not being preformed on anyone less than a -11.00.
15 If we went to the hyperopic side, it would be anyone that
16 was less hyperopic than, what, a +5.00.

17 MS. BOULEWARE: Is there anything else?

18 DR. McCULLEY: Jose, you were going? Are you
19 giving up?

20 DR. PULIDO: I have a more general concern on
21 that.

22 DR. WEISS: I just wanted to bring to the
23 attention of the panel, there are some patients who would be
24 less than -11.00 but still not be good candidates for LASIK,
25 for example, someone who started out with a 42.00 diopter K

1 but they were a 10.00 diopter myo. If you LASIK then, you
2 would make them too flat and give them a bad result. Or
3 someone was a -10.00 or a -8.00 with a very thin cornea.

4 We don't necessarily have to include those in
5 these studies but I just wanted to bring up that
6 possibility.

7 DR. McCULLEY: Thank you. Jose, you had a more
8 general comment the you still want to make?

9 DR. PULIDO: Yes; I do. We have talked about, and
10 Dr. Coleman had alluded to, this pigment dispersion problem
11 which I think is important. In the case of the myopes, many
12 of them, of these high myopes, have tilted discs. I know we
13 are following, as one of the complications raised,
14 intraocular pressure requiring treatment.

15 But these people may have normal intraocular
16 pressures or pressure spikes that you won't be picking up.
17 So how are we going to be determining whether they are
18 developing visual field loss. I don't see anywhere in here
19 about doing visual fields on these patients.

20 These patients have very tilted discs and
21 sometimes it is awfully hard to follow their cup-disc ratio.
22 What is being done to look at this particular problem.

23 In one of the studies I saw, there was, like,
24 20 percent of the patients in a small study had pigment
25 dispersion following placement of a phakic IOL.

1 DR. McCULLEY: Of a phakic.

2 DR. PULIDO: Yes.

3 DR. McCULLEY: But we are talking now about--

4 DR. PULIDO: But, regardless.

5 DR. McCULLEY: As your colleagues--Joel said often
6 when you take the lens out and put an implant in, you cure
7 the process. You stop it.

8 DR. PULIDO: I realize that. I am just looking at
9 it from a general point of view, how are we following these
10 patients to see if they are developing glaucomatous damage.

11 DR. McCULLEY: Should there be a subset that--we
12 have had trials that have required visual fields as a
13 routing. Should there be a required subset of patients
14 having visual fields done or should all have visual fields
15 done?

16 Jose's point is a good one and visual field--when
17 the disc is difficult to examine, it would be even more
18 important.

19 MS. BOULEWARE: We can certainly add that. We
20 would be happy to have a recommendation as to the number of
21 subjects you feel would give you a comfort level for this.

22 DR. COLEMAN: One of my questions is how much does
23 a lens extraction increase the risk of glaucoma in patients?
24 I don't really know the answer to that.

25 DR. McCULLEY: My impression is that it is more

1 often that removing the lens improves the glaucomatous
2 condition.

3 DR. PULIDO: Again, that is why I didn't want to
4 put--this is more looking at it globally from refractive IOL
5 surgery. If we include phakic IOLs and clear-lens IOLs and
6 we have this concern, how are we going to follow whether
7 visual fields are being affected and whether a patient has
8 phakic IOL or clear-lens IOLs.

9 DR. McCULLEY: You are going to deal with this.
10 The message is you need to have a population on which, if
11 not the total population, on which visual fields are done.

12 DR. STARK: You have to lose 40 percent of your
13 optic-nerve function before you start getting a field
14 defect. They are not going to do that in three years. So
15 it is beyond the scope of this study.

16 I think, to document the amount of angle
17 pigmentation and changes in pressure is more important
18 because it might lead you to a suspicion that this patient
19 has now increased their pressure by five points and we need
20 to look closely at them. But they are not going to develop
21 field defects in three years with little increase in
22 pressure.

23 DR. FERRIS: But it will allow the corneal surgeon
24 to detect the retinal detachment.

25 DR. PULIDO: On a field. No; we have got indirect

1 lenses.

2 DR. McCULLEY: We just don't know how to use them.

3 DR. GRIMMETT: I agree and appreciate Dr. Stark's
4 comments. I do think, as previously done, that fields would
5 be important for corneal inlays or corneal implants,
6 however, because they, I would suspect, may theoretically
7 change peripheral vision.

8 DR. McCULLEY: We are getting back more broadly.
9 I would like to focus back in. Do you have any other
10 specific questions about clear-lens extraction and IOL
11 insertion?

12 MS. BOULEWARE: Let me see. You have touched on
13 the different clinical evaluations. Let me put up the
14 reporting periods. These are the reporting periods that
15 match the refractive document. They are slightly different
16 than the reporting periods for the aphakic IOL guidance
17 document.

