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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OPHTHALMIC DEVICES PANEL

96TH MEETING

Thursday, September 23, 1999

8:30 a.m.

Silver Spring Holiday Inn
Silver Spring, Maryland

MILLER REPORTING COMPANY, INC.
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C O N T E N T S

Call to Order, James P. McCulley 4

Introductory Remarks, Ms. Thornton 4

Postmarket Evaluation at FDA's Center for Devices and Radiological Health, Larry G. Kessler, Sc.D. 9

Branch Updates:

Donna Lochner, Chief of the Intraocular and Corneal Implants Branch 24
Dr. Beers, Acting Chief, Diagnostic and Surgical Devices Branch 27

Conflict of Interest Statement, Sara M. Thornton 27

Comments, A. Ralph Rosenthal 29

Open Public Hearing

Formal Oral Presentations:
Michael Bartell, Microtech, Inc. 32
Douglas E. Mastel, Mastel Precision 42
George H. Myers, Hawken Industries 50

Open Public Hearing Discussion:

Session I: Problems Associated with keratomes 55
Session II: Probable Causes 85
Session III: Steps to Mitigate Problems 167
Rank Ordering of Identified Problems 194

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

2 **Call to Order and Introductions**

3 DR. MCCULLEY: Welcome to the Ninety-sixth meeting
4 of the Ophthalmic Device Panel. I will turn it to Miss
5 Thornton for introductory remarks.

6 MS. THORNTON: Good morning, and welcome to all of
7 you here, today. Before we proceed with today's agenda, I
8 have a few short announcements I would like to make, and I
9 would like to remind everyone to sign in on the attendance
10 sheet in the registration area, just outside the meeting
11 room here.

12 Those who want to participate in the panel and
13 public discussion group need to see Ms. Ann Rae Williams,
14 who is over there at one of the tables, to register for
15 that. That is a separate registration. All handouts for
16 today's meeting are at the registration table.

17 You should make a note that the panel meeting
18 tentatively scheduled for November 18-19 has been cancelled.
19 The meeting dates tentatively scheduled for the year 2000
20 are on the FDA web site at www.dot.fda.gov in the medical
21 devices subsection. Also, on the table outside I have put
22 out sheets that have a list of those dates for the year
23 2000.

24 Messages for the panel members and FDA
25 participants, information or special needs should be

1 directed through Miss Ann Ree Williams of Miss Latania
2 Williams, who are available at the registration table, and
3 also Shirley Meeks is there today as well.
4 Those who have requested a reservation for
5 participation during the open public discussion will be
6 seated at the appropriate time. Those who may wish to join
7 them can register inside this room at the designated
8 registration table.
9 You should know that anyone coming to this now
10 will be seated on a first-come, first-serve basis, with a
11 limit of two participants representing any one group.
12 For those of you who have brought your laptop
13 computers, there are diskettes from which you may copy the
14 work sheet for the keratome discussion and the outline for
15 keratome 510(k) submissions. They are available at the
16 registration table and need to be returned there after you
17 have transferred the information, for the use of others so
18 that we can all benefit.
19 For those of you with cell phones and pagers, we
20 ask that you turn them off or put them on the vibration
21 mode.
22 Lastly, will all meeting participants please speak
23 into the microphone and give your name clearly? This is
24 really important today because we have a lot of people who
25 are going to be speaking into the microphone and probably a

1 lot of discussion going on, and it will be very important
2 that the transcriber and the summary writer get accurate
3 information.
4 Now, at this time I would like to extend a special
5 welcome and introduce to the public the panel and the FDA
6 staff, our new panel consultant and our guess discussant who
7 are with us for the first time.
8 Dr. Leo Maguire is our new panel consultant. He is
9 an Associate Professor of Ophthalmology at the Mayo Medical
10 School, and a consultant to the Department of Ophthalmology
11 at the Mayo Clinic in Rochester. Dr. Maguire currently
12 serves as Chairman of the American Academy of Ophthalmology
13 Committee on Ophthalmic Procedures Assessment, and is on the
14 editorial board of the American Journal of Ophthalmology and
15 Cornea. Dr. Maguire has published and lectured extensively
16 on corneal topography and its application to
17 keratorefractive surgery, on keratoconus, ectatic corneal
18 degeneration and associated optical and public health
19 issues.
20 Our guest discussant today is Dr. Dan Reinstein,
21 an Assistant Professor of Ophthalmology at the Weill Medical
22 College of Cornell University in New York, and a Professor
23 of Ophthalmology at the University of Paris, France. He has
24 extensive fellowship sub-specialty training in refractive
25 surgery, ophthalmic ultrasound and ultrasound

1 bioengineering, and combines these in his practice of
2 refractive surgery. Dr. Reinstein has led the development
3 and use of a new 3D very high frequency ultrasound system
4 that provides pachymetry of individual corneal layers with
5 one micron precision. He has pioneered the use of this
6 technology in the assessment of the cornea in Lasik and PRK,
7 with a focus on the study of underlying surgical mechanisms
8 and healing responses within the cornea. His special
9 clinical interests include the assessment and management of
10 the complications of refractive surgery.
11 I would like to now ask the panel to introduce
12 themselves, the remaining panel, starting with Dr. Marcia
13 Yaross.
14 DR. YAROSS: Marcia Yaross. I am director of
15 regulatory affairs at Allergan in Irvine, California, and
16 industry representative to the panel.
17 DR. SUGAR: Joel Sugar, Professor of
18 Ophthalmology, University of Illinois at Chicago; panel
19 member.
20 DR. MACRAE: Scott MacRae, Oregon Health Sciences
21 University, former panel member and consultant.
22 DR. BULLIMORE: Dr. Mark Bullimore, Associate
23 Professor of Optometry, The Ohio State University.
24 DR. MCCULLEY: Jim McCulley, Professor and
25 Chairman of the Department of Ophthalmology, University of

1 Texas Southwestern Medical School in Dallas.

2 DR. HIGGINBOTHAM: Eve Higginbotham, Professor and

3 Chair, University of Maryland School of Medicine, Baltimore.

4 DR. PULIDO: Jose Pulido, Professor and Head of

5 the Department of Ophthalmology, University of Illinois,

6 Chicago.

7 DR. JURKUS: Janice Jurkus, Professor of

8 Optometry, Illinois College of Optometry in Chicago.

9 DR. ROSENTHAL: Ralph Rosenthal, Director,

10 Division of Ophthalmic Devices.

11 MS. THORNTON: Thank you very much. I would just

12 like to note that we are expecting the appearance of our

13 consumer rep. She is missing from the table, as is Dr.

14 Marian Macsai who is a voting member of the panel. She has

15 had a falling out or a falling off of her bicycle --

16 [Laughter]

17 -- and hasn't been able to attend. So I just

18 wanted to note that for the record. But she will be back.

19 We, in the FDA, would like to extend at this time

20 our appreciation to the panel for the time they have taken

21 from their busy schedules to join us here today. I would

22 like to turn it over to Dr. McCulley. I believe Dr.

23 Rosenthal has asked to follow Dr. Kessler's remarks. So, Dr.

24 McCulley, do you want to take it from here?

25 DR. MCCULLEY: Okay. The agenda indicates that Dr.

1 Larry Kessler, Director, Office of Surveillance and
2 Biometrics, will give us a presentation on postmarket
3 evaluation at FDA's Center for Devices and Radiological
4 Health. Dr. Kessler?

5 **Postmarket Evaluation at FDA's Center for**
6 **Devices and Radiological Health**

7 DR. KESSLER: Thank you for the introduction, Dr.
8 McCulley, and thank you to Dr. Rosenthal and Sara Thornton
9 for the opportunity to talk to you about the other side of
10 the house.

11 [Slide]

12 Most often, the panel and guests see the premarket
13 side of the Center for Devices and Radiological Health. I am
14 going to talk to you a little bit about the postmarket side
15 and the critical role the panel can play in helping FDA with
16 its postmarket responsibilities.

17 [Slide]

18 In about twelve minutes I will describe a few of
19 the methods of device postmarket evaluation at the Center
20 for Devices and Radiological Health. I will present the
21 challenges in accomplishing this mission, and then describe
22 the pivotal role that the advisory panel can play in
23 postmarket evaluation.

24 [Slide]

25 To do that, I need to give you an overview of the

1 way we think we work at the Center for Devices from the
2 postmarket world. Most of the action in the medical device
3 world, we recognize at the FDA, happens really out here --
4 industry, customers, patients, physicians, design
5 modification devices is the vast majority of work that
6 happens in medical device technology.
7 FDA gets increasingly involved as any product goes
8 from device design, through evolution toward obsolescence,
9 and we get increasingly involved in this tie of a time
10 scale. From the lab and bench testing, definitely to the
11 clinical testing of devices and then, once we start FDA
12 review procedures, there is a long pre- and then a longer
13 postmarket evaluation process at FDA. All of these steps
14 should have frequent and accurate feedback routes, back to
15 the industry, back to the clinical community, etc., and we
16 should have the clinical community involved here, here and
17 also elsewhere in this diagram.
18 In the postmarket period we have at least five
19 separate regulatory or other mechanisms to monitor product
20 in the postmarket period, and that is as much of FDA's
21 statutory mission as is premarket, to make sure that a
22 device that is placed on the market remains safe and
23 effective.
24 We have the Medical Device Reporting Program. I
25 will talk to you about that for a few minutes. Then I will

1 talk for quite a bit about the postmarket surveillance
2 authority that we have at FDA, as well as our post-approval
3 authority which is connected to PMA type products. I will
4 not talk about our epidemiology program nor our very large
5 field inspection program, which are also critical parts of
6 FDA's postmarket evaluation procedures. Time limits me a bit
7 this morning.
8 [Slide]
9 Well, why do we care? What questions are
10 interesting in the postmarket period? For many products
11 long-term safety is an issue. Some products get reviewed and
12 passed, approved by panel and by the FDA, after a very brief
13 period of clinical testing but a lot of the products we are
14 talking about are in people's bodies or associated with them
15 for many, many years. So, long-term safety is a critical
16 issue for evaluation in the postmarket period.
17 Also, performance of a device in community
18 practice and effects of change in user setting. I want to
19 point to this one in particular, not so much for this panel
20 but in general. Most of you know that for the past twenty
21 years hospital stays in the United States and elsewhere in
22 the world have shrunk dramatically. What is happening is
23 that medical technology is being pushed from the hospital to
24 the bedside faster, faster and faster. Increasingly
25 sophisticated technology is at the bedside of you, your

1 parents, your aunts and uncles, and making sure that
2 products that can be used effectively in the hospital by
3 professionally trained physicians, nurses and other staff
4 can be used at home is a trick, and not all products can be.
5 We discover frequently that products that look safe and
6 effective to you on the premarket side, where you have seen
7 them from highly developed clinical trials with trained
8 staff -- when that product reaches the home, in a home care
9 setting, does not work the same way and patients experience
10 severe, sometimes life-threatening adverse events, and
11 monitoring for effectiveness of technology in settings, in
12 different settings, is important to FDA's postmarket
13 responsibility.
14 [Slide]
15 One of the mechanisms we have for looking at those
16 problems is the Medical Device Reporting Program. By law,
17 manufacturers must report deaths and serious injuries to
18 FDA, as well as malfunctions or something called near
19 incidents. Since 1990, all user facilities in the country
20 have similar requirements. All deaths associated with
21 medical devices have to be reported to FDA, and all serious
22 injuries have to be reported, by law, to manufacturers.
23 [Slide]
24 Unfortunately, that responsibility of user
25 facilities is observed in the breach. We get 95% of the

1 100,000 reports we get every year of adverse events from
2 manufacturers, and only 2% to 3% do we get from user
3 facilities. Information in the Medical Device Reporting
4 Program is supposed to include a device specific set of
5 information, event description, event date, etc.
6 Unfortunately, reports often have very limited
7 information. They provide critical signals to FDA, and I
8 will talk about that in a minute, but in an increasingly
9 litigious environment in the hospital setting, when an
10 adverse event happens with almost any product, the job of
11 the risk manager -- the first job of the risk manager in a
12 hospital setting is to ensure that his facility or her
13 facility doesn't get sued, and then later to think about
14 reporting to the FDA or other authorities. So, we wind up
15 getting a lot of reports that have very limited information
16 from the clinical perspective, and it is hard to deal with
17 that. But, we have a trained staff of about 15 nurse
18 analysts who look at the 100,000 reports we get a year and
19 prompt certain actions in the postmarket period.
20 [Slide]
21 Most commonly, we do directed inspections. Several
22 voluntary reports in the last year with ophthalmic products
23 that had to do with comfort issues -- some physicians have
24 reported some concerns, and we have gone and done
25 inspections in facilities to find out if we could support

1 those concerns.

