

1 for emmetropia being half diopter, that was not
2 achieved at the -6, -7, -15, and -16 diopter groups of
3 implants and the same for 75 percent being within + or
4 -1 diopter was not achieved for the 13 and 15 diopter
5 group.

6 In these specific stratified groups I
7 don't know why that's the case. I don't know if it's
8 a safety issue, an efficacy issue. I need to know
9 more about that. That's only in groups AB. I don't
10 know about the rest of the patients.

11 DR. WEISS: Dr. Bandeen-Roche.

12 DR. BANDEEN-ROCHE: I guess I would just
13 like to remind everyone of a double-edge sword.
14 Certainly the subset analyses are very interesting to
15 look at but there's low precision and low power for
16 many of these analyses so they have to be taken with a
17 grain of salt, particularly statements such that there
18 is no statistically significant different by age. For
19 instance, a statement like that the power may be so
20 low that there really is very little evidence
21 underlying such a statement.

22 DR. WEISS: Dr. Grimmer.

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1 DR. GRIMMETT: This is Dr. Grimmer. I'm
2 just transcribing here.

3 DR. WEISS: And doing it well.

4 DR. GRIMMETT: Thank you. Regarding the
5 second question, I'm uncertain to provide an answer to
6 that right now.

7 DR. WEISS: Dr. Mathers.

8 DR. MATHERS: I'm also concerned about the
9 development of two things, cataract and retinal
10 detachment. I think that the absence of a good
11 control group makes a cataract assessment extremely
12 difficult.

13 Recognizing that cataract exist in a
14 higher percent of these people, I would still like to
15 have a better handle on this because the chronic
16 perhaps low-grade inflammation and other issues will
17 most likely, as we have some indication here, lead to
18 accelerated cataract which has implications for
19 retinal detachment because this group of high myopes
20 do not do cataract surgery well and that risk them for
21 retinal detachment.

22 I am concerned about particularly those

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1 two safety issues. I agree with the other comments
2 that it's difficult to be certain about the other
3 safety issues.

4 DR. WEISS: Dr. Casey.

5 DR. CASEY: I'm not sure either. One of
6 the things I was concerned about is the fact that,
7 again, as I mentioned earlier, there was not a lot of
8 data that was presented on patients who might have
9 irises that might be thicker, might have greater
10 pigment dispersion, particularly minority patients.

11 While a lot of these patients -- well,
12 we're saying that the age with which these lenses can
13 be inserted can start very young, certainly a lot of
14 patients who are in minority groups may not have other
15 diagnoses at, say, 20 or 30 but the rate of diabetes,
16 particularly in patient populations that I see, is
17 significantly greater in those patients that didn't
18 have more pigment dispersion. Pigment dispersion is a
19 big problem for me and its relationship possibly to
20 glaucoma. I'm concerned about that as well.

21 DR. WEISS: Dr. Coleman.

22 DR. COLEMAN: I'm also concerned about

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1 glaucoma as Dr. Casey and Dr. Macsai have pointed out.

2 One of the things I'm concerned about is about the
3 subjects were on medications long-term according to
4 the sponsors. The issue is that this is probably just
5 for elevated intraocular pressure because if they are
6 not looking at the nerves and not doing visual fields,
7 you don't know if they really do have glaucoma so this
8 is really a pressure related treatment.

9 One of the issues is that with high myopes
10 you do have an increased risk for glaucoma and so
11 there could actually be a lot of undiagnosed glaucoma
12 that may or may not have gotten worse by the placement
13 of this lens and we really don't know that.

14 One of the issues, too, is that for those
15 10 individuals that are on long-term medications for
16 the high eye pressures, you really don't know what's
17 going on in the angle because gonioscopy was not done
18 so you don't know if they have peripheral anterior
19 synechiae or exactly why are they having this long-
20 term elevation of their intraocular pressure. Is it
21 part of the natural history or not.

22 In addition, they mentioned that they

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1 didn't have pupillary block in the information for the
2 clinicians. However, there was a case of pupillary
3 block they thought might have had to be reversed by
4 iridotomy so it does look like there are some issues
5 with pupillary block and I'm quite concerned about the
6 glaucoma issues.

7 DR. WEISS: Dr. Van Meter.

8 DR. VAN METER: I think some of the data
9 that we have looks like a little more longitudinal
10 follow-up would help also. For instance, from the
11 concerns we've discussed, in patients that have 8
12 diopters of myopia or less, meaning the lower groups,
13 we have 33 patients only entered into the study and
14 only 16 of those patients are out t three years so
15 that's not really enough information. It would be
16 nice to follow them long enough to get more people in
17 the group.

18 Likewise with your concern about brown
19 iris patients, there were 297 patients that had brown
20 irides entered into the study. We only have
21 information on '98 of those. On those patients that
22 have 8 diopters -- well, I mentioned 8 diopters or

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1 less of high myopia.

2 In the younger patients, 35 or younger, it
3 looks like there are 94 patients entered into the
4 study. We only have information on 23 of those. A
5 little bit more follow-up data on the cohort of
6 patients that we have I think would also help.

7 DR. WEISS: Dr. Smith.

8 DR. SMITH: At the present time I don't
9 think the data presented provide reasonable assurance
10 of safety for the reasons related by my colleagues,
11 the first of which is I can't find a single number to
12 attribute for all adverse events added together per
13 patient.

14 Also roughly about half of the patients
15 enrolled in the study are still ongoing. I think
16 there is longitudinal data that can come about in the
17 future that would provide additional information that
18 is required.

19 DR. WEISS: Dr. Huang.

20 DR. HUANG: I guess I'm a contrarian to
21 the group. I do think that current data have provide
22 enough safety assurance because we really don't have a

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1 safety guideline from the FDA or from the ophthalmic
2 community. I think the high myopic group is very
3 difficult to study. These patients intrinsically have
4 a high risk of glaucoma, high risk of cataract, high
5 risk of retina detachment.

6 Many of the questions I think is important
7 such as endothelial count and such as another
8 potential and longevity of the visual acuity and the
9 patient's associated complication but I think those
10 can be performed in the post-market surveillance. I
11 really don't think we should continue to wear on
12 submitting more data.

13 Our panel member mentioned that more of
14 the stratification sometimes gives you more confusing
15 data. You review the scientific data more on
16 stratification. You have a smaller number subset of
17 the patient and the validity of the instrumentation
18 become much less. Thank you.

19 DR. WEISS: Actually, I'm glad you had a
20 contrary opinion because I would like to -- I hear
21 sort of a consensus -- I'll just make my comment and
22 then get to Dr. Mathers -- hear a consensus of the

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1 interest of either more data or reevaluating the data
2 we have. That doesn't necessarily speak to the device
3 is not safe. It's just that can we get some more
4 information in order to determine if it's safe or not.

5 Now, the way that we can do that is with
6 premarket or post-market. You brought that up and
7 what I would like to do after we have Bill make his
8 comment is have the panel discuss what additional --
9 would this be helped or would your concerns be helped
10 if we had more of the information from three years, if
11 we had people followed out at a longer time point what
12 would you need in order to determine if this was safe.

13 I'm going to open that up to actually the
14 first two questions, not only all of the data, the
15 endothelial cell, the lens data on retinal detachment,
16 etc. What do you need to make a determination? Dr.
17 Mathers first, however.

18 DR. MATHERS: We're asked to make an
19 assessment here which is sort of a global assessment
20 about safety and that's what we've done. I think it
21 can be seen in another context. This is a difficult
22 patient population.

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1 They are requesting permission to do this
2 in a wide range of ages and myopic correction but we
3 are trying to address a need that is very real and
4 safety in this sense can be seen as a relative safety
5 versus the degree of, shall we say, disease that we
6 are trying to deal with.

7 I think if you narrow the window you will
8 come up with the population for which at least some of
9 us would think this wasn't such an unsafe alternative.

10 For instance, a high endothelial cell count, a
11 patient who is relatively older but not perhaps fully
12 into the cataract range because that then just leads
13 them to cataract surgery, and a high myopia.

14 These patients have very little
15 alternatives and this device considering other issues
16 might be more reasonable for them. I think it's not
17 for the wider group but a 45-year-old with a 2,800
18 count and a -15 is a different patient.

19 DR. HUANG: I do agree. I think either
20 modification of the approved indication or
21 modification of the safety requirement is relevant.

22 DR. WEISS: And we are going to be getting

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1 to that in a while when we get to question 3 which is
2 the proposed statement of indications as far as
3 addressing the minimal refractive error and the
4 minimal endothelial cell count which we can also
5 associate with the age.

6 But on this particular issue with safety,
7 does anyone have any comments in terms of aside from
8 reprocessing the data that we already have bringing it
9 out at a longer time point? Is there anyone who feels
10 that would answer their concerns or is that not
11 necessary?

12 Dr. McMahon.

13 DR. McMAHON: I don't know if we can
14 answer that question. I think it's on sponsor's
15 behalf to provide data that would in the case of
16 endothelial cell loss, for example, which we are
17 focusing on, they need to provide data that would be
18 assuring to us.

19 If that can be done with analysis of data
20 that already exist, which I think they would have
21 already presented if that was the case, in terms of
22 completing the analysis of patients that they have

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1 enrolled, that might be enough. If that is the case,
2 yahoo. And if it's not, then I think they need to
3 follow them longer until they can demonstrate a
4 flattening of that slope in my view.

5 DR. WEISS: Dr. Grimmatt.

6 DR. GRIMMETT: Michael Grimmatt. I
7 answered the second one that I'm not certain and I
8 certainly agree with Dr. Schein and Dr. Bandeen-Roche
9 that having some life table analysis would be very
10 helpful regarding these other complications. Looking
11 at the application in general, I wasn't overly alarmed
12 about the other safety features irrespective of the
13 endothelial cell loss data.

14 I don't think necessarily that it's way
15 out of line. I agree with Dr. Mathers that with
16 specific entry criteria including endothelial cell
17 cut-off data and age taking into account high myopes
18 where there are other options in the market place. I
19 think I could be convinced that it may be a calculated
20 risk but one that those patients may be able to take.
21 That is how I feel about the second part of the data.

22 DR. WEISS: Dr. Van Meter.

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1 DR. VAN METER: I also think that when
2 we're talking a about safety it is necessary to
3 separate out surgical position dependent variables
4 from that of the device itself. As I almost said
5 earlier, having a wound leak is not really a process
6 of the device itself. That's a surgeon specific
7 variable. Many of the problems that we have with
8 anterior chamber lenses have to do with surgeon
9 variables and not the piece of plastic that we're
10 putting in the eye.

11 The other point I want to emphasize is
12 that if you eliminate those myopes that are less than
13 8 diopters for which we have little data, those 8
14 diopters and the patients with 9 diopters and higher
15 correction really don't have other good alternatives
16 for them. This device fulfills a niche. Like
17 cataract surgery, there is really no other alternative
18 for these patients.

19 DR. WEISS: So what I'm beginning to hear
20 is that even though there seem to be somewhat of a
21 consensus that the endothelial cell data did not
22 provide reasonable assurance of safety that you could

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1 get around this by having stipulations of minimal
2 endothelial cell count per age so that you could
3 project out at a certain point to try to ensure a
4 certain number of endothelial cell counts when they
5 were elderly if we were using a linear model to do
6 this.

7 DR. VAN METER: Van Meter. If I may add
8 to that, for instance, if you're looking at a 25-year-
9 old that has a cell count of 2,000, even though that
10 is an acceptable cell count, that is not a normal
11 endothelium for a 25-year-old. For someone that age
12 you may want 2,800.

13 DR. WEISS: If there was consensus that
14 this might be a way to go about things to balance the
15 risk and the safety, in that setting would there be --
16 do any members of the panel feel it would be helpful
17 to have a post market or a premarket study in
18 conjunction with that amount of guidance or that's
19 unnecessary?