18 Are these reporting periods you see on the screen
19 acceptable for clear-lens extraction trials or would you
20 recommend something different.

21 DR. SUGAR: I wonder if you would want to extend
22 that to five years, although, presumably they could come in
23 with their PMA with three-year data. It would be worth
24 prospectively expecting them to follow the patients for a
25 longer period of time because of the prolonged risk of

1 retinal detachment.

2 MS. BOULEWARE: Are there other comments about the
3 duration of the study, either prior to PMA or beyond? Dr.
4 Yaross, and then Rick. But, before we do that, you were
5 wanting to interject.

6 DR. ROSENTHAL: I think for an aphakic IOL,
7 wouldn't the panel think that an aphakic IOL protocol--I
8 mean, a patient not be seen for three months? Oh; one day.
9 Sorry.

10 DR. McCULLEY: You missed the whole left column.

11 DR. ROSENTHAL: Sorry.

12 DR. McCULLEY: I did that once, too. So I know
13 what you did. Dr. Yaross?

14 DR. YAROSS: I would just suggest that with the
15 posterior-chamber IOLs we do know a great deal about their
16 performance, and a three-year study, I think, gives a
17 sufficient database to come up with a reasonable assurance
18 of safety and effectiveness. Perhaps, there would be a
19 post-approval follow-on, but I think we are not talking
20 about devices about which a great deal is not known.

21 DR. FERRIS: I think it is fine to come in at
22 three years for the reasons you say. On the other hand, it
23 seems to me it is important in the informed consent if you
24 intend to do a longer follow-on--in fact, most IRBs now
25 require to say how long you are going to be following this--

1 maybe not most, but the ones I am familiar with want you to
2 tell the patient up-front how long you are asking them for a
3 commitment.

4 I think that is the point that Joel was getting
5 at, that we want to make sure that they know we would like
6 to follow them for at least five years and why.

7 DR. McCULLEY: Have we now answered all your
8 questions?

9 DR. STARK: If we are going to five, then why
10 don't we just go to ten.

11 DR. McCULLEY: Have we answered all your
12 questions?

13 MS. BOULEWARE: All the ones I could come up with
14 in five minutes; yes. I appreciate your bringing the topic
15 back up again. This gives us a place to start. Thank you.

16 DR. McCULLEY: Any other comments? Sally, do you
17 have any closing comment?

18 MS. THORNTON: Only that I think we should have an
19 open public hearing session.

20 DR. McCULLEY: Thank you.

21 **Open Public Hearing**

22 DR. McCULLEY: We will now open the floor to the
23 open public hearing session. Anyone who would like to make
24 a comment please approach the podium. Comments will be
25 limited to five minutes per speaker.

1 DR. SHEETS: I have a question for the panel. My
2 name is John Sheets from Alcon Laboratories. The question
3 is about the recent, or the discussion that just concluded,
4 about clear-lensectomy. The question would be would the
5 panel think to have the exclusion criteria down to
6 11.00 diopters, include that for multifocal intraocular
7 lenses, that the indication may be to restore accommodation
8 through presbyopia correction?

9 DR. McCULLEY: That brings up a different aspect
10 which we really did not take into consideration in our
11 discussions. I don't now if we can give you a quick-and-
12 easy answer to that. If panel thinks we can, we will sure
13 try.

14 DR. SUGAR: What are you asking? Are you asking
15 would these criteria--you would consider multifocal lenses
16 as a treatment for presbyopia in an emmetrope?

17 DR. SHEETS: Exactly; through a clear-lensectomy.

18 DR. SUGAR: In an emmetrope.

19 DR. SHEETS: Yes.

20 DR. SUGAR: I think it is a totally different
21 kettle of fish.

22 DR. SHEETS: Because part of the--

23 DR. McCULLEY: Okay. We know what you mean. Does
24 the panel think that we can address that issue now?

25 DR. FERRIS: I think so.

1 DR. McCULLEY: You think so? Do you want to try
2 to address it, then?

3 DR. FERRIS: I can say I am every bit as
4 enthusiastic about doing this for presbyopia as I am for
5 myopia and hyperopia. I just think it is a very high-risk
6 procedure. There may be individuals in which it is okay,
7 but I hope and pray that there is adequate informed consent.

8 DR. McCULLEY: Sally, just mentioned to me--I have
9 gotten off from protocol. This is not meant to be an open
10 discussion. So if you have comments that you wish to make
11 or questions that you wish to pose to us, then we will
12 address those if we choose to.

13 You have a question to us; what would our opinion
14 be relative to insertion of multifocal IOLs for the
15 treatment of presbyopia. Clear-lens extraction, multifocal
16 IOLs for presbyopia.

17 Do you have any other issues you would like to
18 state?

19 DR. SHEETS: No.

20 DR. McCULLEY: Is there anyone else in the
21 audience who would like to come to the podium and bring up
22 issues during this open public hearing? Seeing none, the
23 open public hearing is closed.