2 Recently, in the last few years, we have had the
3 opportunity, based on reports from the Medical Device
4 Reporting Program, to put out two safety alerts, one on
5 retinal photic injuries from operating microscopes during
6 cataract surgery, in '95, and more recently illegal
7 promotion of contact lenses, in September of '98.

8 [Slide]

9 We have two separate postmarket authorities that
10 allow us to require of industry a report to the FDA in a
11 special way. These two authorities are Section 522,
12 postmarket surveillance, and conditions of approval studies
13 or post-approval studies and you are probably familiar with
14 those.

15 Section 522 was originally mandated in 1990 and
16 had both a required and a discretionary postmarket
17 procedure. In 1997 FDAMA dropped the required postmarket
18 surveillance part of that program and left us with a
19 discretionary postmarket surveillance authority. That
20 provides FDA the authority to require manufacturers to
21 submit data to address postmarket concerns. It is quite
22 similar to the post-approval authority which only refers to
23 PMA products, and these are conducted usually as conditions
24 of approval studies.

25 Both of these authorities are seen as complements

1 to premarket review, and in some ways even allow us to
2 adjust the pre- and postmarket balance and allow products on
3 the market where we may have some minor postmarket concerns
4 or marketing concerns and allow them to be handled in the
5 post-approval period.
6 [Slide]
7 The most essential part of trying to conduct any
8 postmarket surveillance study is to identify the critical
9 public health question, and this can come from "for cause"
10 situations. We may get medical device reports of unusual
11 adverse events or injuries and request that industry conduct
12 a postmarket study to see what is going on.
13 Also, new or expanded conditions of use or
14 evolutions in technology may cause FDA to require a
15 postmarket study.
16 Another key question is how will the data be used,
17 and I will come back to that in just a minute.
18 [Slide]
19 Originally in the required postmarket surveillance
20 study authorities we used fairly heavy approaches to try and
21 collect postmarket data. A more recent guidance of the kind
22 of designs that we anticipate recommending in the postmarket
23 period is a much wider range of study designs, from detailed
24 and definitive randomized trials or case-control studies in
25 the postmarket period, all the way down to something as

1 simple as a detailed review of the complaint history or
2 literature that the manufacturer generally keeps, especially
3 under the relatively newly promulgated quality system
4 regulations. That is similar to the GMPs.
5 [Slide]
6 But conducting postmarket studies can be very
7 frustrating. Why? First of all, rapid evolution of
8 technology makes studies obsolete. A number of times we have
9 requested a postmarket study, but the time the agency and
10 the industry and the clinical community have decided on
11 doing a study and getting going, we are already on a second
12 or third or fourth generation of product. So, it really
13 lessens the incentive to do a study on a product which
14 already is outdated and not being used very much.
15 Second, frankly, there is lack of the industry to
16 conduct such studies. Even though we require them, once
17 marketing authority is granted, the news from most
18 postmarket studies are not likely to be, "great! This is a
19 wonderful product." We basically knew that when we approved
20 it. So, the incentive for industry to conduct a postmarket
21 study in trying to address a public health concern can be
22 not so exciting.
23 There is a lack of clinical interest in the
24 community because the technology, again, is already in use.
25 So, conducting postmarket studies is not so interesting

1 clinically principally because not so publishable.

2 Finally, the lack of a clearly specified public

3 health question is the most frustrating thing, and both the

4 FDA as well as panel members have a responsibility to try

5 and figure out what is the right question to ask and that is

6 where I am going to leave you.

7 [Slide]

8 When considering post-approval studies, whether it

9 comes from Section 522 authority or from a post-approval

10 study, we need to ensure that the question we are going to

11 ask is of primary important. Do we really need to answer

12 this question in the postmarket period, because the lack of

13 incentives for doing these studies and doing them well are

14 really serious. So we really want to make sure it is an

15 important study that we want to do. We need to clearly

16 specify the public health question, and we want to note the

17 clinical or regulatory relevance of answering the question.

18 What will we do with the data?

19 And there is a variety of things we can do -- put

20 out safety alerts or public health advisories. We do those

21 on a routine basis. Change the labeling; change indications;

22 expand indications. There is a variety of things that can be

23 done from a regulatory perspective that help the clinical

24 community and the industry, based on postmarket studies, but

25 only if we figure out ahead of time what we really want to

1 do and clearly specify the question.

2 Thanks a lot for your time.

3 DR. MCCULLEY: Thank you. That was an excellent

4 presentation. One of the things that I think often we get

5 into on the panel is having a tendency to want to deal with

6 a grey area by saying, "well, we'll request a postmarket

7 surveillance study" and that gets us off the hook, on the

8 one hand. On the other hand, I get the sense that we are

9 kind of discouraged from doing that.

10 I guess it is still not really clear to me where

11 the panel's role should be appropriately in recommending

12 those kinds of studies, along with the warning that we

13 shouldn't abuse it to get ourselves off the hook.

14 DR. KESSLER: That is a question I have had from

15 panel to panel, and it is the key question. I think we are

16 evolving how this works out. Right now -- let me answer it

17 in two ways. One of the things we are doing is that the

18 Office of Device Evaluation and the Office of Surveillance

19 and Biometrics are going through all of the post-approval

20 studies that have been requested by the panels in the last

21 couple of years. What we are going to start doing in the

22 next year is bringing back that information from studies you

23 have requested in the post-approval arena, try to find out

24 what has happened to them, and has it given us, the FDA, the

25 industry and you, as the panel members, the important

1 information we want to address those concerns.

2 I would encourage you to use the postmarket

3 authority not so much to get yourselves off the hook but if

4 you have a relevant public health question you would like to

5 see identified; if you think it is not sufficient to warrant

6 precluding something on the market that you believe would

7 help you, as the clinical community, to understand better

8 how the product can be used in the most safe and effective

9 manner, and FDA may need to make some changes in its

10 regulatory approach, possibly something as simple as a

11 change in labeling, I would encourage you to suggest those;

12 be clear about what you think you want to do with the data

13 when the question is answered, and we will work out the

14 authority and work with the industry to conduct it. So, I

15 would encourage you to use it.

16 I want to go back to one thing. In postmarket

17 studies we often mistakenly -- and this is in the mid-1990s

18 -- concentrated on asking companies to do very onerous

19 studies, and they found it very difficult. I think there is

20 a lot that can be done at the top end of postmarket

21 surveillance with non-clinical testing of devices or use of

22 existing data sets. For example the Medicare folks have been

23 working with us for the past few years, and we can tap into

24 that and have industry help us work with them to address

25 your concerns. So, I would encourage you to identify those

1 concerns that are of primary importance, that you think
2 could be helpful to you in the clinical community, and we
3 will work with you to address them in a fast and expeditious
4 manner. So, I would encourage you to continue using that.
5 If you have a question, Dr. Rosenthal and the
6 exec. sec., they can call us and we can come and sit down
7 and work with you on the kind of designs and approaches that
8 would be appropriate. My postmarket staff will come and
9 attend the panel meetings and help out. So, any time you
10 have something that you anticipate, we will be here.
11 DR. MCCULLEY: Have we requested any postmarket
12 surveillance studies from this panel in the last few years?
13 DR. ROSENTHAL: Yes.
14 DR. MCCULLEY: Do you remember what they were?
15 DR. ROSENTHAL: You requested repositioning of the
16 toric lens.
17 DR. MCCULLEY: Right. And, I think we use it very
18 cautiously.
19 DR. ROSENTHAL: Yes, you do.
20 DR. KESSLER: And appropriately so. One of the
21 problems that we have had is occasionally some other panels,
22 not this panel, in the past few years have hit a rate of
23 over 50 percent of approvals being recommended with
24 conditions, and many of them postmarket. When the FDA has
25 tried to take action from the recommendations from the panel

1 and turn it into a postmarket study, when we understood the
2 question, the company and the FDA had a lot of problems. So,
3 we need to really work with you to make sure the question is
4 clearly specified. An unclearly specified question is the
5 best way to a bad study.
6 DR. MCCULLEY: Sara and Ralph have made that very
7 clear to us, that we need to do that, and I think we have
8 probably responded to it. I still am not 100 percent
9 comfortable with when we should request it and we shouldn't,
10 but I think we will continue to do it carefully.
11 DR. KESSLER: We will bring you back some findings
12 from some of the studies over the past couple of years. I
13 think that will help you.
14 DR. MCCULLEY: Well, some of the other panels, it
15 sounds like they have done exactly what I suggested, that
16 the postmarket surveillance studies could be used as a
17 mechanism to get off the hook and not make the decision
18 themselves. Yes, Dr. Higginbotham?
19 DR. HIGGINBOTHAM: To what extent, if any, does
20 your surveillance cover, I guess, non-United States adverse
21 events or outside of this country?
22 DR. KESSLER: That is a great question. I will
23 tell you what the law says and then I will tell you what I
24 think is happening.
25 The law says any event that is reportable under

1 the medical device reporting regulations, that occurs
2 anywhere in the world, on a product marketable in the United
3 States is reportable here. Okay?
4 Now, does that happen? Sometimes yes, sometimes
5 no. And I will tell you two stories and then try and get out
6 of your way. The first story: About a year and a half ago we
7 got 13 reports of severe anaphylactic like reactions from
8 chlorohaxine-impregnated catheters in Japan. They worried
9 our analysts quite a bit because they looked unusual. This
10 product had been marketed in the United States seven million
11 times and we hadn't received any reactions. All of a sudden
12 we got 13 from Japan. It just struck us as odd. So we wrote
13 the Ministry of Health and Welfare in Japan and,
14 interestingly enough, in Japan they had only received two
15 reports from their own country.
16 First of all, this was an international company.
17 They tend to respond better to medical device reporting laws
18 than they do anywhere else. So, we get some reports. But I
19 know that we get fewer than we should.
20 The second story is to tell you that right now the
21 United States and three countries in Europe, the United
22 Kingdom, Germany and Norway, Canada, Japan and Australia are
23 involved in an international vigilance reporting system,
24 where we are trading on a routine basis adverse events of
25 significant public health importance around the world. We

1 are trying to build this system so that if something happens
2 with a product in Germany that is of some public health
3 importance we find out about it.
4 We have had several excellent collaborations over
5 the past couple of years with some of our international
6 partners. The chlorohaxine one is an example. This led to a
7 Japanese based recall. We didn't recall it in the United
8 States because we couldn't find any evidence of any
9 problems, but in Japan they had a recall, sat down with the
10 company and looked at the data, and placed it back on the
11 market after a while. But that is a real success. But some
12 companies are careful, the multi-nationals who understand
13 medical device reporting. Most other companies, even if they
14 market things here, if they are not true multi-nationals
15 don't understand and so we miss things. But that is what the
16 program says. Okay?
17 DR. PULIDO: Just as a suggestion, when you give
18 us those examples maybe you could write them as case
19 studies, as they do for business school, and show where it
20 was done properly and where it was done improperly. That
21 way, I think we would all learn better how to use this
22 propitiously.
23 DR. KESSLER: Great! we will have some of both and
24 some of it, in fact, comes from where FDA has done some
25 things improperly. I will be glad to even trot those out. I