20 Dr. Schein.

21 DR. SCHEIN: The question -- this is
22 Oliver Schein. The questions that Dr. Weiss is

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1 currently raising, there is more than one issue
2 simultaneously. One question I think you're asking is
3 is it simply a matter of reanalyzing the existing data
4 to meet my or other individual safety concerns.

5 To that I would say that's a precursor, a
6 prelude for what needs to be done because we then want
7 to look and see what the analyses look like once they
8 were done. Secondly, would I feel that data showed
9 adequate safety when we have on the order of 60
10 percent of patients or eyes meeting two years and 30
11 percent meeting three years no matter what it showed.

12 I think that is a second issue. We may
13 differ on that around the table. I would like to see
14 much more than 60 percent of two years. I understand
15 that the directions or the mandate may have changed in
16 midstream to make it harder to get more data at three
17 years or, at least, to get as much as we would
18 otherwise anticipate.

19 Those are two separate issues. It's hard
20 to predict if one saw the data what one would then
21 make of it in the absence of seeing the data. Now, if
22 analysis of the data which included more extensive

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1 follow-up at two to three years showed reasonable
2 safety, you know that I would feel very strongly that
3 we still needed a post-market surveillance study.

4 That is predictable over here, I know.
5 The issues there are very different because in that
6 setting you want a large sample of patients where
7 you're only interested in the most severe
8 complications. Off the top of my head I would look at
9 explantation, corneal transplantation, retinal
10 detachment. You might think of one or two others but
11 in a very large sample over a several-year period.

12 DR. WEISS: Dr. Bandeen-Roche.

13 DR. BANDEEN-ROCHE: First, I would just
14 like to second Dr. Schein's thoughts on 60 percent at
15 two years being something that I'm not at all
16 comfortable with. I would like to see a much more
17 complete follow-up than that. And the need for a
18 post-market surveillance study.

19 The other thought involves the
20 extrapolation issue. In other words, can we pick an
21 age and a severity at which we are comfortable
22 approving the device. It just seems to me that it's

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1 very complicated and the few issues I would like to
2 raise are, first of all, the measurement of the
3 endothelial cell count. We've heard how variable that
4 is. When we determine a threshold at which a patient
5 is eligible to have this device, that variability is
6 still there and has to be considered in terms of their
7 measurement for eligibility.

8 The second is just to reiterate the point
9 that it's not the mean projectory that is really the
10 most important thing but estimating some percentage
11 who are really at elevated risk.

12 I would just briefly say that I think the
13 analysis that Dr. Gray presented, I really can't think
14 of a better way in light of these data to try to
15 estimate those percentiles other than to maybe also
16 look at the random effects distribution itself and not
17 just the -- the estimated distribution and not just
18 the posterior estimates.

19 And then finally there's the issues of
20 cataract induction and what happens when people then
21 go to have cataract surgery at an older age. I don't
22 have a magic answer but it just seems complicated.

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1 DR. WEISS: From what I hear, and I could
2 use Dr. Rosenthal's input at this point, there are two
3 lines of thinking. One is that there are safety
4 concerns but these are going to be outweighed by the
5 efficacy that has been shown and some of these safety
6 concerns perhaps could be worked out by Agency with
7 request for further data which are already present.

8 The other mode of thought that I'm hearing
9 is that the safety concerns are such that in order to
10 make any further determination on this device the
11 further information about the data must be forthcoming
12 and this would hold everything else up because you
13 don't know if the efficacy would be outweighed by
14 these issues because you don't have the data yet.

15 Ralph, do you have any input as far as any
16 -- that's just two modes of thought and that's how you
17 can think.

18 Dr. Van Meter.

19 DR. VAN METER: I was just going to add
20 that some of the problems can be overcome with the
21 appropriate labeling and informed consent which is
22 another issue that would overshadow both of these two

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1 arms you've mentioned.

2 DR. WEISS: Well, I think there's one mode
3 of thought of that, Woody, but I don't think that Dr.
4 Schein and Dr. Bandeen-Roche would feel that labeling
5 would address their concerns. Am I correct?

6 DR. SCHEIN: You're right because there's
7 an assumption that it has been found safe and
8 effective and here are some labeling issues. There is
9 a contradiction there.

10 DR. WEISS: Any other comments on this?
11 Dr. Coleman.

12 DR. COLEMAN: I was going to say that I'd
13 be interested in gonioscopy even though it has not
14 been done preoperatively the could do it at this point
15 and follow up and that way they could actually look at
16 the amount of pigmentation and the angle would also
17 address some of the concerns that Dr. Casey brought
18 up.

19 If there are PAS they would have to then
20 attribute it to the device instead of not knowing
21 whether it was pre-op or not. We could also indicate
22 in the labeling that there was such a small number of

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1 minority participants you could not really -- we don't
2 have the information in this group.

3 Dr. Mathers.

4 DR. MATHERS: I think that the endothelial
5 cell data and its extrapolations get very complicated
6 and iffy and there are lots of problems. But Dr.
7 Gray's single summary statement that 38 percent of the
8 subjects would have a risk to have a two percent loss
9 which is a 50 percent reduction in 25 years.

10 If we use that as a guideline and figure
11 who could tolerate a 50 percent loss compared with
12 their current circumstances of their disease, we might
13 be able to assign a category of patient but that would
14 fit given reasonable labeling.

15 It clearly wouldn't fit a 20-year-old but
16 you could ascribe an endothelial count and age and
17 myopic degree which would fit that relative loss rate.

18 At least consider this because I know that there are
19 patients who would like to have this who could have a
20 relative level of risk.

21 DR. WEISS: I'll just add one comment on
22 that and then Donna Lochner was going to make a

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1 comment. I think if you did that, then you would also
2 have to add labeling addressing Dr. Schein's concern
3 that basically you would be saying this is safe and
4 effective but that we do not know the safety X number
5 of years down the line and we do not know the risk of
6 endothelial decompensation and corneal edema, etc.,
7 which is why you are suggesting putting a template in
8 there to try to minimize the risk. If we do find out
9 that this does have a continued cell loss or increased
10 cell loss, then we expect it.

11 Donna.

12 MS. LOCHNER: I just wanted to make a
13 comment about the point with respect to percent
14 accountability. That is one of the things we look at
15 when a PMA first comes in, the accountability, and we
16 want to see that we're not seeing high loss to follow-
17 up rate which may be biasing the data for the subset
18 of data that we're looking at, the primary analysis.

19 The company enrolled a large number of
20 subjects. The guidance from the FDA and the panel in
21 the past has been that we need at least 300 after
22 visits to appropriately power the kind of safety

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1 endpoints we're looking for.

2 So I think just the fact that they, first
3 of all, reached 300 was favorable was favorable to FDA
4 in terms of powering the study for these low-level
5 complications. Then, I think, you have to look at
6 accountability separate and look more at was there
7 loss to follow-up within that group that reached the
8 300, the people that were eligible for that visit.

9 Was there a high loss to follow-up rate,
10 not what is the overall percent accountability of the
11 subject so the fact that they have 60 percent
12 accounted for at a visit isn't necessarily a concern
13 in this instance since they reached adequate sample
14 size to power for the kind of complications we were
15 looking for.

16 So I just want to make that clarification.
17 I may or may not have been totally clear as you look
18 at just the overall numbers that you're getting data
19 on at a particular postoperative visit versus how many
20 were enrolled from the start and whether they were
21 eligible for that visit.

22 DR. WEISS: Dr. Macsai. Then we'll just

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1 continue along the table. Dr. McMahon, then Dr.
2 Schein. Then I think we're going to be wrapping this
3 up after those three comments, these particular two
4 questions. But I will want to after these three
5 comments sort of have a poll in terms of what the
6 consensus is at this moment in time as far as the
7 safety issue goes.

8 Dr. Macsai.

9 DR. MACSAI: I wanted to make two comments
10 and one is in regards to Donna Lochner's comment about
11 adequate numbers of 300. If 300 eyes is enough to get
12 this expedited review, then I would expect on those
13 300 eyes data that is analyzable. If it takes 600
14 eyes to get 300 eyes of data that's analyzable to
15 establish safety, then that is what I personally may
16 feel is required in order to answer the question is it
17 safe and is it effective. I guess I was not clear how
18 we got to this expedited review state.

19 MS. LOCHNER: But the numbers don't factor
20 into the expedited. I think you really have to
21 separate the expedited issue from the numbers. When I
22 say 300, that is 300 analyzable. That is 300 people

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1 who have had follow-up in these kind of studies at the
2 one-year visit, at the two-year visit, at the three-
3 year visit. These are the primary analysis points.

4 When you get to 300 that have those data,
5 you have a certain extra number that you needed to get
6 there and the loss to follow-up within that group has
7 to be reasonable. A 10 percent figure is usual. It
8 doesn't mean, though, you can apply that to the total
9 number enrolled and that may still be active.

10 That's my point I'm trying to make. The
11 company should not be sort of penalized because these
12 people are active. When they've reached a sample size
13 that we have given guidance, the panel has given
14 guidance, would be sufficient to power these kind of
15 complications.

16 Dr. Rosenthal, did you have a comment on
17 this?

18 DR. ROSENTHAL: I was just going to say I
19 think we have to be on a level playing field and the
20 original panel input was that in order to power the
21 safety issue, one had to have 300 eyes. If you now
22 feel that in this instance 300 eyes was not

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1 satisfactory and you need more to power the safety
2 issue, that's a reasonable request. But if you need
3 another 300 eyes just to make that accountability
4 table with 90 percent, it would be not a level playing
5 field for the other companies we deal with.

6 MS. LOCHNER: I understand now what you
7 were talking about. I guess my comment would be that
8 I'm not convinced. I don't know that it's actually
9 300 that is required but I'm not convinced that we
10 have enough longitudinal data on the safety issue of
11 endothelial cell loss rate in this group that we
12 analyzed for today. That would be comment No. 1.

13 Comment No. 2 about the pigment dispersion
14 and the comment that Dr. Weiss made about labeling I
15 would actually disagree with. I think that this
16 sponsor has enrolled compared to other levels of
17 enrolling 13 percent minority population, 6 percent
18 Asian, 3 percent Black, 4 percent Hispanic.

19 Although that in no way represents the
20 population of the United States, that's much higher
21 than we normally see in these kinds of analyses so it
22 would be really important to look at those patients.

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1 I don't think that should be included in the labeling
2 in anyway saying that it wasn't looked at in minority
3 populations because, in fact, it was.

4 DR. ROSENTHAL: So I'm gathering that you
5 would like a reanalysis of existing data on the cohort
6 that has come through for two and three years.

7 DR. MACSAI: Yes.

8 DR. ROSENTHAL: Or that you feel in order
9 to get more data for analysis on the minority
10 patients, we need to get to three years so that
11 sufficient number of patients are accumulated.

12 DR. MACSAI: I don't know the answer to
13 that.

14 DR. ROSENTHAL: I don't either.

15 DR. MACSAI: So I don't know.

16 DR. ROSENTHAL: But if you feel that
17 minority -- if the panel feels that it's important to
18 comment on minority data, that is certainly something
19 we can ask of the sponsor to provide us with that data
20 and if they don't have it out to an appropriate time,
21 we can certainly ask them to do so.

22 DR. WEISS: I think the comment I was

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1 making based on Dr. Casey's comment was in terms of
2 the pigment dispersion that you need to look at this
3 category of people to find out if they are having a
4 different rate of problems. My assumption was the
5 data wasn't there but you are 100 percent right.
6 Maybe it's that the data hasn't been looked at.