24 Does the panel wish to address the issue that was
25 brought up at the podium?

1 DR. YAROSS: I think that Dr. Sheets has raised an
2 issue, certainly, that has occurred to other members of the
3 public and to the panel in the past. I think that if a
4 guidance document is promulgated on refractive lensectomy,
5 that sponsors need to be able to bring forward applications
6 and studies for a variety of indications, and presbyopia
7 could be one of them.

8 DR. McCULLEY: Would our criteria be any different
9 than they are for the high myope, high hyperope?

10 DR. YAROSS: I think, again, the risk benefit
11 ratio needs to be looked at for the specific device and the
12 specific patient population.

13 DR. McCULLEY: If we were going to try to lump all
14 of these together, can we lump that with the high myope,
15 high hyperope?

16 DR. WEISS: By virtue of the definition, this is
17 an emmetrope. So it would be different. You would be
18 operating on an eye that might be plano to start off with.

19 DR. McCULLEY: Right. But it is for refractive
20 purposes. You are starting with a different population
21 base. But the same hoped-for outcome would be to relieve
22 the patient of the need for external eye wear.

23 DR. SUGAR: In this situation, I think we would
24 have to have much, much tighter criteria and expectations
25 for outcome. So it would be a different grid for outcomes

1 for presbyopia in an emmetrope.

2 DR. McCULLEY: Dr. Pulido?

3 DR. SUGAR: Just like we had talked about before
4 that the natural history of retinal detachments in myopic
5 patients is spotty, at best, and if someone were to come
6 forward with a non-controlled trial, we would be unhappy
7 looking at the data.

8 Likewise, here, we would probably want a
9 controlled trial, at least I think I would, and my hurdle
10 for something to pass would be very, very high.

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

12 DR. YAROSS: The only other comment I would make
13 about the presbyopic population is that does address one of
14 the concerns raised by the panel with age. So, again, the
15 risk-benefit ratio may look a little different because you
16 are dealing there with an older population. So I think
17 that, again, the panel needs to evaluate each proposal as it
18 comes before it.

19 DR. McCULLEY: I couldn't hear you at the end.

20 DR. YAROSS: Each proposal as it comes before the
21 panel, but in terms of the general product, this fits within
22 the scope of what I was saying earlier about a new
23 indication for an established device and may be able to be
24 addressed through addenda to existing guidance documents.

25 DR. McCULLEY: Other comments?

1 DR. ROSENTHAL: Can I just be sure that there is a
2 feeling that you need controls for anything, any clear lens?

3 DR. McCULLEY: Yes. Absolutely.

4 DR. ROSENTHAL: Thank you.

5 DR. McCULLEY: Does anyone disagree with that?
6 No. Unanimous opinion.

7 DR. BULLIMORE: I will be the sole dissenting
8 opinion.

9 DR. McCULLEY: Do you want to say why?

10 DR. BULLIMORE: No.

11 DR. FERRIS: It is an axiom of clinical research
12 that results are always improved by omitting the control
13 group. It is hard for me to know how you would assess some
14 of these things without a control group of some sort. We
15 are not defining the control, and allowing some flexibility,
16 but a lot of these outcomes, without some kind of comparison
17 group, you are just left guessing at what the natural-
18 history rate is, especially since the methods of measuring,
19 the observational variation is high.

20 I said earlier that some of these things like
21 looking at the vitreous or looking at the lens clinically or
22 the retina clinically are very noisy. Noise is one thing.
23 You at least have some measurement--you have to for the
24 noise. But you need some sort of control group to compare
25 with. Otherwise, you have no idea. At least I don't know

1 how you have any idea.

2 For statisticians, it is always, "compared to
3 what?" You need some "compared to."

4 DR. BULLIMORE: I was voting on the issue of
5 control group. I didn't want to exclude to possibility of a
6 sponsor of bringing in adequate and appropriate comparison
7 data to us.

8 DR. McCULLEY: Thank you.

9 Other comments? Do you have any closing comments,
10 Sally?

11 MS. THORNTON: Only to thank the panel for their
12 hard work and deliberations. There has been a lot to go
13 through today and I appreciate your thinking on these
14 topics. They will be of great assistance to us, I'm sure.

15 I would also like to make an announcement for the
16 public that was not at the meeting yesterday that the July
17 meeting that was scheduled has been canceled. I will let
18 you all know in July about the September meeting.

19 DR. McCULLEY: Meeting adjourned.

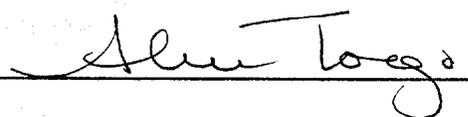
20 [Whereupon, at 3:55 p.m., the meeting was
21 adjourned.]

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C E R T I F I C A T E

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



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