1 am sure the industry will appreciate seeing where we have
2 asked them questions that have not been well done and gives
3 industry headaches. Right?
4 DR. MCCULLEY: Any other questions?
5 [No response]
6 Dr. Kessler, that was excellent. We will welcome
7 you back to come and speak to us any time.
8 DR. KESSLER: Thank you.
9 DR. MCCULLEY: I think we are ready now for the
10 Branch updates. Since Dr. Rosenthal isn't here to introduce,
11 we will ask Donna Lochner, Chief of the Intraocular and
12 Corneal Implants Branch, to give us an update.
13 **Branch Updates**
14 MS. LOCHNER: Thank you, Dr. McCulley. And, I
15 would like to thank Dr. Kessler for a wonderful segway into
16 my Branch update.
17 At the July 23, 1998 panel meeting, the panel
18 recommended that Staar Surgical Company's toric posterior
19 chamber intraocular lenses, Model AA4203TF and Model
20 AS4203T, be approvable with conditions.
21 The approvable condition was that the sponsor
22 conduct postmarket surveillance of lens repositioning in the
23 first 1000 implants. In the PMA clinical data cohort, there
24 was a 12% rate of lens repositioning. The panel was
25 concerned that the actual rate of lens repositioning, when

1 the lens was marketed, could potentially be higher than the
2 investigational rate.
3 FDA approved the sponsor's application on November
4 4, 1998, with the condition as recommended by the panel. I
5 would like to report to you the results of the postmarket
6 surveillance study.
7 The first 1029 implants following PMA approval
8 were enrolled in the study. At the time of the firm's
9 submission to FDA, data for 931 patients had been reported.
10 This represents 90.5% of the total number of patients
11 enrolled. Of these 931 patients, 64, or 6.8%, were reported
12 to have had a repositioning of the IOL. There were no
13 reports of adverse events or lens dislocations associated
14 with these repositioning.
15 It should be noted that the reported rate of
16 repositioning of the IOL is not necessarily the observed
17 rate of misalignments. It only reflects those cases of
18 misalignment that were significant to the patients' visual
19 comfort and/or optimal functioning. As a result of this
20 postmarket reporting requirement, the sponsor has modified
21 their product labeling to include this newly obtained
22 clinical information.
23 Thank you for your attention. This concludes my
24 panel updates.
25 DR. MCCULLEY: I am sorry, I think you said it but

1 what was the repositioning rate in the study, in the PMA?

2 MS. LOCHNER: Twelve percent.

3 DR. MCCULLEY: And it dropped to 6%.

4 MS. LOCHNER: Almost 7%, yes.

5 DR. MAGUIRE: So, the repositioning rate observed

6 in the initial study wasn't actual repositioning rate; it

7 was clinically significant repositioning.

8 MS. LOCHNER: Right.

9 DR. MAGUIRE: So we are comparing apples and

10 apples.

11 MS. LOCHNER: Yes, it was an analogous comparison.

12 DR. MCCULLEY: Dr. Pulido?

13 DR. PULIDO: For the record, I would like to say I

14 think this was a necessary postmarket surveillance.

15 MS. LOCHNER: And I think, building on Dr.

16 Kessler's comments, it was focused and directed enough that

17 I think it was able to be done and the firm was able to

18 complete it and basically do exactly what the panel

19 requested.

20 DR. MCCULLEY: I think you have given us good

21 direction today on how to do these, and kept us from

22 misusing them. Do you have anything further?

23 MS. LOCHNER: No.

24 DR. MCCULLEY: Dr. Rosenthal, would you like to

25 introduce the next update -- well, I will. Dr. Beers is

1 Acting Chief, Diagnostic and Surgical Devices Branch, and
2 will give us a Branch update.
3 DR. BEERS: Thanks. This will be really a quick
4 update on items from previous meetings of the panel. First,
5 P970001, which is Emory Vision Correction Center's
6 refractory surgery and laser for myopia using Lasik, is
7 still under review.
8 In fact, all of the following PMAs are still under
9 review. P990010, the CRS PMA using the Visix for Lasik, is
10 still under review.
11 P980034, Supplement 13, Summit's PMA supplement
12 for Lasik for myopia is still under review.
13 P980051, the Sunrise laser for laser thermal
14 keratoplasty for hyperopia is still under review.
15 DR. MCCULLEY: Any questions?
16 DR. BEERS: Quick, as I said.
17 DR. MCCULLEY: Thank you. I would like to turn the
18 floor for a moment to Miss Thornton, who has some other
19 housekeeping issues -- administrative issues. Strike
20 housekeeping!
21 **Conflict of Interest**
22 MS. THORNTON: I am sure you have all made your
23 beds this morning --
24 [Laughter]
25 The following announcement addresses conflict of

1 interest issues associated with this meeting, and is made
2 part of the record to preclude even the appearance of an
3 impropriety.
4 To determine if any conflict existed, the agency
5 reviewed the submitted agenda and all financial interests
6 reported by the committee participants. The conflict of
7 interest statutes prohibit special government employees from
8 participating in matters that could affect their or their
9 employers' financial interests. However, the agency has
10 determined that participation of certain members and
11 consultants, the need for whose services outweighs the
12 potential conflict of interest involved, is in the best
13 interest of the government.
14 Waivers have been granted for Drs. Scott MacRae
15 and Eve Higginbotham for their interests in firms that could
16 potentially be affected by the panel's decisions. A copy of
17 these waivers may be obtained from the agency's Freedom of
18 Information Office, Room 12A-25 of the Parklawn Building.
19 We would like to note for the record that the
20 agency took into consideration certain matters regarding
21 Drs. Higginbotham, MacRae, Mark Bullimore and Janice Jurkus.
22 These panelists reported current or past interests in firms
23 at issue but in matters not related to what is being
24 discussed today. Therefore, the agency has determined that
25 they may participate fully in today's deliberations.

1 In the event that the discussions involve any
2 other products or firms not already on the agenda for which
3 an FDA participant has a financial interest, the participant
4 should excuse himself or herself from such involvement, and
5 the exclusion will be noted for the record.
6 With respect to all other participants, we ask in
7 the interest of fairness that all persons making statements
8 or presentations disclose any current or previous financial
9 involvement with any firm whose products they may wish to
10 comment upon.
11 Thank you, Dr. McCulley.
12 DR. MCCULLEY: Thank you. I would now like to turn
13 the floor to Dr. Rosenthal.
14 DR. ROSENTHAL: Thank you, Dr. McCulley. We have
15 invited you, the stakeholders -- and that includes the
16 clinical community, the companies and, of course, the panel,
17 to this meeting today to help us develop a guidance document
18 for keratomes. By your participation in this process, we
19 hope to develop guidance that will address the pertinent
20 safety and effectiveness issues for all indications for use
21 of keratomes, including making corneal flaps for Lasik.
22 Recently we approved the first PMA for an
23 individual laser for Lasik. In addition, several PMAs have
24 been presented to this panel for commercially produced
25 lasers seeking the Lasik indication. Keratome manufacturers

1 have also submitted applications to FDA through the 510(k)
2 process seeking to revise their labeling to include the
3 Lasik indication as well. To date, we have not cleared an
4 application for a keratome with labeling for Lasik.
5 The outline, which will be provided for you today,
6 identifies the information we currently expect in a 510(k)
7 application for a keratome when indicated for lamellar
8 resection of the cornea. Corneal lamellar resection is
9 considered a general indication for the use of keratomes.
10 This outline, however, does not address data expectations
11 for the specific indication for making corneal flaps for
12 Lasik.
13 Using this outline, which Miss Hoang and Dr. Beers
14 will present to you, and Mr. Glover, we are seeking input
15 from the panel, from the industry and from the clinical
16 community that would identify additional information, if
17 any, that would be needed to determine the safety and
18 effectiveness of keratomes for the use in Lasik.
19 As part of this process, we ask that you discuss
20 the risks associated with a keratome when used in Lasik, and
21 the types of clinical and non-clinical information which
22 would be required to assess those risks.
23 This is being brought to your attention now
24 because in the opinion of the Division there is a major
25 potential public health issue related to the Lasik

1 procedure. It will be done a large number of times in this
2 country, on a large number of eyes, and we would like your
3 opinion as to how we should approach this issue at this
4 point in time.
5 Thank you very much.
6 DR. MCCULLEY: Would you entertain questions if
7 the panel has any relative to that?
8 DR. ROSENTHAL: Sure.
9 DR. MCCULLEY: Any panel members have questions or
10 points of clarification for Dr. Rosenthal?
11 Seeing none, we will now move on to the open
12 public hearing session. There are three individuals who have
13 previously requested time to speak. Each individual, whether
14 by prior arrangement or time allowing to speak following
15 them, will be limited to a maximum of ten minutes. At the
16 conclusion of these presentations, it is my understanding
17 that panel members, if they have questions or points of
18 clarification, may then make appropriate query.
19 The first person who has requested time is Michael
20 Bartell. I would ask you to come to the podium and remind
21 everyone, please, not only to identify yourself for the
22 record but to state the affiliations and conflicts that
23 would be of note for these discussions.
24 **Open Public Hearing**
25 **Formal Oral Presentations**

1 MR. BARTELL: I welcome the opportunity to speak
2 to you today. I appreciate it. I am Mike Bartell, President
3 of Microtech, Inc., a Pennsylvania corporation. We are the
4 exclusive distributors for Moria Microkeratomes product line
5 in both North and South America. We have been involved in
6 the refractive field since the early days of RK, and with
7 the microkeratome market specifically for the past five
8 years.
9 Microtech has been very closely involved with
10 Moria in the development and evolution of their
11 microkeratome line. We are here today to discuss and define
12 the scope and purpose of the proposed guidelines for
13 microkeratome 510(k) submissions. During the course of these
14 discussions we are going to address the potential concerns
15 related to the Lasik procedure that has evolved in the past
16 years, and we will make an attempt to rank those concerns in
17 their order of priority, determine the possible causes, and
18 look at how we might best eliminate them.
19 In doing this, we will try to determine and
20 confirm some of the specific responsibilities that fall
21 firmly on the shoulders of the microkeratome manufacturers.
22 In this way, we can agree upon the standards that must be
23 met by a responsible manufacturer prior to the introduction
24 and marketing of new microkeratomes in the United States.
25 My purpose in addressing this group today is to

1 make one very important point on behalf of the microkeratome
2 manufacturers. It is extremely important that you protect
3 the integrity of the microkeratomes that have take the time
4 and the effort in proving themselves worthy of obtaining and
5 receiving the 510(k) market clearance by the FDA. Generic
6 microkeratome blades are proliferating in this country at an
7 alarming rate. When a generic blade is substituted in a
8 manufacturer's system, all control, traceability and
9 accountability goes right out the window as far as that
10 manufacturer is concerned.
11 [Slide]
12 This slide represents the evolution of the
13 microkeratome system currently manufactured by Moria of
14 Paris, France. It is sold throughout the world. The unit
15 does have 510(k) approval in the United States, and it is
16 manufactured under the strict guidelines established for an
17 ISO-9000 approved marketing facility and manufacturing
18 facility.
19 [Slide]
20 A microkeratome is a very sophisticated piece of
21 equipment. When you pop the top off you begin to get a feel
22 for some of the complexities that the surgeon takes for
23 granted.
24 Dual vacuum pumps serve as a safety backup to each
25 other ensuring an uninterrupted vacuum and the proper