7 Now, I know you don't know the answer to
8 this question but I'm going to ask you anyway. Not
9 knowing the answers to things hasn't stopped us even
10 at this point so we can still discuss it. Do you want
11 data going out at a longer time point either premarket
12 or post-market?

13 DR. MACSAI: Yes.

14 DR. WEISS: And what would you want?

15 DR. MACSAI: Me?

16 DR. WEISS: You.

17 DR. MACSAI: I would want data going out
18 at a longer time period looking at --

19 DR. WEISS: What time period? Not the
20 details of it but would you want further premarket in
21 terms of going out to four years or post-market?

22 DR. MACSAI: Well, Dr. Gray said four to

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1 five years and so I don't know if he meant four or
2 five or 4.5. I don't know what but he said four to
3 five years might help. Then, again, we have to do
4 kind of like blind extrapolation on mushy data so I
5 don't know. When we were talking about the pigment
6 dispersion, I can't tell you if those darker pigmented
7 patients and darker irides need to go out further
8 because we haven't looked at them.

9 DR. WEISS: I think what Dr. Gray was
10 saying is even if we brought out four or five years it
11 wouldn't help us to project to 20 years.

12 DR. MACSAI: Dr. Gray, can you clarify?

13 DR. WEISS: Dr. Gray will tell us exactly
14 what he said.

15 DR. GRAY: Let me just clarify what I
16 think I might have said. If you are trying to
17 distinguish between a linear and a nonlinear function,
18 then I think we need a lot more time to make that
19 distinction.

20 DR. WEISS: Can you quantify a lot more
21 time?

22 DR. GRAY: Like 10 years.

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1 DR. WEISS: Okay.

2 DR. GRAY: That's just a guess.

3 DR. WEISS: Ten additional years?

4 DR. GRAY: Out 10 years maybe but you need
5 a longer term follow-up. When you're feeling a
6 regression and you are trying to -- more years matter
7 more than more patients so every time you add on an
8 extra year at the end, it really helps. It's like
9 holding a stick at one end and trying to poke at
10 something with the other end.

11 You don't have a lot of leverage. If you
12 grab toward the middle more, it's like having more
13 years in your regression and the variability will go
14 down a lot. Every time you add on a year or so, it
15 makes a pretty big difference in terms of the
16 variability you'll get at the end.

17 DR. WEISS: Okay. So every little bit
18 helps. Dr. McMahon, did you have a comment? Then Dr.
19 Roche and then Dr. Schein.

20 DR. McMAHON: I imagine 30 years ago the
21 panel when they are dealing with the first IOLs on the
22 market had a very similar conversation not knowing

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1 what the future was. The way around that at that
2 point was, "We'll let you implant these lenses in 75-
3 year-olds or 65-year-olds and let them go for a while
4 and if they fall apart, then we know we made the wrong
5 decision.

6 And that is because the need was great,
7 the need for high myopes is great as well, as Dr.
8 Mathers pointed out. We have a problem, though, in
9 that the cap here is that there is potential
10 cataractogenesis component of this. In the practical
11 use of saying, "Let's implant this in 70-year-old and
12 let you go for another five years and reassess,"
13 doesn't seem very practical.

14 At the same time we're bordered by the
15 fact of not being able to adequately extrapolate with
16 any high degree of assurance and endothelial cell
17 dropout over a period of time so we're in a catch 22.

18 Our ultimate obligation is to our patients and I
19 think if this is going to be approvable, I think we
20 need to be highly conservative and pick an older age
21 group with a high density count in a select group of
22 higher myopes that really would benefit from this.

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1 The notion of doing this at 5 diopter
2 myopes right now, I think, is ludicrous. I think the
3 notion of doing this in 20-year-olds is absurd. I
4 think the point is do you pick and where do you pick.

5 If we are going to think in terms of
6 approvable versus nonapprovable, which in my view, the
7 panel should kind of make a decision right now because
8 if it's not approvable at this point in the majority,
9 I don't think we need to have any further discussion
10 unless the Agency really needs to know more. The
11 other is if it is approvable with conditions, the
12 notion is how restrictive are those going to be?

13 DR. WEISS: Then the Agency needs to know
14 more.

15 DR. ROSENTHAL: May I just comment?

16 DR. WEISS: Yes, Dr. Rosenthal.

17 DR. ROSENTHAL: Approvable with conditions
18 we need the conditions. Not approvable we need to
19 know what is necessary for the company -- what issues
20 are necessary for the company to deal with in order to
21 put it into an approvable package understood that we
22 carried the direction -- the discussion in two

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1 different directions based upon that.

2 DR. WEISS: That's why we're going to
3 reach a little bit of consensus after this one to see
4 which way we're going.

5 Dr. Bandeen-Roche.

6 DR. BANDEEN-ROCHE: On the point of the 60
7 percent at two years it's not a power issue. The
8 concern is that those are perhaps systematically
9 different than the subsequent 40 percent. I don't
10 have a good sense for in this case whether that is
11 likely or not.

12 In terms of the endothelial cell count,
13 I've been sitting here thinking a lot about something
14 we've discussed before which is the issue of
15 flattening out. From the discussion going around the
16 table today, it seems there hasn't been nearly as much
17 discussion about it.

18 I don't know whether the clinicians are
19 comfortable if, in fact, the rate of decline is linear
20 or if safety could only be demonstrated by flattening
21 out. And then, Dr. Gray, I guess I would ask if -- I
22 suppose if the rate were just about to flatten out

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1 then another three years of data might at least give a
2 reasonable indication. I don't know but maybe not 10.

3 DR. WEISS: Dr. Schein.

4 DR. SCHEIN: The issue has been addressed.

5 DR. WEISS: Dr. Bradley.

6 DR. BRADLEY: Yeah. I think we've talked
7 about the issue of endothelial cell count a lot and
8 I'm trying to put it into some terms that would allow
9 us to come to a decision. I think Dr. Mathers and Dr.
10 Huang raised the obvious point that those patients
11 with high-cell density and those who are older are at
12 less risk.

13 I think the obvious implication is that by
14 changing the guidelines for what patients are eligible
15 for this procedure, we might be able to reduce the
16 risk. The question is how do we do that. I think Dr.
17 Stulting gave us a little diagram which captured the
18 essence of how one would proceed.

19 The question is where are those lines
20 drawn and based upon what data do we draw those lines?

21 In the end if we are going to approve this product
22 for a restricted group of patients, we have to come up

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1 with some numbers. It seems to me that is a very hard
2 number to generate.

3 I wondered if maybe Dr. Gray might be in
4 the best position of anybody to answer that. But it
5 seems to me if we are going say this procedure appears
6 to have risk rather than set a cell count today, maybe
7 we could give FDA guidance on what risk we are willing
8 to tolerate, what percentage of patients we are
9 willing to have experience this risk, the risk being
10 ECC dropping to some criterion level.

11 DR. WEISS: Dr. Rosenthal.

12 DR. ROSENTHAL: May I just comment? I
13 actually think the Agency -- you may not believe it
14 but I think the Agency can probably come up with a
15 reasonable table based upon your input and you don't
16 have to actually do it cell by cell while you sit
17 here, and year by year.

18 DR. WEISS: Ralph, just for my
19 edification, if we gave you a minimum age and how many
20 cells we would like someone to end their life with,
21 would that be sufficient?

22 DR. ROSENTHAL: No.

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1 DR. WEISS: What do you need from us to
2 come up with it?

3 DR. ROSENTHAL: Actuarial. Yeah, I think
4 anything you would like -- any input you would like to
5 give we can put into an equation and hopefully come up
6 with an answer.

7 DR. WEISS: So you could start out with --

8 DR. ROSENTHAL: I would like age. I mean,
9 we would obviously like what should end up after a
10 certain period of time. It's a gestalt, isn't it?
11 It's not the easiest thing but if that's the way you
12 want to go rather than have you do it here, I think we
13 could possibly do it for you. That's all I'm saying.
14 I'm not saying that's the way you should go.

15 DR. WEISS: Dr. Mathers.

16 DR. MATHERS: Clinicians make a similar
17 kind of assessment all the time in dealing with
18 patients, a relative risk based on the patient's
19 individual circumstances. It may be a little more
20 difficult here but I'm certainly willing to take a
21 shot at it. Given that, if you set the age too high,
22 the patients don't need this because they've all got

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1 cataracts. Then they undergo a higher risk for
2 cataract because the endothelial cell loss in cataract
3 is higher than this.

4 DR. WEISS: I would add that you are
5 starting with someone who has a visual decrease that
6 is corrected where these people do not.

7 DR. MATHERS: That's right, but it plays a
8 role here.

9 DR. WEISS: Yeah.

10 DR. MATHERS: Because the cataract surgery
11 fixes the myopia, they are induced to have that
12 procedure even if they don't have a cataract. I would
13 say over 40, high myope nine or higher and an
14 endothelial cell count of 2,500 would give you a
15 window of 10 to 15 years of patient age where they are
16 going to be okay for 30 years or so and when you are
17 40 to 50 years old and you are projecting 30 years
18 downstream, that's not way out of line.

19 DR. WEISS: It seems to me, though, you're
20 taking the -- you're targeting the presbyope myope to
21 get rid of their myopia and would you not want to give
22 the nonpresbyope the benefit of the fact that the lens

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1 is going to still be able to have some accommodation.

2 DR. MATHERS: But with 38 percent of the
3 population that's going to get this, having a 50
4 percent reduction in 25 years, that's a great
5 reduction so if you go down too far --

6 DR. WEISS: The problem is we don't know
7 what their reduction.

8 DR. MATHERS: I know. That's an
9 assumption based on our best available data. Of
10 course, we would like guidance from Dr. Gray about
11 that. When we're considering that we care about the
12 means but we actually care about the outliers even
13 more, we have to draw a conservative view here and go
14 on a higher rate. That's my opinion.

15 DR. WEISS: Forty.

16 DR. MATHERS: Forty.

17 DR. WEISS: So, Ralph, I can see after
18 some optimism on how this meeting was moving along we
19 can easily get bogged down in an age, in an
20 endothelial cell count, or whatever, but is this the
21 route that you would like us to take in terms of
22 discussing it?

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1 DR. ROSENTHAL: Yes, in general. I think
2 based upon some generalities if you feel the device is
3 acceptable, approvable, we will work on those lines to
4 come up with some answers. We may be coming back to
5 you or individually with questions.

6 DR. WEISS: We're going to have Dr.
7 Grimmatt, Dr. Macsai, Dr. Schein, and then Dr. Van
8 Meter.

9 DR. GRIMMETT: Michael Grimmatt. That
10 first question we answered was do the data provide a
11 reasonable assurance of safety. Around the table we
12 heard no, a couple of uncertainties, but generally it was
13 no. There are two ways to interpret that the way I'm
14 looking at it. One is we think it's unsafe. Or
15 option B, the data was not sufficient to tell us it
16 was safe, the positive affirmation of safety.

17 I'm troubled with if the conclusion is
18 truly it's unsafe, if we believe that is the case,
19 then approving it for over 2,500 cells greater than 9
20 diopters at a certain age, we are allowing a patient
21 to consent to an unsafe procedure simply because
22 there's no other alternatives. I don't agree with

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1 that.

2 I think that if we believe that it's not
3 safe, then we need to have sufficient data to prove
4 that it is reasonably safe. I just want to clarify
5 with the panel by voting no on that first question
6 we're thinking it's unsafe or we're not sure that it
7 is safe? What did we think?

8 DR. WEISS: Dr. Macsai.

9 DR. MACSAI: You want me to answer Dr.
10 Grimmett's question, Dr. Weiss? Is that the question?

11 DR. WEISS: I guess Dr. Grimmett would
12 like you to answer his question.

13 DR. MACSAI: Well, my answer to Dr.
14 Grimmett's question would be, based on the data that I
15 was given to evaluate, I would say not safe. Not
16 approvable based on the endothelial cell data.