1 elevation of intraocular pressure for making the cut and
2 creating the Lasik flap.
3 State-of-the-art power systems ensure power to the
4 unit independent of fluctuating wall current. This unit will
5 continue to operate even if there is a complete power
6 outage, just as we experienced last year up and down the
7 East Coast. This is depicting some of the inner workings of
8 these units.
9 It has completely computerized circuitry and
10 provides uninterrupted power, ensuring proper functioning
11 and a system of self-checks that prevents a cut from being
12 made even if all systems are not a go at one time. So, there
13 is a complete system of checks and balances in it.
14 [Slide]
15 There are actually five different suction rings,
16 two of which are shown here. This selection of five
17 different rings allows the surgeon to select the size of the
18 flap he wants to cut in relation to the specific corneal
19 curvature of the patient. These are very specific
20 specifications.
21 [Slide]
22 This little stop ring, here on the left, is
23 actually responsible for creating the hinge in relationship
24 to various size flaps that are created during the Lasik
25 procedure. Again, if they are used properly there should be

1 no reason for the surgeon to experience some of the free
2 flap complications that have gone on in the past. It has
3 four different settings as far as adjustments are concerned.
4 [Slide]
5 The new microkeratome heads that are evolving
6 today are now made out of one solid piece of solid stainless
7 steel. There are no more tiny plates, screws, or cams that
8 need to be assembled. This has basically eliminated the vast
9 majority of the operator error complications that could
10 potentially occur due to omissions or incorrect assembly of
11 the microkeratome.
12 [Slide]
13 This is another style of a one-piece head
14 manufactured by Moria that provides a pivoting motion to
15 provide the cut and create the flap. There are three
16 different heads available that give 130, 160 or 180-micron
17 depths of cut. The tolerances within these heads are
18 incredible. They have to be because we are being held
19 responsible for cuts that are a tenth of a millimeter as far
20 as the cutting accuracy.
21 This particular head depicts the insertion here of
22 a one-piece blade into the side. It is sort of like the old
23 Schick injector razor where it just slips into the side. You
24 can't get it in upside down; you can't get it in wrong.
25 Again, this is going towards eliminating the potential

1 problems as far as assembly on the part of the medical
2 personnel. The tolerances within the head, as I said, are
3 just very incredible. The blade, one it is put into the
4 system, becomes a part of that total system. Once the blade
5 is inserted in there it has to operate within the absolute
6 tolerances of the head itself. If there is any variance, it
7 can create metal against metal or metal against plastic,
8 creating wear of the head; it can lead to damage of the
9 head, irregular cuts, debris in the inner face, and
10 compromise patient safety.
11 [Slide]
12 The head, when it is screwed onto the motor, as
13 shown here, locks the blade into place, fixating it within
14 the area that it must operate on. It is centered on the
15 pivot point of the suction ring and --
16 [Slide]
17 -- depicts the motion of the microkeratome as a
18 cut is effected by the surgeon. If you go from the starting
19 position, here, and activate the forward pedal it begins to
20 rotate around towards the stop and, of course, at the stop
21 position is where your flap is created.
22 My purpose in putting up these nine slides is to
23 convince you of the systematic approach that has to be taken
24 if we are expected to produce incisions in the human cornea
25 within tolerances of a tenth of a millimeter.

1 [Slide]

2 If you change one component within a very exacting
3 system, that system no longer is the same system. Blades now
4 are made so that there is no assembly necessary, and the
5 relationship to the this surface, the angulation of this
6 plastic piece to the blade, the overall length, the overall
7 width, the sharpness and all of these things are critical.
8 Once a generic product is substituted within a 510(k)
9 approved system all quality control is lost. Currently, a
10 generic manufacturer has only to show equivalency to the FDA
11 for a system's component parts to receive a 510(k). If it is
12 stainless steel here, it is stainless steel here; if it is
13 plastic, it is plastic; it has a sharp edge so it must,
14 therefore be the same. That is not true.

15 It is impossible for a generic manufacturer to be
16 aware of the exact specifications in the internal head
17 components that the blade must fit into. They cannot
18 possibly be aware of slight variations that commonly occur
19 in the course of a product's lifetime. Moria microkeratome
20 blades currently undergo 100% inspection before release.
21 They reject approximately 30% of their own blade manufacture
22 due to either the steel portion of the blade, the plastic
23 portion of the blade or the combination of the two. The
24 majority of these blades are rejected because they don't
25 meet specifications that are known only by us.

1 We should like to request that the current FDA
2 policy for generic component products for microkeratome
3 systems be changed. We request that the substitution of
4 generic components to an approved microkeratome system be
5 reviewed by the FDA as an off-label use of that system.
6 If we are to be held responsible for the function
7 of our system, then we must have control of the components
8 that comprise that system. If the FDA continues to grant
9 510(k) market clearance to manufacturers of generic
10 components, we feel that the FDA is potentially jeopardizing
11 patient safety and should be willing to assume the product
12 liability for that whole system.
13 I thank you for your time on behalf of Microtech
14 Moria, and a number of other companies, I am sure, that have
15 spent hundreds of thousands or millions of dollars to bring
16 safe ophthalmic products to the marketplace.
17 DR. MCCULLEY: Thank you very much. I think you
18 had a very clear message. I am not certain, as a scientific
19 advisory panel, quite honestly -- well, I will stop that
20 sentence that I didn't finish. During the time I have been
21 here, we have never dealt with the specific issues related
22 to regulation of blades, and I think we are probably
23 relatively -- I know I am -- unfamiliar with the FDA's blade
24 regulation process, and that may be appropriate and the FDA
25 may feel that there are no scientific issues related to that

1 that they would want to bring to us. So, I understand your
2 message. I am not sure what our role in that would be than
3 to hear and understand. I think we can say we have done
4 that, and I guess unless the FDA has any other direction to
5 us as the panel, then I would ask them to provide that. And,
6 these issues may come up subsequently, but our role is as a
7 scientific advisory panel, not a policy advisory panel. Dr.
8 Pulido?
9 DR. PULIDO: I think though he makes a very cogent
10 argument for the idea that the whole system is a system in
11 and of itself, and I think we and the FDA need to hear that.
12 DR. MCCULLEY: Right. I agree.
13 DR. SUGAR: May we ask questions?
14 DR. MCCULLEY: Yes.
15 DR. SUGAR: You mentioned tolerances of tenths of
16 a millimeter. A tenth of a millimeter is 100 microns.
17 MR. BARTELL: That is correct, and --
18 DR. SUGAR: That seems very broad. And, you are
19 talking about a blade that is specified for 160 or 180
20 microns. A tenth of a millimeter tolerance is probably
21 unacceptable.
22 MR. BARTELL: I am referring to the depth of cut
23 of the microkeratome head, not necessarily the blade but the
24 blade, the head, the entire microkeratome system. You need
25 to leave about 250 in the bed to 300 microns, and sometimes

1 it is very close. So, when we present the head in
2 combination with the blade that is going to give 160 micron
3 depth of cut, not 180 micron depth of cut, we are talking
4 about 20 microns. You put someone else's blade in there, and
5 yet you want to hold me responsible for not giving you a 200
6 micron cut. That is what our reference is to, the depth of
7 the cut of the head, not tolerance on the blade.
8 DR. MCCULLEY: Does FDA feel this is the
9 appropriate time to get into these issues or that we should
10 do this subsequently?
11 DR. ROSENTHAL: I appreciate the issue being
12 brought to our attention, and I think we can certainly
13 address the issue when the final guidance is written. In the
14 process of getting a guidance document, you know, finally
15 completed there will be a lot of opportunity to discuss this
16 issue.
17 DR. MCCULLEY: I know in the issues that have been
18 brought to us in the matrix that you are wanting us to
19 address the depth of cut is a recurrent theme.
20 Any other panel questions or comments? Dr.
21 Higginbotham?
22 DR. HIGGINBOTHAM: I have a question. Is there a
23 shelf life per safety and efficacy for these blades, a
24 period beyond which you cannot actually guarantee their
25 accuracy?

1 MR. BARTELL: No, it would be more the sterility
2 concern. As long as they are in their protective packages
3 and so forth, I believe there is an expiration date per
4 safety and efficacy but it has to do with the sterility.
5 DR. MCCULLEY: Other panel questions or comments?
6 Dr. MacRae?
7 DR. MACRAE: I just want to thank the presenter
8 and also acknowledge that these systems aren't always being
9 used the way the manufacturers recommend, such as, I think
10 the use of generic blades is an extremely common phenomenon
11 now and it brings out the issue of if there are problems
12 occurring, are they occurring as a result of the device
13 being used in a way that it wasn't really originally
14 designed to be used, yet holding the manufacturers
15 accountable to that. So, I do think that you have a very
16 legitimate concern and, yet the panel has difficulty
17 assessing that. We are not engineers and we have very
18 limited data in terms of that. But I acknowledge sort of
19 both sides of this issue. It is a difficult issue and I
20 suspect as time goes on it will be more explored.
21 DR. MCCULLEY: Thank you very much.
22 MR. BARTELL: Thank you.
23 DR. MCCULLEY: The next speaker is Douglas E.
24 Mastel, President, Mastel Precision.
25 MR. MASTEL: It is going to get me a minute to get

1 this --

2 DR. MCCULLEY: I won't start the clock until you

3 start.

4 MR. MASTEL: Thank you. Doug Mastel, from Rapid

5 City, South Dakota. I will try not to overpower you with

6 this microphone. My wife complains I am too loud all the

7 time; says I don't listen to her.

8 [Slide]

9 Our company is located in Rapid City, South

10 Dakota. It is a fitting tribute to be here, in Washington,

11 D.C. We have the distinction of having Mount Rushmore in the

12 Black Hills. We also have a more dubious distinction, the

13 Sturgiss motorcycle rally. If any of you are Harley riders,

14 you can come sometime and watch all the people from all over

15 the world riding hogs, chasing cattle.

16 [Laughter]

17 [Slide]

18 I have a little bit different perspective, I

19 suppose, and I really appreciate Mr. Bartell. They are a

20 quality company, and I appreciate what they are suggesting.

21 As a metallurgical engineer though, I would come from a

22 little bit different angle, and I want to look at the

23 science behind the blade, being a diamond blade manufacture.

24 [Slide]

25 This is the edge of the blade. It is a little bit

1 underexposed here but these blades were cut on the edges
2 with electron discharge machining.
3 [Slide]
4 In a different perspective now you can see the
5 sputter, which we look at under a different magnification
6 now.
7 [Slide]
8 If you are looking at interface debris and various
9 problems with the blades, I think that the blade has to be
10 the most important consideration of the whole event. You are
11 sectioning the cornea.
12 [Slide]
13 What is the microstructure of the material
14 properties of these blades? Should we be using Rockwell?
15 Should we be using indentation, hardness characteristics?
16 What is the actual alloy that the manufacturer is using?
17 They are buying ribbon stock, most of them. Some people are
18 making their own, but what is that steel? That would be a
19 question I would have for you.
20 Should we be doing tensile testing? Should we be
21 doing testing at all? What is the microstructure? I can
22 guarantee you after that blade was heated with that electron
23 discharge machining that the blade was distempered -- thin
24 cuts, buttonholes -- you name it.
25 What is the surface finish of the blade? Should we

1 be using RMS characterization, common manufacturing
2 principles that seem to be not applied to this industry? And
3 what about the cleanliness of the blade? We talk about sands
4 of the Sahara and all the things that are going on and
5 everyone says it is multifactorial, and I will get into that
6 in a minute.
7 [Slide]
8 This is that same blade. You can see the molten
9 appearance here. Electron discharge machining works like a
10 reverse arc welder. It just simply burns and dematerializes
11 the stuff that is there like a laser goes through. But the
12 heat here is the problem.
13 [Slide]
14 Another blade. It was not quite heated to the same
15 level.
16 [Slide]
17 Here is another manufacturer and you can see that
18 it is an entirely different morphology. In my estimation it
19 could be better but it is pretty good.
20 [Slide]
21 You can see the granular appearance of the
22 microstructure, indicating that it has had minimal thermal
23 input.
24 [Slide]
25 Again, at 10,000 times magnification. I find

1 oftentimes, having had some scanning electron microscopy
2 training personally, SEMs are used in a way to make
3 something look unreal, unrealistic.
4 [Slide]
5 What is edge sharpness? First of all, the edge
6 profile, the angle alpha is normally around 33 degrees in
7 diamond technology and in steel. So, the edge bevel has to
8 be a primary consideration in the effectiveness of the
9 microkeratome. It cannot be refuted. What are the included
10 angles on the blades of the manufacturer? This should be a
11 prime determinant.
12 Are there secondary bevels and tertiary bevels?
13 Should safety and efficacy be using optical microscopy and,
14 if so, what magnification? Should we be using scanning
15 microscopy, which is impractical in a manufacturing
16 environment? What is the edge radius? Should we be looking
17 down at the angstrom range? In environment blade technology
18 we can get down to atomic bevel edges, which is in the
19 anagstrom range. Steels are not quite capable but still you
20 can generate a very good edge on steel.
21 What about physical testing? We have no testing to
22 determine how effective a blade is going to be. It seems to
23 me that we should come up with some sort of a standard. You
24 make a cut. How much pressure is used -- pascals, whatever,
25 newtons, whatever we are going to be looking at -- and find

1 out how effective a cut is in a standardized material.

2 [Slide]

3 This is another blade. You have a primary, a

4 secondary and a tertiary grind on this particular blade. It

5 was sent to us because it was problematic, several years

6 ago. Here you have an edge of 1000 X. It looks fine.

7 [Slide]

8 At 10,000 X -- you can see this is a very good

9 blade.

10 [Slide]

11 This is not.

12 [Slide]

13 Now, here is one with a primary and a secondary

14 grind. You can see the first grind angle here and the second

15 here. Now, what is this profile here? That is that angle out

16 that we talked about.

17 [Slide]

18 Here we have a primary, secondary and that

19 tertiary grind again.

20 [Slide]

21 That is this blade, and it is masked because of

22 the radically pathetic surface finish here on the edge.

23 [Slide]

24 But this has an entirely different sharpness --

25 [Slide]

1 than this. This is much more acute, and this blade
2 was much better.
3 [Slide]
4 Now, we talk about interface debris. That is those
5 grinding lines that are posterior to the blade. The blade
6 runs this way. That is going to be sandpaper to the stroma.
7 It is also a dirty surface. What we found in our research
8 was -- first of all, this is going to also carry epithelium
9 into the interface and lay it down. A slick surface is a
10 clean surface.
11 [Slide]
12 So we did some x-ray diffraction on some blades
13 just to find out what they were.
14 [Slide]
15 We found out that the best material is 440C. This
16 is a couple of years ago.
17 We wanted to find out what is the stuff we are
18 seeing here because x-ray diffraction does not look for
19 organic materials? We were seeing sulfur, chlorate, silicone
20 -- we were wondering what the heck we were seeing on the
21 surfaces versus a clean scan.
22 [Slide]
23 So, prior to Dr. Bobby Maddox who was the first to
24 present -- or he called me personally because we don't sell
25 microkeratomes. We have been a developer of a microkeratome

1 for nearly four years now -- still not available. And, he
2 called me because he had these stromal interface problems; a
3 couple of stromal melts -- a disaster. Now it is common
4 today to talk about sands of the Sahara. Where is it coming
5 from?
6 Well, he sent us some of his blades after having
7 this problem. We submitted them to a company in California
8 that did FTIR spectroscopy. That is how you look for
9 hydrocarbons. We found polyamides, benzenes and esters --
10 common machining lubricants used in electron discharge
11 machining, or whatever. And, we looked at the surface
12 finish. It is going to be hard to clean these now. How are
13 the blades being cleaned? The doctor is looking with a
14 surgical microscope, going, "that's clean and that's not." I
15 see it all the time. That can't be in this business. It
16 needs to be a factory finish. Okay?
17 Then Dr. Maddox sent another one, with silicone
18 oil. Talk about sand -- you bombard silicone, you are going
19 to get silica and free radicals.
20 [Slide]
21 So we tore a microkeratome apart recently and I
22 was expecting to look at the O-rings that were sealing the
23 drive because Dr. Maddox said that is coming out of the gear
24 boxes and I was looking for the O-rings. There were none.
25 What is in the gear box, and how is it isolated from the

1 cornea?

2 Thank you.

3 DR. MCCULLEY: Thank you. Could you tell us what

4 Mastel Precision is, what kind of business you are in and

5 what your specific interest is in this so that we know how

6 to put your comments in perspective relative to the overall?

7 MR. MASTEL: We have been manufacturing

8 instruments for nearly two decades. We have been in

9 development and Dr. Stulting did the research at the

10 microkeratome face-off. We have been in development for four

11 years of a diamond keratome, using a diamond blade. I

12 personally elected not to put a microkeratome on the market

13 because I was confident it was going to be safe and

14 effective, and it has almost killed us. We were almost there

15 but Dr. Stulting would say, "it looks pretty promising;

16 you'll never make it work." So, we hope to have a

17 microkeratome some day, but it was a matter of coming here

18 and trying to share some information I have had for several

19 years. If we can be of assistance, we would like to do that.

20 DR. MCCULLEY: I appreciate your information. I am

21 sure that the FDA engineers really appreciate your

22 information, and I think that is at the level where those

23 issues would be.

24 Any other questions or comments?

25 [No response]

1 Thank you very much.

2 MR. MASTEL: Thank you.

3 DR. MCCULLEY: The next presentation will be by

4 George H. Myers, Consultant, Hawken Industries.

5 MR. MYERS: Thank you. You will have to excuse my

6 hoarse voice today. Dr. Dibbs, who is the president,

7 unfortunately, couldn't be here today.

8 Hawken makes a disposable microkeratome which has

9 received 510(k) clearance. It just occurred to me, it

10 completely avoids all these problems of blade replacement

11 because you have to replace the whole microkeratome.

12 My comments are split into two parts. One is what

13 measures might be taken with tests of 510(k) submissions to

14 get information to see what is actually necessary in a

15 microkeratome for Lasik. Most of them are actually used for

16 that, but when the original device was made nobody had even

17 heard of it.

18 Some of the questions -- I have to apologize for

19 not having slides -- are how smooth does the stroma have to

20 be? How well defined should the edges be? How thick a flap

21 is needed? All that is known now is that if the flap is too

22 thick greater than 250 microns one had problems. What

23 effects do corneal curvature and geometry have on the flap?

24 What is the intraocular pressure necessary for a good flap?

25 And, what is the difference between nasal and superior

1 hinges?

2 So, what we are suggesting -- now, the question is

3 whether FDA can actually require this -- is that certain

4 data be included with the 510(k) even though clearly there

5 is no way of establishing substantial equivalence from it,

6 and this eventually would be used with a registry to try and

7 find out what makes a good microkeratome for Lasik.

8 For example, we suggest animal tests to establish

9 flap thickness, with the intraocular pressure recorded and

10 the flap dissected measured. Some human tests to

11 substantiate the animal tests. Scanning electron microscope

12 of the stromal beds and edges on the animals. Of course,

13 then you would have to have some criteria for the SEMs.

14 But we think if enough data is acquired, then we

15 are sort of proposing using the 510(k) as a process for

16 requiring the data and eventually we will find out what

17 makes a microkeratome suitable for Lasik since the FDA

18 cannot itself carry on research.

19 The rest of my comments, having just completed a

20 510(k) clearance with Ms. Hoang, who is sitting here -- some

21 things occurred to us which are not on the outline. There

22 are presently guidelines for the maximum pressure used for

23 the device -- the suction used to hold the device onto the

24 cornea. We actually had a clinical evaluation and we just

25 reported whatever the investigator used and we were told

1 that this was much higher than the accepted standard. Well,
2 it was accepted but our fellow who did the clinical studies
3 said he thought that the level cited was way too low, and
4 maybe that can be corrected.
5 This is not exactly a scientific thing but
6 applicants, for example us, have been asked to submit test
7 results and specifications on a lot of the complements of
8 the device. This is, to me, the case that should be
9 specifically mentioned in the guideline. It is very easy to
10 do these beforehand. When one gets the comments, with 30
11 days to answer, and when one requires all these tests it can
12 be very difficult.
13 That question is really related to Lasik. There
14 are a great many different devices called microkeratome,
15 from old hand-operated ones to completely automatic ones.
16 Are all these really suitable for Lasik?
17 Then related to this, we have been told that there
18 are some devices that have been cleared by the agency which
19 have actually not succeeded at all in the market. The
20 suspicion is that there are not too well suited for Lasik
21 but they are probably very good microkeratomes. Is there any
22 knowledge as to why this might be the case? Is there any way
23 of learning about this?
24 Thank you very much.
25 DR. MCCULLEY: Thank you. Any questions or

1 comments for Mr. Myers? Dr. Higginbotham?

2 DR. HIGGINBOTHAM: Just a point of clarification,

3 I am sure you didn't mean human tests but tests on cadaver

4 eyes.

5 MR. MYERS: Well --

6 DR. HIGGINBOTHAM: I don't want the public to

7 think that we are doing human tests.

8 MR. MYERS: Well, our device -- this may be a

9 special situation but our device was used on human tests.

10 The investigator had a PMA actually for Lasik for the

11 surgery but he needed a keratometer. Obviously, this was

12 described in his PMA. Yes, we are suggesting human tests.

13 This is the typical thing, that they are first used in

14 animals to demonstrate the safety and then used in humans.

15 We suggested animal studies first.

16 DR. ROSENTHAL: I think we should clarify that

17 there is an issue of clinical testing, a clinical trial for

18 the use of a keratome. Ultimately you would have to use it

19 on humans but there is pretesting on animals and cadaver

20 eyes. So, I think we should actually think about what is

21 required from a clinical standpoint and the use of humans if

22 the panel feels that it is an appropriate think to include

23 in this guidance document.