17 DR. WEISS: I would actually want -- I'm
18 going to narrow your question. When we talk about
19 endothelial cell count going down, is it not safe
20 because your count is dropping or is it really only
21 unsafe if you get to the critical point which we,
22 unfortunately, can't determine here that your cell

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1 count causes corneal edema? Which one of those is it?

2 DR. MACSAI: It's the same.

3 DR. WEISS: I think one of them we don't
4 have the answer to. One of them we don't have the
5 answer to. It looks like we know your cell count
6 drops off for a period of time but what Dr. Mathers
7 and Dr. Huang, I think, were suggesting is that if we
8 suppose it's 1.7, 1.8 percent per year for 20, 30, 40
9 years, if you're going by that, how can we make it so
10 that your corneal function will still be good enough
11 so that even if you have a lower endothelial cell
12 count it won't have any -- it won't have the same
13 import as the concern that many people have raised
14 here of the fiasco with the old anterior chamber IOLs.

15 If there is some way not to guarantee but
16 to give you a better chance that you'll have the
17 critical number of endothelial cells. Because, of
18 course, with this sort of device, we will never be
19 able to prove it's safe unless we review this in 20,
20 30 years which is also not reasonable.

21 DR. MACSAI: Are you asking me?

22 DR. WEISS: I guess so.

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1 DR. MACSAI: Then I would say to you if is
2 the \$10 million question here. If it's 1.8 or if it's
3 1.9. That if is based on nonstandardized data and I
4 have personal concerns about making an if on something
5 that I couldn't scientifically validate or analyze.

6 An if that is going to go out into the
7 general public, not into the creme de la creme
8 surgical hands, be used on patients who have
9 alternatives for vision. I've said this before at
10 this table, people aren't dying out there from myopia.
11 It's not AIDS.

12 DR. WEISS: Dr. Rosenthal, do you have a
13 comment?

14 DR. ROSENTHAL: You can deal with some of
15 these issues by putting contraindications in the
16 labeling and making the issue a liability for the
17 surgeon himself. That's just an option. We've done
18 that before, as you well know.

19 DR. WEISS: The medical community would be
20 glad to hear about it.

21 DR. GRIMMETT: Can you define that a
22 little better?

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1 DR. ROSENTHAL: You can say
2 contraindicated under the age of such and such. Would
3 a surgeon go to the trouble of putting it in somebody
4 under that age with FDA labeling saying it's
5 contraindicated? They can do it as a practice of
6 medicine.

7 They can use any device that's on the
8 market in anybody they want at anytime as a practice
9 of medicine. You know that. And for not even the
10 indication. But would they if you put certain
11 warnings and contraindications in labeling? I don't
12 know the answer to that.

13 DR. WEISS: Dr. Schein.

14 DR. ROSENTHAL: I thought no but maybe I'm
15 wrong. Oliver?

16 DR. SCHEIN: Well, I have hesitation in
17 taking the extrapolated data with all its problems and
18 then doing what Bill Mathers wants to do. I feel it's
19 what the clinician would do, as you say, once
20 something is approved but there are so many ifs in the
21 extrapolation that to then for us to go beyond that
22 and subjectively put in age limits and endothelial

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1 count limits and so forth, I think, is really adding
2 uncertainty to uncertainty.

3 I, frankly, feel that when it comes to
4 endothelial cell counts, there is nothing that the
5 sponsor can do with its current data set to give many
6 of us the long-term assurance we need. That's why I
7 have come back to focusing on these other adverse
8 events which I think are measurable and we can get
9 from further two and three-year data.

10 Now, what could the sponsor bring to the
11 table regarding endothelial cell counts that we
12 haven't seen that might make me change my mind? Well,
13 if there are cohorts of patients in Europe or Canada
14 that are five and 10 years out, even if we don't have
15 preoperative endothelial cell counts, one could easily
16 get endothelial cell counts on this group and then an
17 age match control that didn't have an implant put in.

18 That would, at least, detect large
19 differences that you might ascribe. I think there are
20 things that can be done to address that but there is
21 nothing that they can do with existing data in three
22 years that will make more precise the 30-year data.

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1 DR. WEISS: I would like to just have two
2 more comments and then we're going to have a straw
3 poll on this issue. Dr. Bradley and then Dr. Van
4 Meter.

5 DR. BRADLEY: Just a couple of points. If
6 we take Dr. Schein literally and decide that we really
7 can't make anything of these endothelial cell count
8 data in terms of predicting safety, then it seems to
9 me that we should never ever request these data again
10 because if we cannot use them, they are really a waste
11 of time.

12 I think, although in difference to Dr.
13 Schein, implicitly around the table everybody is
14 inferring the future from these data. In fact, we are
15 of the belief, although implicit, that, in fact, we
16 can predict the future from these data. That's why we
17 collect these data and that's why we are here
18 discussing them right now. I have a feeling although
19 on strict statistical grounds you're right. We simply
20 can't predict the future from them. We are doing it
21 and we in some ways are obliged to do that.

22 Second point I would like to make is that

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1 if we set the criteria for who may or may not obtain
2 this procedure based upon the likelihood that they
3 will during their lifetime suffer a dangerously low
4 level of endothelial cells based upon the data that we
5 have now, it seems that it would be in the sponsor's
6 self-interest to collect longer-term follow-up data to
7 try and see if the curve, in fact, flattens out and
8 then these probabilities will start to change.

9 In fact, the curve that Dr. Stulting
10 presented to us would start to lower or change shape
11 and the number of patients who could be safely
12 included might expand.

13 Of course, the converse could happen and
14 we might find the number of patients who could be
15 safely included -- safely employ the procedure might
16 decrease with those data but it would be incumbent
17 upon the sponsor to collect those data to try to give
18 us better predictability and potentially expand the
19 range of patients who could safely use the procedure.

20 DR. WEISS: Dr. Van Meter.

21 DR. VAN METER: We know the risk of
22 endothelial cell loss cannot be determined from the

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1 technology that we have. I think the risk of cataract
2 formation is fuzzy from the data that we have, but we
3 do know the surgical skill affects both. The surgical
4 procedure of implanting the lens is probably more the
5 variable than the lens itself is.

6 I wrote down the same numbers that Dr.
7 Mathers did, incidentally, before I heard his. I
8 think in the patients that are greater than 9 diopters
9 myopic, patients have 2,500 cell count, and I use 30
10 instead of 40 because I think people that are 30 years
11 old can make better decisions than patients that are
12 21. Anectodally it seems like many of the refractive
13 surgery problems that come from elective patients
14 often are in younger patients rather than older
15 patients just because of the processing.

16 We should remember that there are not that
17 many high myopes around so to ask the sponsor to
18 gather a number of patients, I suspect they have
19 thrown their nets fairly widely thus far to find the
20 patients that we have.

21 This is different than the -4 to -6 group.
22 I feel like with appropriate labeling there is a

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1 subset of the population who can be well served by
2 this device and for whom the risks and the benefits
3 are favorable. I think that this would come with
4 appropriate labeling.

5 DR. WEISS: So that's going to be the last
6 word on this particular issue but what I did want to
7 do is sort of have a poll at this point separating it
8 into the two camps basically. The one group believing
9 that this is not safe and the other group with the
10 thoughts that this is safe in certain situations which
11 can be addressed in labeling and/or post-market
12 studies and/or requests for analysis of the data --
13 reanalysis of the data that is already present.

14 So with that in mind, what I would like
15 the panel to do is if you can raise your hands if you
16 feel that this is not safe. When I say not safe, I
17 mean the issues cannot be address post-market.

18 They would have to be addressed premarket
19 so you don't have enough data at this point to say
20 that this is safe with the data that you have and you
21 would not feel comfortable in addressing the issues
22 with the stratification and labeling.

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1 DR. SCHEIN: So the question is is the
2 data we have to date does it demonstrate --

3 DR. WEISS: Safety.

4 DR. SCHEIN: -- on its own today does it
5 adequately demonstrate safety.

6 DR. WEISS: To the level that you would
7 not be -- maybe I'll rephrase it in the other
8 direction because I think I'll have a better chance of
9 getting a vote in the other direction.

10 Those of you who feel that the safety
11 issues that are of concern can be addressed with
12 stratification of endothelial cell count and age in
13 the labeling and, in that case, if you got those put
14 in the labeling, you would feel more confident about
15 giving this your vote for reasonable safety, can you
16 raise your hand?

17 DR. VAN METER: I'm confused.

18 DR. WEISS: You're confused.

19 DR. VAN METER: We're voting that it is?

20 DR. WEISS: We're saying it's safe enough.

21 It's not a vote. This is just a poll.

22 DR. VAN METER: Straw poll.

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1 DR. WEISS: A straw poll that it's safe
2 enough that your concerns about safety could get
3 addressed in labeling modifications. Are you clear on
4 that?

5 DR. VAN METER: Yes. Thank you.

6 DR. WEISS: Okay. Now can we have a poll
7 of that again? If you could raise your hands. Dr.
8 McMahon is that -- okay. We have how many?

9 MS. THORNTON: Five.

10 DR. WEISS: Okay. Those of you who did
11 not raise your hands, what I would like is a vote how
12 many of you feel that you need more premarket data to
13 decide whether this is safe?

14 DR. WEISS: Dr. Rosenthal, and FDA, would
15 that give you enough of a poll on those first two
16 questions? Are you satisfied with that? Okay. Seven
17 to five that was. It doesn't matter. It's a poll and
18 polls are polls.

19 FDA again. This is the season for polls
20 and we're in Washington and we know they can change.
21 The proposed statement of indications read, "The
22 reduction or elimination of myopia in adults with

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1 myopia ranging from -5 to less than -20 with less than
2 two degrees of astigmatism at the spectacle plane,
3 patients with documented stability of refraction for
4 the prior six months as demonstrated by spherical
5 equivalent change of less than or equal to 0.5
6 diopters.

7 Does the panel recommend any modifications
8 to the proposed statement of indications with respect
9 to..." There are three parts to this question. (a)
10 Minimal anterior chamber depth. Anterior chamber
11 depth of less than 3.2 mm were excluded in this
12 study." We are going to go around on this one. We
13 are going to start with Dr. Huang. Do you think there
14 should be any modification in the proposed statement
15 that the minimal anterior chamber depth should be 3.2
16 or greater?

17 DR. HUANG: Yes. Also proposed age
18 limitation as well as the --

19 DR. WEISS: We're just going to answer
20 that particular one and then we'll get into others.
21 Is that agreeable to you or you would like a different
22 anterior chamber depth?

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1 DR. HUANG: It's agreeable.

2 DR. WEISS: Dr. Smith.

3 DR. SMITH: Greater than 3.2 is agreeable.

4 DR. WEISS: I think right now it would
5 read greater or equal to 3.2. Am I correct?

6 DR. LEPRI: No. I think it would be
7 greater than 3.2.

8 DR. WEISS: Oh, just greater than 3.2.

9 DR. LEPRI: It was those that were 3.2 and
10 less.

11 DR. WEISS: Okay. Fine.

12 Dr. Coleman.

13 DR. COLEMAN: Greater than 3.2 is
14 agreeable.

15 DR. WEISS: Dr. Casey.

16 DR. CASEY: I agree.

17 DR. WEISS: Dr. Mathers.

18 DR. MATHERS: Greater than 3.2.

19 DR. WEISS: Dr. Grimmett.

20 DR. GRIMMETT: Ditto, greater than 3.2.

21 DR. WEISS: Dr. Macsai.

22 DR. MACSAI: I guess greater than 3.2 but

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1 I'm a little bit confused about how we are going about
2 this.