24 DR. MCCULLEY: Other questions or comments? Dr.

25 Sugar?

1 DR. SUGAR: Can I just ask you, you have a
2 marketed device? Is that correct?
3 MR. MYERS: Yes, that is right.
4 DR. SUGAR: 510(k) approved. What kind of
5 marketing surveillance do you do? Not FDA required, but do
6 you do any follow up on the efficacy of your device?
7 MR. MYERS: Good Manufacturing Practices require
8 certain procedures with all complaints, with all
9 communications provided to the manufacturer. That is kept
10 up, is followed up. Also, the device has a CE market that is
11 sold in Europe which requires its own pooling of the
12 complaint file and the manufacturer is kept informed --
13 there haven't been any, I might add -- of any complaints
14 overseas. But aside from that, there has not been a attempt
15 to actually reach out, as far as I know, to the users.
16 DR. SUGAR: Thank you.
17 DR. MCCULLEY: Any other questions or comments by
18 panel members?
19 [No response]
20 Thank you very much.
21 MR. MYERS: Thank you.
22 DR. MCCULLEY: The next thing scheduled is
23 actually a break. The next thing after that is unusual
24 formatting that we have, or different formatting, for a
25 broader opening of discussions. So, I think it is probably

1 wise for us to go ahead and take our break now rather than
2 trying to break once we get that ball rolling. So, let's
3 take a 15-minute break.
4 [Brief recess]
5 **Open Public Discussion**
6 DR. MCCULLEY: Let me call the panel session back
7 into order. We are now going to begin an open public
8 discussion period, which is, in my experience, a new
9 phenomenon. Hopefully, we can keep this reasonably well
10 organized. I will remind people again that any time an
11 individual speaks, please state your name. If it is the
12 first time you are speaking, please indicate your
13 affiliations and any conflicts that would be germane to the
14 discussion.
15 Now I would like to ask Dr. Beers and Ms. Hoang to
16 introduce this session and maybe lay down some ground rules
17 and directives.
18 **Session I: Problems Associated with Keratomes**
19 DR. BEERS: Everette Beers, Acting Branch Chief
20 for the Diagnostic and Surgical Device Branch. We are moving
21 into the guts of this session today.
22 My sole function here is to introduce the next
23 session and to introduce the presenters for FDA. Quynh Hoang
24 is a scientific reviewer in the Division of Ophthalmics and
25 Diagnostic and Surgical Devices Branch. She is an electrical

1 engineer. She has been with us five or six years -- almost
2 ten years in FDA but five or six years in our Branch. She
3 has been intimately involved with keratomes.
4 Also, I wanted to recognize Joe Glover, who is
5 also a scientific reviewer. He is a biomedical engineer and
6 he is going to help Quynh present this.
7 At this time, I am going to relinquish my seat to
8 Mr. Glover and I am going to turn this over to Quynh, who
9 will give you an outline and some indication of how to
10 proceed, and direct you through this process.
11 MS. HOANG: Thank you, Dr. Beers. Dr. McCulley,
12 panel members and participants, we envision this open public
13 discussion period as a brainstorming session in which all
14 problems associated with the use of keratomes can surface,
15 as well as the causes of the problems and, most importantly,
16 the ways to mitigate the problems.
17 The discussion period is divided into three
18 sessions that correspond with the above topics, as you can
19 see from the agenda. We have provided you with a work sheet
20 that will be used to capture the points brought up during
21 the discussion. The work sheet will be displayed on the
22 projection screen and modified concurrently with the
23 discussion, but only at the direction of the panel chair.
24 So, please, ensure that Dr. McCulley acknowledges your point
25 and directs us to either add or delete from the work sheet

1 as appropriate.

2 As you are aware, this is the first time that we

3 have tried this format, and Joe and I will be trying to

4 input the data expeditiously. Please bear with us if we

5 encounter any difficulties. Thank you.

6 DR. MCCULLEY: Thank you. Do you have any further

7 directive to us up front, before we start on the charge?

8 MS. HOANG: No, I don't think so.

9 DR. MCCULLEY: Let me point out again, everybody

10 please look at the agenda. We have three different sessions

11 or sections to this. The first is to enumerate the problems

12 and to add to or take from this list. The second charge, in

13 the second hour, is to discuss the possible causes. The

14 third charge is to try to determine why these occur and how

15 we might avoid repeats of the problem.

16 It is going to be difficult for us to keep things

17 pigeon-holed and we are going to have a potential problem to

18 get ahead of ourselves and, therefore, not have time to deal

19 with some of the issues per charge. So, the first hour will

20 be devoted to the list -- adding to, taking from and not a

21 lot of editorial comment about causes, how to prevent, and

22 so on and so forth, unless the comment relates to "this

23 should come off of the list," or "this is why it should

24 remain on or be added to it."

25 So with that, we have the list projected. I assume

1 those of you in the audience who are participants also have
2 a copy of the list. I guess the first question would be is
3 there anything on this list that should be removed? Does
4 anyone have any thoughts about that? Things that should be
5 added to the list? I certainly have a long list of things.
6 Are there other issues?
7 You guys who are out there, you are equal
8 participants in this portion of the discussions so please
9 join in, including those of you who participated in the
10 formal open discussions. So this, in effect, is an expanded
11 group for discussion, with the panel only being a part of
12 the group.
13 Anyone have any other issues that they would like
14 to add to this list?
15 DR. MAGUIRE: Yes, I think there is a number of
16 things that relate to the clinical problems that come up.
17 One would be variability in flap thickness from case to case
18 and issues related to that.
19 DR. SUGAR: You can look at it as accuracy.
20 DR. MAGUIRE: More likely to call it consistency
21 of cut.
22 DR. SUGAR: Reproducibility.
23 DR. MAGUIRE: Correct, and also the kind of
24 standard deviation reproducibility. Dr. Reinstein can talk
25 to this very well, and he has done elegant work. We don't

1 have good scientific basis for saying that 250 microns is,
2 in fact, the place where we see an increased risk of
3 ectasia, and certainly corneal ectasia should be on this
4 list.
5 DR. MCCULLEY: So that is one to add, corneal
6 ectasia.
7 MS. HOANG: Did you want to add corneal
8 reproducibility?
9 DR. MCCULLEY: You need to get to a mike.
10 MS. HOANG: I am sorry.
11 DR. MCCULLEY: There are a number of things up
12 here and I don't know how we are going to put them together,
13 but we have accuracy of cut. We have too thick; too thin;
14 irregular thickness. We have those issues there and I am not
15 sure how we are going to want to state them or maybe group
16 them together, but those are there. But a specific problem,
17 as Dr. Maguire is stating -- a specific outcome is ectasia
18 or progressive corneal ectasia, however, one wants to state
19 it. But I think that there would be agreement that that
20 should be added to the list.
21 DR. REINSTEIN: We should really use the terms as
22 per engineering definitions. Accuracy is the conformity
23 between the measured and the actual thickness. Precision, or
24 colloquially known as reproducibility, is the concordance
25 between repeated measurements of the same point or object.

1 So, if we are going to define accuracy of cut,
2 which is a colloquial term for what we really want to know
3 which is the mean and the standard deviation for that
4 specific keratome. II think that is really what we should be
5 defining.
6 DR. MCCULLEY: And what term do you want to use
7 for reproducibility?
8 DR. REINSTEIN: We could use either
9 reproducibility or precision.
10 DR. MAGUIRE: And what Dan is saying is that
11 accuracy has both to do with the mean and the standard
12 deviation of the cut, and it is important that both of those
13 components of accuracy be looked at separately because they
14 are both extremely important in preventing one of the
15 catastrophic complications of Lasik, which is progressive
16 corneal ectasia. So, there are two different components. In
17 other words, a 180 micron keratome, does it consistently
18 create, or does it have a mean thickness of 180, or 160,
19 200? That is important. The other thing that is important,
20 if 180 micron keratome has a standard deviation of
21 plus/minus 30 microns versus plus/minus 60 microns, that is
22 extremely important too. And, so they have to be looked at
23 separately.
24 DR. REINSTEIN: Of course, the standard deviation
25 is an experimentally derived number from a series of points

1 in an experiment, and they describe a statistical chance of
2 another cut being at a certain distance from the mean. I
3 think a separate descriptor which may or may not be
4 important for a specific keratome would be the thickest
5 possible flap observed in an appropriate number of cuts by
6 experiment, this being because a standard deviation only
7 describes the probability of being thicker than the mean. It
8 is not a description of an outlier or of an event where
9 different clinical characteristics of a patient and the
10 surgeon and the environment would cause the keratome to cut
11 deeper than the standard deviation probability curve would
12 have predicted. So, the deepest cut may be a factor that
13 would give us an indication as to the safety of the
14 keratome.
15 DR. MCCULLEY: Leo, could I ask you to -- let me
16 please remind you again, each time you speak -- I am not
17 going to do it because I keep jumping in, but will everyone
18 else, please, at least say something that allows the
19 transcription people to know who is speaking? If I could ask
20 Leo maybe to -- we have accuracy of the cut; we have too
21 thick, too thin, regular thickness; we have donuts up there;
22 free cap should be up there. All of those things that are
23 issues, and then the corneal ectasia is one of the secondary
24 events related to some of those things. Can you possibly put
25 all of that together in a category that unifies that issue

1 that relates to the accuracy, precision, outlier?

2 DR. MAGUIRE: I think what we are interested in is

3 trying to avoid all complications in refractory surgery as

4 much as possible, paying particularly attention to more

5 catastrophic complications. What happens is that a lot of

6 these things are related to each other. So, I think one way

7 of looking at the problems is to start with the more

8 catastrophic complications observed in Lasik and work down.

9 Certainly the most catastrophic complication in Lasik I have

10 seen is guillotining of the anterior segment, leading to

11 loss of the eye and light perception. That is catastrophic,

12 and that can happen. And, I have one patient who I take care

13 of for somebody else where something equivalent to that has

14 happened.

15 DR. MCCULLEY: Let me ask Scott. What we need to

16 try to do now, we need to create our list. Right now we need

17 to try to get this list so that -- you know, the first thing

18 up there is accuracy. The last two things relate to the same

19 thing. We need to try and get this in reasonable logic.

20 Scott is real good at this. Let me ask Scott if he can.

21 DR. MACRAE: Let me just suggest that we use cut

22 accuracy and precision, or reproducibility, as one category

23 and that will take care of thin flaps, thick flaps. Dan,

24 you may want to refine that in terms of the way that we

25 described it, but I think that is one category. We want a

1 consistent flap that is of a reproducible depth that we
2 know. And, one of the problems that we are having with the
3 manufacturers is they have a number on their plate but it
4 doesn't correspond to the type of data that Dan and other
5 people are generating.
6 DR. REINSTEIN: I think we should stay away from
7 the word "accuracy" because we can't define accuracy. We
8 don't know the actual thickness of a flap; we only know how
9 thick we measured it. So, strictly speaking, we should only
10 be talking about the reproducibility or the precision of
11 depth, central depth.
12 DR. MCCULLEY: Let me try this then -- I don't
13 want to end this discussion, but if we had a heading that
14 was cut mean and standard deviation with thickest outlier --
15 not elegant, under that we have the issues of thick, thin,
16 free, donut, AC perforation, ectasia.
17 DR. MACRAE: Can you go through those again?
18 DR. MCCULLEY: Okay. The heading would be cut mean
19 and standard deviation with thickness outlier. It says it
20 but not elegantly. Then the list would be thick, thin, free,
21 donut, AC perforation and ectasia. Irregularity would come
22 under a different heading, regular, irregular.
23 DR. SUGAR: I would suggest the word range instead
24 of thickest outlier. The range is always going to be 100
25 percent --

1 DR. MCCULLEY: Well, it is for the keratome, but
2 okay. Standard deviation and range. Dr. Pulido?
3 DR. PULIDO: Dr. McCulley, I think that is
4 reasonable. How about if we just look at it in groupings --
5 characteristics of the keratome, characteristics of the
6 keratome flap? That would include reproducibility, etc.
7 Corneal complications, anterior chamber complications. Other
8 ocular complications, for instance intraocular pressure
9 monitoring isn't up there.
10 DR. MCCULLEY: There are a lot of different
11 grouping possibilities. It could be blade; blade plate;
12 interaction; mechanical oscillation; translational speed
13 related to such and so forth. Your proposed overall
14 categorization was -- say that again.
15 DR. PULIDO: Characteristics of the keratome;
16 characteristics of the keratome flap. You can change that.
17 Under that would be reproducibility, etc. Then corneal
18 complications; anterior chamber complications; other ocular
19 complications. Included under that would be intraocular
20 pressure.
21 DR. MCCULLEY: Okay, let's keep that in mind as
22 maybe a final unifying approach that we could take. Mr.
23 Mastel?
24 MR. MASTEL: Thanks, Dr. McCulley. I believe that
25 the proper way to go about this would be to establish flap