3 DR. WEISS: We're just answering the
4 Agency's questions.

5 DR. MACSAI: It definitely has to be
6 greater than 3.2.

7 DR. WEISS: Dr. Bradley.

8 DR. BRADLEY: I agree.

9 DR. WEISS: Dr. McMahon.

10 DR. McMAHON: As I.

11 DR. WEISS: Dr. Bandeen-Roche.

12 DR. BANDEEN-ROCHE: Yes.

13 DR. WEISS: Dr. Schein.

14 DR. SCHEIN: Yes.

15 DR. WEISS: Okay. So you have the panel's
16 answer on that one. Everyone agrees.

17 (b). Maximal pupil size. The two models
18 of the ARTISAN are intended for patients with pupil
19 sizes up to 5.0 mm and up to 6.0 mm. So the question
20 on this one is what recommendations would you -- well,
21 can you restate the question? What is your question?

22 DR. LEPRI: I would restate the question

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1 as does the panel recommend a maximum or minimum size
2 pupil with respect to the available model size.

3 DR. WEISS: So the panel could also say
4 that the nighttime pupil size should not be any larger
5 than the optic if they wanted to say that?

6 DR. LEPRI: Yes, that's fine.

7 DR. WEISS: So the way I'm going to do
8 this is what would your statement be as regards to
9 pupil size? Do you think it's relevant? Do you think
10 it's not relevant? Is there a maximal pupil size that
11 you would recommend photopic, scotopic?

12 Dr. Huang.

13 DR. HUANG: I prefer your last statement
14 using the optical size up to the size of the mesopic
15 pupil.

16 DR. WEISS: That was my statement. I will
17 just let you know that is based on absolutely no
18 evidence whatsoever but that was my statement.

19 Dr. Smith.

20 DR. SMITH: At present there's no evidence
21 to suggest that pupil size did -- it wasn't correlated
22 to any of the visual phenomena so I'm not basing it on

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1 any evidence but nighttime pupil size of no greater
2 than the size of the optic.

3 Dr. Van Meter.

4 DR. VAN METER: The pupil size of 5 and 6
5 as is written here is fine.

6 DR. WEISS: Dr. Coleman.

7 DR. COLEMAN: I agree with Dr. Van Meter.

8 DR. WEISS: Dr. Casey.

9 DR. CASEY: I agree as well.

10 DR. WEISS: So I just want to get
11 clarification, Dr. Lepri. The way it's presently
12 written is the pupil size, is that mesopic should not
13 be -- it should be 5 or less if you're using the 5 mm
14 optic and it should be six or less if you are using
15 the 6 mm optic?

16 DR. LEPRI: That would be correct because
17 that would be the circumstances which we would have
18 concern for the potential --

19 DR. WEISS: Is that how it presently reads
20 or are we now changing things by saying that?

21 DR. LEPRI: It's not in the indication
22 statement.

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1 DR. WEISS: It's not --

2 DR. LEPRI: Those are the available
3 models. In light of the data that was presented with
4 the questionnaire is with respect to development of
5 symptoms, problems, and complaints, we wanted to know
6 if the panel had a recommendation.

7 DR. WEISS: We are sort of getting
8 consensus here but I do want to reiterate that we
9 don't have a lot of data to go along with our biases.

10 This is how a lot of us do refractive surgery but
11 then, again, there is the one article not showing
12 there's any correlation so we should just be careful
13 and put some thought into it while this recommendation
14 is being made. Of course, biases are a stalwart part
15 of practicing medicine.

16 Dr. Casey.

17 DR. CASEY: I agree.

18 DR. WEISS: You agree? Dr. Mathers.

19 DR. MATHERS: Respectfully I disagree. I
20 don't think the data supports the restriction.

21 DR. WEISS: Okay. So one for no
22 restriction.

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1 Dr. Grimmett.

2 DR. GRIMMETT: Intuitively I believe that
3 having the lens optic smaller than the pupil size is
4 probably a bad idea but basing it on the data in and
5 of itself, I didn't find evidence that was the case so
6 I agree with Dr. Mathers.

7 DR. WEISS: Dr. Macsai.

8 DR. MACSAI: I would agree with Dr. Van
9 Meter and I would ask that the incidences of pr-op
10 response no and post-op response yes for glare,
11 starburst, halos as stratified by mesopic pupil size
12 be included.

13 DR. WEISS: Can you add that later when we
14 get into labeling recommendations?

15 DR. MACSAI: Sure.

16 DR. WEISS: Just hold that thought.

17 Dr. Bradley.

18 DR. BRADLEY: I think it's clear that
19 theory predicts that if the pupil is larger than the
20 optic zone, you are going to have a whole slew of
21 optical problems. The fact that they didn't appear in
22 this group of patients who happen to have a pupil size

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1 larger than the optical zone seems to contradict
2 theory so where does that leave us? Do we go with the
3 data or do we go with theory? I think at this point
4 you can't make that choice with any certainty.
5 Perhaps that has to be laid out to the patient.

6 DR. WEISS: So you might not put the
7 recommendations in there but you might put in labeling
8 that there is no information as to the impact of the
9 optic size versus the pupil in terms of things? Is
10 that sort of what --

11 DR. BRADLEY: You can state the data of
12 the study but I think it would be prudent also to
13 mention that theory says there should have been
14 effect. It's a bit odd that they didn't find it.

15 DR. WEISS: So you would not put in there
16 that it is limited in terms of the preexisting pupil
17 size? You're putting data in the labeling as opposed
18 to saying this is contraindicated if you have a 9 mm
19 pupil and using a 6 mm optic?

20 DR. BRADLEY: Correct.

21 DR. WEISS: Dr. McMahon.

22 DR. McMAHON: I feel as Dr. Bradley does.

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1 DR. WEISS: Dr. Roche.

2 DR. BANDEEN-ROCHE: I defer to my vision
3 science colleagues. I don't feel that the data bore
4 very strongly on the question.

5 DR. WEISS: Dr. Schein.

6 DR. SCHEIN: I can't see any advantage to
7 using a 5 mm optic when 6 mm covers the same dioptic
8 range.

9 DR. WEISS: If you have an 8 mm pupil is
10 that a contraindication for getting this lens?

11 DR. SCHEIN: I have no idea.

12 DR. WEISS: I'm going to have a poll on
13 this one, too.

14 Dr. Grimmett.

15 DR. GRIMMETT: Dr. Grimmett. I'm not
16 exactly sure the advantage of the 5 mm but just
17 intuitively if these are myopic lenses they would be
18 thicker at the periphery and if you have a relatively
19 shallow anterior chamber going a smaller diameter
20 would keep the lens further away from the corneal
21 endothelium so maybe the 5 mm optic is meant perhaps
22 -- I don't know. Perhaps it's meant better for

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1 patients with shallower anterior chambers.c

2 DR. SCHEIN: Your logic makes sense but if
3 you are now going to restrict it to 3.2 mm or larger,
4 that probably doesn't exist anymore as an issue.

5 DR. WEISS: I also recall, and this is not
6 a question I ask sponsor, that one of the lenses had
7 double the number of lens opacities and I thought it
8 was the smaller optic. I don't know if anyone
9 remembers that.

10 So we're going to have a poll on this one.

11 For those of you who want to have something in
12 labeling or indications that this would be indicated
13 if you're pupil size is the same size or smaller than
14 the optic size, that was a necessary part of this.
15 For those of you who would like that in labeling, can
16 you raise your hand in the affirmative?

17 So Dr. Huang, Dr. Van Meter, Dr. Coleman.

18 And for those of you who did not vote in the
19 affirmative, what I would like is a straw poll of
20 those of you who would then want something in labeling
21 to indicate the theory versus the practice. Namely,
22 what Dr. Bradley was mentioning, that theoretically

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1 this should make a difference, although it wasn't
2 shown in this study.

3 Basically what I see is the majority of
4 you would like this issue addressed in labeling rather
5 than in indications to say that for optical reasons
6 this might make a difference.

7 DR. SCHEIN: It may.

8 DR. WEISS: It might make a difference.

9 DR. SCHEIN: May is a very powerful word.

10 DR. WEISS: But we didn't prove it in the
11 study so this might be something you want to think
12 about and that would be in patient labeling as well as
13 physician labeling.

14 Dr. Macsai.

15 DR. MACSAI: Dr. Macsai. Is this the
16 appropriate time to talk about the glare and halos and
17 starbursts for labeling or no?

18 DR. WEISS: Coming up soon.

19 DR. MACSAI: Okay. I'll wait.

20 DR. WEISS: Hold that thought. We are
21 coming up to it soon.

22 3(c). Minimum preoperative endothelial

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1 cell density. The outcomes of ECC change was reported
2 in No. 1 above could be used to determine acceptable
3 minimal endothelial cell density. I think what we're
4 speaking about is what was brought up by Dr. Huang and
5 Dr. Mathers, a template for --

6 Perhaps, Dr. Lepri, this might be the time
7 to mention minimal age in association with minimal
8 endothelial cell count with that age. Maybe we should
9 first talk about minimal age, get a little consensus
10 on that, and then we can go to minimal endothelial
11 cell count that would be associated with that age.

12 Dr. Van Meter mentioned 30. Dr. Mathers
13 mentioned 40. Why don't we go around. Dr. Schein. I
14 know this is sort of contrary since --

15 DR. SCHEIN: We are talking about
16 labeling. We haven't talked about the big questions
17 yet.

18 DR. WEISS: We're not talking about
19 labeling. We're just talking about indications which
20 is a separate issue from safety.

21 DR. GRIMMETT: You can only ask the five
22 who voted yes on that option. The other seven don't

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1 think that's the right thing.

2 DR. WEISS: You don't feel comfortable?
3 If you don't have an answer, you don't have to have an
4 answer, in other words. If you don't have an answer
5 to that one, that's fine.

6 Dr. Bandeen-Roche, do you have an answer?

7 No. Dr. McMahon, do you have an answer?

8 DR. McMAHON: Not simply but I propose a
9 different way of looking at it if you want to get
10 around to it.

11 DR. WEISS: Sure. Give us your way of
12 looking at it.

13 DR. McMAHON: Again, I'm not sure if I'm
14 comfortable with the whole provability issue but for
15 the sake of argument, let's say we did. One way to
16 address this problem is to first assign a tolerance
17 level of the number of eyes that would be based upon
18 projected extrapolations that we currently have that
19 would reach 1,200 cells per square millimeter.

20 For example, if you assigned a value over
21 a 30-year exposure rate of, let's say, one percent,
22 then you can draw a table from that that is composed

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1 of age and preoperative endothelial cell count to put
2 you within that expected tolerance rate.

3 Under that circumstance you might hedge
4 your bet, as Dr. Mathers has been trying to get to for
5 some time. At least in theory. What that would do is
6 for potentially younger individuals, and personally if
7 we are going to do this, I would say probably a
8 minimum of age 30, probably in the -9s as we're
9 talking about. You can then actually stratify for any
10 individual. You actually have to take into
11 consideration some life table analysis or there might
12 be a difference in that for men versus women. I think
13 the possibility to construct that kind of table would
14 not be all that difficult to do.

15 DR. WEISS: So we're talking about is age
16 30 minimum -9, minimum amount of myopia, and 1,200
17 cell count at your death whatever your death might be
18 and have someone figure out that actuarial table.

19 DR. McMAHON: That would be sort of -- you
20 could either do it that way or you could just do it
21 assigned on a 30-year exposure rate.

22 DR. WEISS: The other variable in there is

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1 what is the percentage. Are you using 1.8 percent per
2 year?

3 DR. McMAHON: No, I used the one percent
4 rate of individuals reaching 1,200.

5 DR. WEISS: What is the cell loss rate per
6 year?

7 DR. BRADLEY: Whatever the data shows.

8 DR. McMAHON: That comes from the
9 extrapolated information we have at the moment. As
10 new data appears over time, those tables could be
11 adjusted.

12 DR. WEISS: Dr. Bradley.

13 DR. BRADLEY: The issue that we have to
14 address if we follow Dr. McMahon's suggestion is what
15 percentage are we willing to tolerate of these eyes
16 reaching this critical level of 1,200 count? Is it
17 one percent? Is it two percent? Is it 5 percent? If
18 we can give the FDA that number, then they can come up
19 with the -- they can delineate those eyes that can
20 safely have the procedure and those that cannot.

21 DR. WEISS: So we're going to back up one
22 because we are adding another part to the question.

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1 What percentage of the -- Dr. Schein, do you have an
2 opinion on that? If you don't, I see Dr. Bandeen-
3 Roche does in terms of percentage of eyes that you
4 could see getting to the minimum endothelial cell
5 count right before they expire.

6 DR. BANDEEN-ROCHE: Actually I just wanted
7 to follow up not on a comment about what that number
8 should be but just if we say FDA can calculate that
9 number, they can also calculate how variable that
10 projection is to within lots and lots of uncertainties
11 about the model. That is, of course, equally
12 important.

13 DR. WEISS: Did you have a percentage that
14 you might have in your mind, Dr. McMahon, as far as
15 acceptable percentage to get to 1,200?

16 DR. McMAHON: I picked a very low number,
17 one percent based upon the uncertainties that we're
18 dealing with.

19 DR. WEISS: You're saying one percent of
20 patients you would like to get to 1,200 in 30 years?

21 DR. McMAHON: Yes.

22 DR. WEISS: That's pretty stringent.

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1 Dr. Bradley, do you have a percentage that
2 you would want to get there in 30 years also one
3 percent?

4 DR. BRADLEY: I would certainly refer to
5 my colleagues who deal with these problems on a daily
6 basis.

7 DR. WEISS: Okay. With that deference in
8 mind, Dr. Macsai. Or how would you like to handle
9 this question? First we're going to start with age.
10 As long as everyone is handling everything at once,
11 why don't we do it all in one package. So age, number
12 of years, and percentage you want to get to 1,200.

13 DR. MACSAI: This is quite the conundrum
14 because you can't randomly pick age, number of years,
15 or the actual number. If we're going to work
16 backwards, we look at actuarial tables, as Dr. McMahon
17 intimated, and we say that at 75 years the average
18 female develops cataracts and for cataract surgery we
19 want her to have -- I'm making it up -- 1,200 cells.

20 Then we take Dr. Gray's assumed -- and you
21 know what happens when we assume -- assume the rate of
22 endothelial cell loss and work backwards. From that

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1 we determine the age. That's how you do it. I can't
2 give you a random age or a random number but I can
3 tell you that I think going into cataract surgery with
4 1,200 cells if you assume 10 percent loss from the
5 surgery, that brings you down to 1,080, you should be
6 able to hang in there for a while. But then you have
7 to look at the fact that everyone is living longer and
8 I think it's a complicated actuarial problem that I'm
9 not sophisticated enough to solve.

10 DR. WEISS: Dr. Lepri, if we gave you that
11 sort of guidance and said we want to start at what was
12 just suggested, at the older end and work backwards to
13 then determine the age and then determine the minimal
14 endothelial cell count, is that something that Agency
15 could work with?

16 DR. LEPRI: From my perspective it would
17 be but I would certainly consult with everyone here to
18 see if they are in agreement.

19 DR. WEISS: I see --

20 DR. LEPRI: It would make much more sense
21 taking into effect those factors that Dr. Macsai
22 identified which are very important.

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1 DR. WEISS: I see nods in the affirmative
2 that we could work backwards.

3 Dr. Grimmett, you had a comment?

4 DR. GRIMMETT: I'm clarifying Dr. Macsai's
5 suggestion starting backwards if we specify the target
6 cell count at death.

7 DR. MACSAI: I don't know the information.

8 DR. WEISS: Okay. Dr. Mathers is chomping
9 at the bit.

10 DR. MATHERS: What we are not asking them
11 to comment on is whether we think Dr. Gray's
12 assessment
13 -- what the endothelial cell loss rate is that we
14 should assume. Of course, we don't really know that
15 but we have to go with the conservative, i.e., high,
16 loss rate because it's got to account for the
17 relatively high percentage of outliers versus the
18 mean.

19 I do think that Dr. Gray's assumption of a
20 two percent loss rate, which is 38 percent will have a
21 two percent loss rate. That's a fairly high rate and
22 if we just start with -- if we use that we can get

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1 some table that we can at least look at. The whole
2 thing depends on what you think is the loss rate, 1.8,
3 1.9, 2.0, 3.0. It changes enormously.

4 DR. WEISS: What I'm wondering if you're
5 going to start with a 75-year-old woman and an
6 assumption of a two percent loss rate are we going to
7 allow three people to have this phakic IOL because
8 those are the only ones who qualify after we do this
9 calculation? I don't know the answer to that.

10 Dr. Van Meter?

11 DR. VAN METER: I think you should be
12 extremely conservative with your loss rates because,
13 No. 1, when some of these 40-year-olds get to be 65,
14 they might need cataract surgery for other reasons
15 anyway and in 30 years from now there is going to be a
16 real shortage of donor corneas.

17 DR. WEISS: Because of LASIK you're
18 saying?

19 DR. VAN METER: Yes.

20 DR. WEISS: Dr. McMahon.

21 DR. McMAHON: I would propose that you use
22 not only the mean but the lower quartile of those

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1 projections as your basis. That way you have the
2 fastest droppers and then the average as well so you
3 have --

4 DR. VAN METER: That would be a 2.1 or
5 2.2.

6 DR. McMAHON: I'm talking lower quartile
7 of that projection. The worse guise, all right? So
8 that's a harder criteria to meet than the mean is.
9 But if those are real is what you want to know.

10 DR. WEISS: Dr. Mathers.

11 DR. MATHERS: The two percent would not
12 quite get there but it would be close. I certainly
13 think that's a reasonable way to do it, too. That's
14 what we're talking about and I think that's a
15 reasonable discussion point.

16 DR. WEISS: Dr. Huang.

17 DR. HUANG: I just want to clarify that
18 endothelial density and the age is a dependent
19 phenomenon so when you are younger, you will have a
20 higher endothelial density. When you are older you
21 have a lower endothelial density so arbitrary number
22 doesn't really justify the safety issue. If you were

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1 going to put a age limitation, 30 years of age or
2 higher for this surgery, then you probably should say
3 is 30 years or higher with endothelial density of
4 certain amount and 40 years of age. It's a sliding
5 scale rather than a fixed scale.

6 DR. WEISS: I think what we're presently
7 working on is Dr. Macsai's suggestion of looking at it
8 from the older age and working backwards and then
9 having the agency come up with the sliding scale
10 perhaps on a two percent endothelial cell count than
11 to indicate what you might need at the lower age which
12 would not be determined at this meeting because we
13 don't know what that sliding scale looks like yet.

14 Dr. Grimmett, did you have any other
15 comments on this point? Are you in agreement with
16 trying to go about things that way?

17 DR. GRIMMETT: Yes.

18 DR. WEISS: Dr. Mathers, any other
19 comments on this point?

20 DR. MATHERS: No, I've said enough on
21 that, I think.

22 DR. WEISS: Dr. Casey? Dr. Coleman? Dr.

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1 Van Meter?

2 DR. VAN METER: Fine.

3 DR. WEISS: Dr. Smith? Dr. Huang? So
4 what I understand is there's consensus from the panel
5 to defer to FDA and say we have an elderly cataract
6 patient. Let's work backwards, use a two percent cell
7 loss, and then calculate.

8 How many cells, Dr. Macsai, do you want
9 this cataract patient -- what percentage of people
10 should have a 1,200 cell count before -- what is the
11 Agency using for the cell count when this 75-year-old
12 woman has cataract surgery? What is her cell count?
13 What do you want it to be? If I don't hit you to get
14 your number when they're 30, I'm going to hit you to
15 get their number when they're 70 or 75, whatever.

16 Dr. Schein.

17 DR. SCHEIN: If you're fishing for a
18 number, 1,600.

19 DR. WEISS: 1,600. And what percentage of
20 people do you want to have 1,600?

21 DR. SCHEIN: Well, it gets to the
22 endothelial loss with cataract surgery. Mean is

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1 around 10 or 12 percent. Mean.

2 DR. WEISS: Okay.

3 DR. SCHEIN: I think about 20 percent --

4 DR. MACSAI: That's 2.5 percent per year.

5 DR. SCHEIN: They lose that acutely and
6 that's the mean. I think even if you were down to a
7 quartile, it's much more than 10 percent.

8 DR. WEISS: You know what? Dr. Lepri and
9 also the Agency, do you require that level of detail
10 from us or you do not? Because if you do not, I don't
11 want to go there. If you do not, fine, we're not
12 going there. That's easy.

13 DR. BRADLEY: Just to make a point,
14 although it seems imminently sensible for us to lay
15 out the guidelines the way we have and for the FDA to
16 do the calculations, we should be aware that we may
17 end up approving a device for which nobody is
18 qualified to have it.

19 DR. WEISS: I had three patients that
20 you've gone down a couple of notches.

21 Dr. Lepri, is there any other information
22 you need for us on Question 3? Otherwise, we'll go on

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1 to labeling recommendations.

2 DR. LEPRI: I think we go on to Question
3 4.

4 DR. WEISS: Okay. So now Question 4. Do
5 the panel members have any additional labeling
6 recommendations? Dr. Macsai, now is the time.

7 DR. MACSAI: I have to wake up. Okay. I
8 would want the table of pre-op response no, post-op
9 response yes, symptoms of glare, starbursts, halos
10 included in labeling for patients and physicians with
11 the mesopic pupil size as the segregation tool.

12 DR. WEISS: So we are going to go around
13 the table in terms of individual panel members and any
14 labeling additions. We'll start with Dr. Huang. No?
15 Dr. Smith.

16 DR. SMITH: Janine Smith. I would like
17 the panel to think about whether they would like to
18 include any labeling recommendations regarding the
19 patient having failed contact lens wear, the patient
20 not able to get full vision correction, whatever their
21 potential vision is, because these are the high myopes
22 that we're talking about with contact lenses so that

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1 these people would have explored every other option
2 for vision correction before proceeding to having the
3 surgery.

4 DR. WEISS: I think you should just list
5 alternatives rather than forcing someone to try
6 contact lenses. I think the sponsor has in their
7 handbook listed the alternatives of refractive
8 surgery, RK. I believe they must have listed contact
9 lenses.

10 I don't think they listed orthokeratology
11 but that is a much lower myopic range so it probably
12 would be irrelevant. I personally, and we can get
13 everyone else's opinion, don't think you should have
14 to force someone to try contact lenses before they
15 have this. Does anyone feel that you should, that one
16 of the indications should be contact lens failure?

17 Dr. Van Meter.

18 DR. VAN METER: I would just take that.
19 One of the things that I would suggest is since there
20 was some difficulty in refracting the really high
21 myopes and some of that led to lens exchanges, it
22 might be worth trying to do a contact lens refraction

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1 on these patients diagnostically to pick the lens
2 power.

3 DR. WEISS: Good suggestion. That's a
4 very good suggestion.

5 Dr. Coleman.

6 DR. COLEMAN: For labeling?

7 DR. WEISS: Yeah, did you have any other
8 labeling additions? Dr. Smith, Dr. Van Meter, any
9 other labeling?

10 DR. VAN METER: No, ma'am.

11 DR. WEISS: Dr. Coleman.

12 DR. COLEMAN: Yes, I do. For the draft
13 directions for use, page 10, they have for precautions
14 medically uncontrollable glaucoma. I don't think that
15 was shown. I would just say 8 should be glaucoma.