1 tolerances which are the deviation from the standard.
2 Tolerances are what you are willing to accept as the
3 variance. Then other complications would, I think, be a
4 separate grouping.
5 DR. REINSTEIN: The heading of that column says
6 keratome problems. Are we defining the criteria that a
7 keratome should have?
8 DR. MCCULLEY: The approach we are taking is
9 problems associated with the keratome. I think that one
10 thing we are going to have to be careful with here -- and
11 there is overlap and I am not sure how that is going to be
12 dealt with, and that is the clinical problems associated
13 with the use of the keratome, and the other relates to the
14 engineering issues and tolerance of the instrument. And, we
15 are not an engineering advisory panel. Some of us, like Dan
16 and Mr. Mastel, have obviously engineering backgrounds and
17 expertise. How much we get into that, I am not sure. I think
18 our expertise is going to be going at it, as Dan suggested,
19 from the keratome-related problems. We will get into causes
20 of how they can be dealt with, and some of that will relate
21 to recommendations about engineering issues.
22 DR. MAGUIRE: I think you might want to change
23 that heading, like Dan says, instead of blaming it on a
24 keratome to say clinical problems associated with lamellar
25 flaps because some of these are multifactorial, or their

1 etiology remains unclear or controversial. So, if we just
2 say clinical problems because that is what we are really
3 after, and this is problems associated with these
4 procedures. What we can do is then bring in the keratome-
5 related problems. I think that is really the right way to
6 work on it because a lot of these things are interrelated.
7 DR. MCCULLEY: You need to put in that first
8 category, as suggested, ectasia as well.
9 DR. REINSTEIN: The mean and standard deviation or
10 range are not a clinical problem. They are descriptors that
11 are going to help us avoid problems.
12 DR. MCCULLEY: You know, we can have some really
13 major semantic discussions here. I think as long as we know
14 what we are talking about, we can let the FDA subsequently,
15 if they want to have consistency in semantics, deal with
16 that.
17 MS. HOANG: Dr. McCulley, I am sorry to interrupt.
18 The reason why we put down accuracy is that it is relative
19 to the specification for the device. For instance, if the
20 physician keys in 160 microns, is he getting the 160
21 microns? That is what we meant by accuracy.
22 DR. MCCULLEY: We know that, and that is what we
23 are trying to get at, and trying to refine it a bit more
24 than using as loose a term as accuracy, even though that
25 might end up being the best term for the average clinician

1 to be faced with. We will leave, you know, the final wording
2 to you. But I think the important thing here is that we use
3 words that we understand, and that we stay to the points.
4 DR. MACRAE: I would like to suggest that rather
5 than sort of being directed by the computer that we use this
6 as a brainstorming session, and that what Dan says and what
7 we say just kind of be thrown into the pot and then at the
8 end we can come to a clear consensus about the verbiage
9 because it seems like the computer, and Quynh having to do
10 that, is going to be -- in a sense, it is sort of going to
11 lead us rather than --
12 DR. MCCULLEY: That was the format laid out, that
13 we would work from that and continually upgrade it. I
14 understand your point but we are going to end up needing to
15 create this, and I think probably in terms of trying to
16 manage it within the time frame, we ought to still try to
17 work with this, add or take from it, and not get too much
18 caught up in word usage. Then we can fine-tune the word use
19 as long as we know what we are talking about.
20 DR. MACRAE: I would like to add just one thing
21 that Jose mentioned, and that is intraocular pressure and
22 the reproducibility of the intraocular pressure system
23 because of the potential damage to the optic nerve. I got a
24 letter from Jack Hertzman, that was sent to the FDA,
25 basically talking about the concerns with intraocular

1 pressure. So, I think we do need to address that as well.

2 DR. MCCULLEY: We could put that maybe under --

3 would it be appropriate to put that under suction?

4 DR. MACRAE: Actually, that is what I did. I put

5 it under intraocular pressure and suction loss.

6 DR. MCCULLEY: Yes, if we put suction we could

7 have suction, suction loss, consistency of suction of IOP

8 created, and one of the major problems under that is going

9 to be ischemic globe issues. So, if we could add that:

10 consistency, maintenance of, and potential ischemia.

11 DR. MAGUIRE: IOP.

12 DR. MCCULLEY: Then after suction, put in

13 parentheses IOP. I think if we are discussing clinical

14 problems, the clinical problems that arise as a consequence

15 of that, we can say central artery occlusion --

16 DR. MAGUIRE: That is the ischemic globe.

17 DR. MCCULLEY: Yes.

18 DR. MAGUIRE: You could have pupillary

19 abnormalities; you can have retinal damage; you can have

20 central artery occlusion.

21 DR. YAROSS: I would like to make a suggestion.

22 What we are actually trying to do is a risk management

23 exercise, and in risk management there are some tools --

24 obviously, we don't want to get into engineering tools here

25 but one of the things that one does is to identify both the

1 hazards and the failure modes and the consequences. And, one
2 of the things that is confusing us a little bit is that we
3 are mixing failure modes, hazards and consequences.
4 What I would suggest is that, using the outline
5 that we have there for clinical problems, is focus first on
6 what are the clinical events, for example, an undesired flap
7 thickness. That is really a clinical event. Then we can go
8 back and the next column is possible causes, and we can get
9 into the failure modes such as improper tolerance.
10 Then also, in considering what are the clinical
11 issues, use the clinical knowledge of this group to look at
12 what are the consequences, such as ischemia, things of that
13 sort, to come up with what are the failure modes that we are
14 worried about.
15 But I think part of the issue is that we are
16 trying to do all three of these at once, and we may want to
17 try to take them one at a time.
18 DR. ROSENTHAL: May I also say we know what the
19 possible clinical problems are. We don't need this panel to
20 enumerate them for us, unless you feel that it is important
21 to.
22 DR. MCCULLEY: Your first charge to us was to
23 enumerate, add to and subtract from your list. I am trying
24 to do what you asked us to do. If you want us to do
25 something else then, okay, tell me what.

1 DR. ROSENTHAL: No, it is just that we don't need
2 a discussion of frequency --
3 DR. MCCULLEY: No, I agree. But you need on your
4 list ischemic globe.
5 DR. ROSENTHAL: We need IOP, yes.
6 DR. MCCULLEY: Yes.
7 DR. ROSENTHAL: And its consequences.
8 DR. MCCULLEY: Right, and that is what we are
9 trying to do. I don't disagree that there may be much better
10 approaches and more sophisticated approaches. What we have
11 been presented with is a charge that I think we need to stay
12 with and not reinvent.
13 DR. YAROSS: No, I am not suggesting that. What I
14 am saying is some of these things, which are the failure
15 modes, really belong in the next column.
16 DR. MCCULLEY: Right.
17 DR. YAROSS: So, in terms of some of these
18 tolerance issues, if they are fairly simple in terms of what
19 are the clinical issues in terms of irregular cut or an
20 undesired depth -- those are really, I think, simple ways of
21 formulating what are the clinical issues.
22 DR. MCCULLEY: I understand.
23 DR. YAROSS: And then we can come back to causes.
24 DR. MCCULLEY: Okay. I think probably what we will
25 end up doing -- I will try to do that as we go -- but what

1 we may end up doing is creating a longer list here and
2 moving some of those over to be certain we don't miss some
3 of the issues. But I will try to keep it as clean as
4 possible.
5 Okay, so we just had the suction issues. Another
6 suction issue, to my mind, is decentration of the flap. So,
7 under suction issues we have consistency of, maintenance of,
8 ischemic globe, decentration of flap.
9 DR. MACRAE: That is a separate issue from
10 suction.
11 DR. MCCULLEY: Decentration is? It is the suction
12 ring and its placement and where it sits that determines a
13 lot of decentration. So I put it there. So humor me for a
14 minute.
15 DR. PULIDO: What is the difference between that
16 and flap [comment off microphone].
17 DR. MCCULLEY: They are postop. Flap dislocation
18 is a postop event.
19 DR. MACRAE: I would like to add partial flap.
20 DR. MCCULLEY: Partial flap, to me, Scott, is not
21 just -- I would put that somewhere with irregularity because
22 a partial flap can be because of malfunction of the machine
23 or obstruction of the pass. It isn't so much a depth related
24 issue.
25 DR. MACRAE: It can be if it is --

1 DR. MCCULLEY: If you amputate it.

2 DR. MACRAE: Yes, or if you are using a relatively
3 thin microkeratome, which I have seen, where the surgeon
4 used a 130 plate on a relatively flat cornea and you get
5 just a partial pass essentially.

6 DR. MCCULLEY: You mean it stopped in its coursing
7 or it cut a piece off?

8 DR. MACRAE: It cut an incomplete, a very thin
9 flap that was irregular. So, maybe we should call that
10 category irregular flaps.

11 DR. MCCULLEY: Yes. That event you describe I
12 would put under irregular. Where do we have partial? We do
13 need partial flaps because that usually is a mechanical
14 event.

15 DR. MACRAE: It is. This kind of comes into a
16 category, I think, in terms of donut flaps, irregular flaps,
17 and some of this is because of the corneal curvature, the
18 anatomy that you are confronting, and sometimes it is a
19 surgeon error, that the cornea is just too flat. Sometimes
20 it may be microkeratome related. It is actually a very
21 complex arena but I just want to bring that out.

22 DR. MCCULLEY: Okay. Let's put that down under
23 irregular. We have up here interrupted movement, which would
24 result in partial flap, which is another category. What you
25 are talking about, let's put that under irregular flaps. Dr.

1 Pulido?

2 DR. PULIDO: Dr. McCulley, I am not a cornea

3 doctor, nor do I play one on TV, but --

4 [Laughter]

5 -- Dr. Sugar and Dr. Thu have shown a few cases of

6 Lasik to me where you can see some metal shavings in the

7 flap. Do we want to include that?

8 DR. MCCULLEY: I think another category that isn't

9 up there has to do be interface debris.

10 DR. HIGGINBOTHAM: That was exactly my question,

11 considering the debris we saw on scanning electron

12 microscopy on those blades. I would think from a very

13 innocent standpoint -- I too am not a cornea specialist and

14 don't plan to be -- that you could get trapped debris in the

15 interface.

16 DR. MCCULLEY: So, interface debris is a major

17 heading. Dr. Reinstein?

18 DR. REINSTEIN: Under the chatter lines, perhaps

19 we could make the heading of that box quality of the bed

20 because the bed may contain chatter lines. It may contain a

21 nick in the blade. It may contain a step due to a change in

22 the depth during the passage of the keratome.

23 DR. MCCULLEY: Thank you. A good point.

24 DR. REINSTEIN: A second point, I thought I saw

25 edge -- is there an edge box?

1 DR. MCCULLEY: No, I don't think there is.

2 DR. REINSTEIN: So, edges. It is important that
3 the keratectomy be clean through the epithelium and not
4 tearing through the epithelium. So, if we could describe the
5 sharpness of the edge of the flap.

6 DR. MCCULLEY: I understand as well that the entry
7 angle of the blade and the characteristics of the periphery
8 of the flap are also important issues. Could you put that
9 all together? I mean, it fits with what you are talking
10 about. Actually, you could put that into your bed. You could
11 put characteristics of entry, wound and bed into one.

12 DR. SUGAR: It could be perimeter characteristics.

13 DR. MCCULLEY: Right. So perimeter and bed
14 characteristics.

15 DR. REINSTEIN: These are important with respect
16 to the risk of epithelium ingrowth.

17 DR. MCCULLEY: And probably continued alignment of
18 the flap after it is in place. But there we get into causes.
19 I guess the question here would be the outcomes -- the
20 chatter, the bed characteristics, stand alone, the periphery
21 characteristics result in things. Let's leave it here for
22 now. I mean, we have some things in different places; we are
23 moving them around.