16 In addition, for No. 7 they say secondary
17 glaucoma and I'll just tell you what I think it should
18 be. It should be elevated eye pressure has been
19 reported occasionally in patients who have received
20 lens implants.

21 DR. GRIMMETT: What page are you on?

22 DR. COLEMAN: I'm on the labeling.

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1 DR. GRIMMETT: Labeling? Okay. Just so I
2 can transcribe.

3 DR. COLEMAN: Page 10.

4 DR. GRIMMETT: Thank you.

5 DR. COLEMAN: So No. 7 is elevated IOP has
6 been reported occasionally in patients who have
7 received lens implants. I have deleted "with
8 controlled glaucoma" because these patients didn't
9 have it. In addition, deleted "secondary glaucoma"
10 because that wasn't really demonstrated. Actually,
11 they had elevated intraocular pressure in patients who
12 may or may not have had glaucoma because they didn't
13 look for it so I deleted "with glaucoma" in that
14 sentence. Do you want me to read it again?

15 DR. WEISS: Can you write it down and then
16 we'll give it to Dr. Grimmert so he'll have it.

17 DR. COLEMAN: The other issue is on page
18 11. Do you have it right there? They have summary of
19 other complications and they have that there's no
20 incidence of macular edema or pupillary block. I
21 disagree that there was no incidence of pupillary
22 block because they did have a patient that they

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1 thought had presumed pupillary block and they had to
2 redo the iridotomy so I think that should be deleted.

3 In addition, they said that they had no
4 incidence of iriditis. I thought an inflammatory
5 response wasn't iriditis so I thought that should be
6 deleted because that's up there in other adverse
7 events.

8 In addition, they said persistent raised
9 intraocular pressure was not reported during the study
10 and I disagree with that, too, because they had about
11 10 patients or approximately slightly less than one
12 percent of subjects who needed medications for
13 intraocular pressure control which I assume was for
14 raised intraocular pressures. That should also be
15 deleted there. It should be mentioned that about less
16 than one percent of the patients did need medications
17 for a long-term intraocular pressure control.

18 In addition, I also would suggest that
19 they include that the effects on patient's risk of
20 glaucoma in the future unknown. In addition, I think
21 they should include the effect on the drainage angle
22 is unknown because they didn't do gonioscopy so you

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1 really can't state what's happening with that.

2 Then in terms of patient labeling, are you
3 ready for that?

4 DR. WEISS: Just with pity to Dr.
5 Grimmett, if you can just describe some of these
6 things. He's doing pretty well.

7 DR. GRIMMETT: My college note taking
8 helps me here immensely so I did pretty well. I got
9 those.

10 DR. COLEMAN: Okay. Page 12 for the
11 patient labeling is very similar warnings which would
12 be glaucoma instead of medically uncontrollable
13 glaucoma. Precautions would be elevated eye pressures
14 have been reported occasionally in patients who
15 receive lens implants and the intraocular pressure of
16 patients should be monitored postoperatively. Once
17 again, I deleted all reference to glaucoma because
18 they didn't really show whether or not patients had
19 glaucoma or not.

20 Then I thought in the index on page 17
21 they should include glaucoma and they should also
22 include intraocular pressure or eye pressure,

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1 whichever one they used. Thank you.

2 DR. WEISS: Thank you.

3 Dr. Casey.

4 DR. CASEY: No additional recommendations.

5 DR. WEISS: Dr. Mathers.

6 DR. MATHERS: No additional
7 recommendations.

8 DR. WEISS: I just had a couple in the
9 patient booklet as well. On page 8 under benefits of
10 the ARTISAN IOL it says, "It may allow you to see
11 clearly at far distances." I would rather say
12 improved distance vision but maybe that is being too
13 picky.

14 The more important one was actually under
15 precautions. I thought it was interesting on page 13
16 the sponsor writes, "The safety and effectiveness of
17 the ARTISAN IOL for the correction of near sightedness
18 have not been established in patients." Gee, that's
19 interesting to put. I don't think that is something
20 we would want in there if it ends up getting FDA
21 approved saying that the safety and efficacy has not
22 been established. I was surprised. You guys should

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1 have someone reread your stuff because that's not a
2 good one.

3 I think we should have something there and
4 I'm sure someone else will speak to this in terms of
5 the long-term effect on corneal function and the
6 potential risk for corneal edema has not been
7 determined because of the lack of long-term data and
8 that in short-term that the endothelial cell count has
9 decreased in the three-year period of time and we
10 don't know what that decrease is going to be or what
11 the curve is long-term. Obviously to wordsmith it.
12 The FDA will wordsmith it a lot better than I just
13 did.

14 Dr. Grimmett.

15 DR. GRIMMETT: Nothing to add at this
16 time.

17 DR. WEISS: Dr. Macsai.

18 DR. MACSAI: I would echo your sentiments
19 about the corneal endothelial cell loss rate being not
20 established as safe. I would also not be happy if
21 this device was marketed as that which improved
22 contrast sensitivity and improved lines of vision one

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1 can read because I think those were the results of
2 magnification and simply taking a spectacle lens which
3 mine when they are dirty do decrease my contrast and
4 eliminating the refractive index problems. I wouldn't
5 like that to be a tool that is used to promote this
6 device.

7 DR. WEISS: The only way I could see you
8 address that is if you said either contact lenses or
9 phakic intraocular lenses may improve vision over
10 spectacles. You could indicate that if you wanted.

11 DR. MACSAI: That would be a good way to
12 do that.

13 DR. WEISS: I would also just add -- I
14 assume someone else will but the same issues with lens
15 opacities long term would go with cornea. We don't
16 know what it's going to be 20 years down the line for
17 lens opacities. Anyone can add anything else they
18 want because 20 years down the line actually we don't
19 know any of these things but certainly lens opacities
20 and corneal endothelial changes are the highest
21 concern it seems.

22 Dr. Bradley.

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1 DR. BRADLEY: First I would reiterate a
2 couple of things. I think the product should be
3 clearly stated that when switching from spectacle
4 correction to this IOL there will be magnification for
5 myopic eyes. That magnification will lead to
6 potential improvements in visual acuity. Make it
7 clear why those improvements are occurring.

8 Second point, and perhaps the most
9 important one, I think both the physician labeling
10 and, perhaps more importantly, the patient labeling
11 should include a very clear understandable statement
12 describing our concerns about the future risks of this
13 product and that, in fact, the criteria for who and
14 who might not be eligible for this procedure are based
15 upon those concerns.

16 Somehow that should be communicated to the
17 patient and, therefore, the risk that they -- the
18 perceived risk that they are about to embark upon by
19 having the procedure. Somehow that risk needs to be
20 communicated to them, although I agree at this point
21 in time we are really just extrapolating to come up
22 with this risk and the patient needs to know that,

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1 too.

2 DR. WEISS: Maybe that's the way to say it
3 is we cannot extrapolate to what the risks will be
4 with A, B, C, D, E.

5 DR. BRADLEY: No, I wouldn't say it that
6 way because I think the fact is that we are suggesting
7 that, indeed, the criteria for who and who is not
8 eligible is based upon that extrapolation. Therefore,
9 we can extrapolate. We are going to do it. I don't
10 think we can sort of palm it off and say who knows
11 what's going to happen in the future.

12 Let them know that this panel and the FDA
13 although we have uncertainties about extrapolating in
14 the future have enough faith in the data to use those
15 extrapolations to guide us in who and who cannot have
16 this procedure.

17 DR. WEISS: I think that would be
18 ultimately determined by the vote that takes place
19 here.

20 DR. BRADLEY: Yeah, but you know what I
21 mean.

22 DR. WEISS: Dr. McMahon.

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1 DR. McMAHON: Nothing additional to add.

2 DR. WEISS: Dr. Bandeen-Roche?

3 DR. BANDEEN-ROCHE: Yes, certainly this
4 does not condition what my vote will be but I would
5 just second and third all the comments about very,
6 very clear section being needed describing what are
7 the risks that we are concerned about and that we have
8 vast uncertainty about what the long-term outcomes
9 will be.

10 DR. WEISS: Dr. Schein. And I would
11 indicate, Dr. Schein, you have the opportunity to
12 suggest any premarket, post-market whatever studies
13 because that has not -- there was not a question about
14 that but this might be the time to say it if you want
15 to.

16 DR. SCHEIN: First, I have a few labeling
17 comments that are based on the draft that was given to
18 me. The first has to do with adverse event recording.
19 The number 662 is listed there and that excludes some
20 of the patients that underwent the procedure in the
21 study. And the rates as written imply that they are
22 based on a full cohort of 662 individuals. In fact,

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1 they imply that it's a three-year study upon which the
2 adverse event rates are calculated and that's not
3 accurate.

4 The term "nonadverse event" I have trouble
5 with that in the main document but to find that in
6 patient labeling I thought was really wrong. I would
7 make the same suggestion as before, that they simply
8 list how many individuals. Not just eyes but how many
9 individuals require additional refractive surgical
10 procedures, additional surgeries or procedures to
11 address complications such as wound leak and lens
12 repositioning, etc., again, on a per-eye and per-
13 person basis.

14 Under complications I didn't see cataract
15 listed. I didn't see lens opacity listed. Perhaps I
16 missed it but I didn't see it under that heading. I
17 think that is the biggest concern in my mind is lens
18 opacities and cataract. When endothelial cell data is
19 presented, I again would not limit it to the means but
20 I would indicate the proportion of losing, 10 percent
21 or 15 or 20 percent, some reasonable thresholds at a
22 specific time period such as two years.

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1 Finally, I would delete this reference to
2 the FDA grid for secondary implants for all the
3 reasons that we discussed before because, again, it
4 gives the wrong impression.

5 Do you really want me to talk about post-
6 market surveillance?

7 DR. WEISS: I guess the way you phrased
8 that, the answer would be no.

9 DR. SCHEIN: I mean, is this the time to
10 do that?

11 DR. WEISS: Well, actually hold on one
12 moment. We are going to have Dr. Van Meter and Dr.
13 Rosenthal, I think, is going to address that.

14 Dr. Van Meter.

15 DR. VAN METER: One quick question. Did
16 we get the risk of dislocation from trauma?

17 DR. WEISS: Actually, that's an excellent
18 point. We should put that in labeling.

19 DR. VAN METER: That's not on my draft and
20 I don't know if it was --

21 DR. WEISS: I had mentioned that should be
22 put in labeling before and I forgot about it so thank

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1 you, Woody. There is risk of dislocation with trauma
2 so if you are engaging in any activities, you might
3 want to avoid them or avoid having this lens.

4 Dr. Rosenthal.

5 DR. ROSENTHAL: I would like to have a
6 sense of the panel regarding a post-market study if
7 the device is ultimately comes to approvability
8 regardless of what the panel votes today.

9 DR. WEISS: What we'll do is we'll finish
10 the labeling issues and I'm going to go on to Mr. Balo
11 and then Ms. Such.

12 MR. BALO: I never had the labeling to
13 review so I can't make any comments but relative to
14 premarket, post-market usually that's done when you're
15 voting in the conditions for the device. You would
16 basically state if you were doing a premark or post-
17 market study.

18 DR. WEISS: We have to decide those things
19 now and then we'll have our vote so that's why we are
20 going to have everyone have their say on these issues
21 before we have a vote.

22 Ms. Such.

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1 MS. SUCH: I have a few issues actually.
2 One is in the two and a half years I've been on this
3 committee I've not seen us approve an age bracket
4 where it's not been in the study. I see that in this
5 patient brochure we're saying about 18-year-olds being
6 approved when the youngest group that has been used in
7 this has been 21 years of age. That's my first
8 comment.

9 My second comment is on putting something
10 in there as I've heard about starbursts. I would like
11 to see something in there about low-level lighting and
12 activities, that that should be a precaution using
13 about starbursts and halos.

14 The last thing -- another thing is about
15 activities. I don't know how to put this without
16 saying boxing but to put something in there, a
17 precaution. There should be some precaution put in
18 there about participating in activities that would be
19 somewhat more eventful for head trauma. That could be
20 anything from operating a jackhammer or something that
21 would be more likely to have that type of activity.

22 I don't know that would particularly do

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1 that but you are more the experts than I but something
2 to that effect. Football is definitely something that
3 you would think about or some of these type of
4 activities. Especially when you're talking about if
5 they were to go ahead and do it for 18-year-olds who
6 were still playing football or doing those type of
7 activities.

8 The other is that I looked at the glossary
9 of this and I have to say that the glossary is very,
10 very, very short and inadequate. Someone really needs
11 to wordsmith this in a way that somebody could
12 actually use the glossary. I have to commend, though,
13 the people that did the introduction to this patient
14 brochure. The beginning of this brochure was very
15 thorough.

16 It gave a lot of information. It gave
17 people a good understanding of what the device was
18 about and explains how the eye worked and it gave a
19 very comfortable lay explanation. Then when it went
20 on further and it went into the precaution, who
21 should, who shouldn't, warnings and things like that,
22 terminology was used that quite frankly I tried out on

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1 people that work at the Lighthouse, a place for
2 vision, and I lost over 80 to 90 percent of the people
3 when I asked terminology.

4 I think that says a lot so you need to go
5 through and look at things that are specifically
6 visually connected and go through and put that in the
7 glossary or don't bother putting a glossary in. I
8 really think a glossary is important that you do put
9 in because people are going to look at that and they
10 are just going to blank out. They really want to know
11 what these words mean. I would put in the beginning
12 of this, "See glossary for further terms." That's all
13 the comments I have.

14 DR. WEISS: Thank you. One thing I just
15 wanted to add with the labeling, we were talking about
16 cataract and corneal decompensation. Just to the
17 Agency, if you could elucidate what that meant in
18 terms of if you have a cataract your vision goes down
19 and you may need surgery and if you have corneal
20 decompensation, your vision may go down and it might
21 hurt and you might need surgery so it makes it
22 something more relevant than something that a patient

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1 couldn't identify with.

2 If we have no other labeling issues, then
3 i'm going to go to a question on --

4 Yes, Dr. McMahon.

5 DR. McMAHON: We had our discussions about
6 some of those minimum criteria. One of the ones was a
7 minimum age of 30 was thrown out there. Current
8 labeling does say 18 or 21. The issue is do we want
9 to address that.

10 DR. WEISS: We can address that but from
11 what I understood, we were going to work backwards on
12 the age starting with an elderly cataract patient with
13 a minimum endothelial cell count of perhaps 1,600 and
14 then seeing what the ages would be.

15 My impression is using a two percent cell
16 loss rate and ending up with 1,600 cells we are going
17 to be much more conservative than what has been
18 presented to us so we are going to have a much older
19 age. But it's probably smart to stipulate a minimum
20 age if my impression is incorrect.

21 Why don't we go around. Dr. Schein, do
22 you have a minimum age that you would suggest for

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1 this? If you don't, you can pass. Dr. Bandeen-Roche?

2 DR. BANDEEN-ROCHE: No.

3 DR. WEISS: Dr. McMahon.

4 DR. McMAHON: 30.

5 DR. WEISS: Dr. Bradley.

6 DR. BRADLEY: No.

7 DR. WEISS: Dr. Grimmett.

8 DR. GRIMMETT: Don't know.

9 DR. WEISS: Yes, Dr. Mathers.

10 DR. MATHERS: Even those don't know. If
11 you have the other stipulation, you don't need the
12 minimum age.

13 DR. WEISS: Dr. Casey. Don't know? Dr.
14 Coleman.

15 DR. COLEMAN: I don't know.

16 DR. WEISS: Dr. Van Meter.

17 DR. VAN METER: I said 30 pulling it out
18 of a hat but I would certainly defer to the table that
19 we're talking about developing.

20 DR. WEISS: But you wouldn't feel
21 uncomfortable going down to 18, would you? Oh, you
22 would?

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1 DR. VAN METER: I would feel uncomfortable
2 going down to 18.

3 DR. WEISS: Uncomfortable going down to
4 18.

5 Dr. Smith.

6 DR. SMITH: Refer to the table.

7 DR. WEISS: Does anyone feel comfortable
8 going down to 18? If anyone does, can you raise your
9 hand? You feel comfortable going down to 18?

10 DR. MATHERS: Uncomfortable.

11 DR. WEISS: Dr. Huang.

12 DR. HUANG: I don't know.

13 DR. WEISS: I think for minimum age for
14 Agency we don't know it but you're getting a sense of
15 the panel it would be older than what was presented
16 rather than younger. Certainly it wouldn't be 18 if
17 the youngest patient they did was 21. At least the
18 people who have expressed an age it has been 30 to 40,
19 in that range, for those who expressed an age. The
20 majority don't have the knowledge or don't want to
21 express an age.

22 We are going to then go on to final

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1 question before a 10-minute coffee break before we
2 have the open public hearing session, closing
3 comments, and then the vote.

4 The final question here is post-market
5 study. Ralph, we don't really need to talk about pre-
6 market study because that's a separate issue. Post-
7 market study. Dr. Schein, you would like a post-
8 market. Can you tell us about this?

9 DR. SCHEIN: I think this device satisfies
10 the criteria that I would suggest are appropriate to
11 request a post-market surveillance. Some of those
12 criteria would be that there's a relatively large
13 population at risk for which there are alternative
14 treatments that are already available with lower risk
15 profiles.

16 The serious complications that we're
17 concerned about, although relatively rare, can be very
18 devastating. The sample size of the premarket
19 studies, 300 patient or 600 eyes or anything in that
20 range, is really inadequate to get an accurate
21 estimate of complications that may be occurring in one
22 in 100, one in 300, one in 500, complication rates

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1 that would be very important were this applied to a
2 large population.

3 The other condition is that there's
4 concern that the rates of complications may actually
5 be different once the product has been approved and
6 the population of patients is larger and the
7 population of surgeons is larger.

8 All of those things taken together, I
9 think, suggest that a post-market surveillance study
10 is appropriate here. As I said before, the purpose of
11 this is to pick up very serious events which are easy
12 to pick up but deemed by everyone to be important such
13 as cataract surgery, corneal transplantation surgery,
14 need for explantation of the device, retinal
15 detachment, perhaps one or two others that others
16 might think about in a large population. To define
17 large, again, I would have to do some calculations but
18 in the order of more than 1,000.

19 DR. WEISS: You want a post-market study
20 going out how long?

21 DR. SCHEIN: Well, I would say two or
22 three years.

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1 DR. WEISS: So you would like five to six
2 years data?

3 DR. SCHEIN: No.

4 DR. WEISS: An additional two to three
5 years?

6 DR. SCHEIN: No, no. This is not on the
7 existing cohort.

8 DR. WEISS: A new cohort.

9 DR. SCHEIN: By definition this is a
10 different cohort after the procedure is penetrated
11 successfully into the market and there's a larger
12 distribution of patients and doctors. It has nothing
13 to do with the existing cohort.

14 DR. WEISS: A new cohort, five to six --
15 how many years?

16 DR. SCHEIN: Two to three years.

17 DR. WEISS: Two to three years of a new
18 cohort with a number of patients being determined by
19 the Agency.

20 DR. SCHEIN: Well, we're talking about the
21 Agency. Based on the way to go about it is to simply
22 look at the precision of an estimate so if you want to

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1 be able to say confidently that retinal detachment is
2 one per 100 and that would be unacceptable, that would
3 generate a certain sample size. We have to go through
4 a process to get there. I don't want to make up a
5 sample size sitting here.

6 DR. WEISS: Does the Agency need anymore
7 information on that or not?

8 DR. ROSENTHAL: I'd like a sense of the
9 panel on the concept.

10 DR. WEISS: The concept for the panel, and
11 please add to this, we have to suggest that we have
12 the least burdensome for the sponsor so this is
13 because you have continued concerns that it might be
14 voted to be reasonably safe and efficacious but,
15 indeed, it might not be reasonable to believe safe, so
16 then you're doing this study. I would assume that is
17 the reason for this. Why do you want the post-market?

18 DR. SCHEIN: For those five or six reasons
19 that I listed a moment ago. Basically I have concern
20 about serious adverse events not being adequately
21 addressed by the premarket study.

22 DR. WEISS: So you are concerned it may

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1 not be reasonably safe.

2 DR. SCHEIN: For example, distinctly
3 burdensome to propose a study that went out long
4 enough to detect long-term corneal edema rates. I
5 think that is infeasible and impractical.

6 DR. WEISS: Again, Dr. Rosenthal, correct
7 me if I'm wrong. Obviously if you had extreme
8 concerns about safety, then you would not be voting in
9 the affirmative for the PMA because to pull a device,
10 while you can do it, is quite difficult. Is that
11 correct, Ralph?

12 DR. ROSENTHAL: No. I mean, if a device
13 ultimately goes on the market that is shown to be in
14 some aspect unsafe, it can be recalled, Dr. Weiss.

15 DR. WEISS: But if you feel -- however, if
16 you feel it's unsafe based on this data, you would not
17 be voting in the affirmative for this PMA.

18 DR. ROSENTHAL: If you feel it's unsafe
19 based on this data, then it does not have a reasonable
20 assurance of safety and efficacy and you will vote not
21 approvable but you won't need a post-market study
22 because it didn't get approved.

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1 DR. WEISS: It didn't get to market.

2 DR. ROSENTHAL: But if it ultimately -- if
3 the company ultimately fulfills the conditions under
4 which you have voted not approvable and then gets
5 approvable nod, then knowing about whether the panel
6 would think a post-market study is indicated would be
7 very important to us.

8 DR. WEISS: Dr. Schein.

9 DR. SCHEIN: I'm not sure, Dr. Rosenthal,
10 I understand that completely. Were you saying that a
11 sponsor completes a PMA and that it is then either
12 safe or effective or not and if it is safe and
13 effective, there's never any -- there's no calling for
14 further data?

15 DR. ROSENTHAL: I'm not saying that at
16 all.

17 DR. SCHEIN: I misunderstood.

18 DR. ROSENTHAL: I'm saying if there's not
19 a reason -- if this panel does not feel there is a
20 reasonable assurance of safety and efficacy, they will
21 not give an approvable or approvable with conditions
22 recommendation. Therefore, we'll get not approvable.

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1 With a not approvable recommendation we cannot ask
2 the sponsor to do a post-market study --

3 DR. SCHEIN: Now I understand.

4 DR. ROSENTHAL: -- because it hasn't
5 gotten a nod to go on the market. If they fulfill the
6 conditions which you feel needs to be fulfilled to
7 show a reasonable assurance of safety and efficacy,
8 because we have to provide that to the sponsor, if
9 they get a not approvable recommendation, then if they
10 ultimately fulfill those conditions, then I would like
11 to know whether or not this panel would feel that a
12 post-market study would be indicated.

13 DR. SCHEIN: So to comp my thoughts,
14 whether the device is deemed approvable today or at
15 some future date, my argument stands that I think a
16 post-market surveillance study would be necessary. I
17 think a good analogy is the extended wear contact lens
18 for which such a study was mandated for complication
19 of ulcerative keratitis when, indeed, there was not a
20 single case of ulcerative keratitis in the premarket
21 study.

22 DR. WEISS: Dr. Bandeen-Roche.

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