24 DR. REINSTEIN: Sorry, there is another at least
25 observed characteristic that I have noted, which is

1 epithelial defects over the flap, despite the fact that they
2 are not intended at all.
3 DR. MCCULLEY: I think that should be a category
4 as well, epithelial defects.
5 DR. REINSTEIN: Then we could maybe separate them
6 into central and peripheral --
7 DR. MCCULLEY: Put in parentheses central versus
8 peripheral. Mr. Bartell, I saw your hand.
9 MR. BARTELL: I was going to bring up epithelial
10 abrasions.
11 DR. MCCULLEY: Okay, we got it.
12 DR. REINSTEIN: Can I ask, on our outline of
13 content of keratome 510(k) submissions, Part 5, Section
14 A2(b)(7), methods and components used to produce variable
15 hinge diameter or thickness. May I suggest that that not be
16 a fifth order subdivision.
17 DR. MCCULLEY: Well, wait. If you are getting to a
18 point that relates to this, all right; if you are talking
19 about something down there, that is way on in the afternoon.
20 DR. REINSTEIN: Well, the thing is that it is --
21 DR. MCCULLEY: Relate it to our list.
22 DR. REINSTEIN: It is related, as Marcia pointed
23 out, to the next columns --
24 DR. MCCULLEY: No, we are on this column. Put
25 something in this column. If you want to put a reminder in

1 this column that doesn't necessarily go, I think that is
2 okay but we don't want to get into -- right, we will do that
3 later.
4 Any other things relating to this list to add or
5 subtract? I think, you know, just by way of the interstitial
6 keratitis -- I mean, that is the sands of Sahara; that is
7 the diffuse lamellar keratitis. Interstitial keratitis is
8 probably not the best term. The one that I have seen that is
9 probably the best, and I have asked for help from everybody
10 else, is diffuse lamellar keratitis. There are some nods.
11 Doyle, how do you feel about that?
12 DR. STULTING: It is a reasonable term but it is
13 not always diffuse. I would call it non-specific interface
14 keratitis.
15 DR. MACRAE: I would say lamellar keratitis, and
16 then we can talk about diffuse versus focal.
17 DR. MCCULLEY: Okay.
18 DR. MACRAE: I have seen a number of cases now --
19 DR. MCCULLEY: But we don't want to use
20 interstitial. So, lamellar keratitis is our term for this.
21 Under the flap dislocation we have slippage and
22 poor alignment that probably need to be added to that as
23 additional terms so that we can potentially deal with those.
24 DR. REINSTEIN: On slippage, I don't know where we
25 would want to categorize it but, clearly, microfolds and

1 Bowman-layer cracks, which can be visually significant,
2 should be mentioned on a list of problems. I don't know how
3 they relate to the keratome necessarily. They might be more
4 to do with surgical technique.
5 DR. MCCULLEY: Yes, we want to put that in. I have
6 that on my list too -- flap wrinkles resulting --
7 DR. REINSTEIN: Microfolds, cracks.
8 DR. MCCULLEY: Whatever -- wrinkles, microfolds,
9 cracks will be all-inclusive, and the potential clinical
10 issue there is irregular astigmatism. So, put the irregular
11 astigmatism as well.
12 Have we dealt effectively with the perimeter of
13 the flap? Where is that? Scott, as I understood, what you
14 were talking about was amputation of the flap. Was I
15 following you or not?
16 DR. MACRAE: Right, where you kind of have a
17 skipping type microkeratome pass where you are relatively
18 superficial on a flat cornea, you get a little cornea and
19 then essentially the microkeratome bounces out a little bit
20 and then comes back in again. So, you have a donut shape or
21 a partial, just little --
22 DR. MCCULLEY: Slivers.
23 DR. MACRAE: -- slivers of cornea.
24 DR. MCCULLEY: We can put that under irregular
25 flaps.

1 DR. MACRAE: Right.

2 DR. MCCULLEY: So, wherever you have irregular
3 flaps just put the word slivers.

4 DR. MAGUIRE: Dr. McCulley, I think if you had
5 some little graphics of each of those in the final output so
6 that there is no semantic confusion, that would be useful,
7 and have the entire cornucopia of type of things that can
8 happen because some of them have different keratome causes
9 or multiple things can come into effect, and some of the
10 things don't have anything to do with the keratome; they are
11 characteristics of the individual patient.

12 DR. MCCULLEY: Where are the chatters and all of
13 those? Are they higher up, off the screen? Okay, chatter.
14 Where is our periphery? We need something related to the
15 perimeter of the flap. Where is that? We need to expand
16 that. It is not just jagged. It is angle of entry; it is
17 cleanness of entry.

18 DR. REINSTEIN: The Barraquer defined terminology
19 for the edge is the bevel of the entry. So, if there is a
20 shallow bevel it is not the same as if it is a regular 26
21 degree bevel. That is how he classified the quality of the
22 edge.

23 DR. MCCULLEY: Okay, better word. We are going to
24 have some real fun things, you know, in cleaning this up but
25 I think my goal actually ended up here being trying to get

1 everything included that we would want to include and we can
2 move categories. But are there any other problems? Yes, Mr.
3 Bartell?
4 MR. BARTELL: I think you mentioned free flap and
5 I don't believe it was put up there.
6 DR. MCCULLEY: Is free flap not up there?
7 [Multi-member discussion]
8 DR. MCCULLEY: A free cap is intraoperative. Where
9 do you have donuts? There is free. Thank you. It is there.
10 What you might want to put is free cap, not just the word
11 free. Now, initially this all fit on the screen.
12 DR. REINSTEIN: I am sorry to interrupt, free cap
13 is related to an unwanted diameter because the stop is
14 beyond where the diameter actually occurred, and donut is a
15 function of the thickness.
16 DR. MCCULLEY: Right, and pressure and curvature
17 and all sorts of things. So, how would we split those? Why
18 don't we put free/small -- free cap or small flap?
19 DR. REINSTEIN: Unwanted thickness, unwanted
20 diameter are headings really.
21 DR. MCCULLEY: Okay, let's get all the concepts up
22 there, and we want to add the concept of a small flap, with
23 the ultimate in that being a free cap.
24 DR. MAGUIRE: I think what you are looking at is
25 some unwanted width. That would be another way of going

1 about it because a free flap occurs when a hinge fails to
2 present itself --
3 DR. MCCULLEY: Okay, rather than trying to argue
4 which is which, let's add to this in that same area,
5 undesired hinge width. And, we are going to work on these
6 things. Right now, quite honestly, my goal is to get
7 everything up there that we need. Mr. Mastel?
8 MR. MASTEL: How about free donuts?
9 [Laughter]
10 DR. MCCULLEY: Any combination of anything up
11 there is assumed as a possibility. We have irregular and the
12 slivers, so I put that under the irregular and the slivers.
13 Any other things that need to be on the list for
14 us to be all-inclusive?
15 DR. REINSTEIN: Infections.
16 DR. MCCULLEY: I think that is already there,
17 isn't it?
18 MS. HOANG: Yes.
19 DR. MCCULLEY: We have other things we have not
20 mentioned.
21 [Multi-member discussion about the lost screen]
22 DR. MCCULLEY: If you lost it all we are going to
23 kill you!
24 [Laughter]
25 MS. HOANG: Well, let's see.

1 DR. MCCULLEY: We are assuming that the other
2 things that are on here that we have not mentioned are still
3 there -- epithelial ingrowth, infection. Somebody had better
4 have been taking notes.
5 MS. HOANG: We have been taking notes.
6 DR. MCCULLEY: A question to you, you did still
7 have on the list the other things we have not mentioned.
8 Epithelial ingrowth should still be there. We have not
9 talked about that. Infection should still be there; we
10 haven't talked about that. Everything else we have talked
11 about. So we are assuming that those things are still there,
12 that nothing was taken from the list.
13 While they are looking to recoup, are there any
14 other additions to this list that anyone can think of? Not
15 that things will not be move to another column, but anything
16 that should not be on this list? I assume no.
17 DR. REINSTEIN: We sometimes cut the lids -- we
18 sometimes inadvertently cut the lid of the patient. Perhaps
19 that might be included.
20 DR. MCCULLEY: Lid lacerations? Do we want that? I
21 mean that is an issue with one type of keratome compared to
22 another.
23 DR. MAGUIRE: And, I think lid laceration is
24 something -- again, these things interact -- that can relate
25 to risk of infection. So, it probably should be included.

1 And, it also can relate to interface debris and effects on
2 the blade before it actually enters the cornea. So, I think
3 that is appropriate.
4 DR. MCCULLEY: Right.
5 DR. REINSTEIN: And on that topic, there are
6 keratomes that are difficult to place, difficult to get
7 suction ring placement --
8 DR. MCCULLEY: That is going to come potentially
9 under ischemia and those kinds of things, things that add
10 time to the suction time.
11 DR. MACRAE: We get into a whole sort of category
12 of complications like pain, ptosis from the pressure. These
13 are all relatively non-critical areas in terms of the public
14 health issue.
15 DR. MCCULLEY: I don't know where they fit here.
16 So, thanks for bringing it up. I don't think that would fit
17 here.
18 DR. MAGUIRE: One other one is complications in
19 patients who have had previous refractory surgery.
20 DR. MCCULLEY: I think that is a different issue.
21 DR. MAGUIRE: Well, it is an issue with the
22 keratomes.
23 DR. MCCULLEY: Right, but it is a clinical setting
24 issue. I think it is a point well taken that it is a concern
25 for us but I don't think it fits into this, as I see it.

1 DR. MACRAE: What I would suggest is that we kind
2 of put that on the back burner for now. That comes with the
3 patient issue later on, the third column.
4 DR. MCCULLEY: Mr. Bartell, you have had your hand
5 up back there. Do you still want to speak, Mr. Bartell?
6 MR. BARTELL: No, he brought up the eyelid
7 cutting.
8 DR. MCCULLEY: Okay. Any other issues? And, there
9 is nothing that we want to take off the list. We have a long
10 list up there that covers more than the screen. From a
11 functional standpoint, what I would like to see is all of us
12 have a printout, a hard copy of that now for the next step.
13 MS. HOANG: If you don't mind, could we have a
14 break first though? We have to hook up the printer to print
15 it out.
16 DR. MCCULLEY: Okay. You have recovered it, I take
17 it from that.
18 MS. HOANG: Not --
19 DR. MCCULLEY: We are confident you will. You are
20 going to produce everything that has come out of our brain
21 and our mouth so far on a hard copy, and why don't we take a
22 break for you to accomplish that, of ten minutes, fifteen
23 minutes?
24 MS. HOANG: Fifteen minutes.
25 DR. MCCULLEY: Fifteen minutes.

1 [Brief recess]

2 DR. MCCULLEY: Look at your hard copy handout.
3 Hopefully, everyone has been taking the last couple of
4 minutes to look down and read the list. Our second charge --
5 let me find our charge here. In looking through, it looks
6 complete; the list that we have been provided appears to be
7 complete, to me. Everyone has hard copy, right? Mr. Bartell?

8 MR. BARTELL: I would like to suggest possibly one
9 more addition, and that would be bleeding. If you try to
10 make every eye fit to vacuum rings you are going to get some
11 large flaps. You know, when you stop bleeding you delay the
12 ablation; you change your hydration to the cornea; and I
13 think it could well be a responsibility of the manufacturer
14 to assure that you have some options to avoid bleeding, or
15 you have pannus, particularly hyperocupations with high Ks
16 and you try to force them into a ring.

17 DR. MCCULLEY: Okay, I initially considered
18 putting that on my list before I came to the meeting, and
19 then didn't. What is the consensus? Do you think that should
20 be there? It does relate to the diameter. So, if you only
21 have large diameter options there is going to be more of an
22 issue with the bleeding. Should that be on our list? Well,
23 let's put it on. So, bleeding. And, you certainly don't want
24 the blood in the ablation zone.

25 Does the list look complete relative to what we

1 said before? Anyone see any omissions?

2 [No response]

3 **Session II: Probable Causes**

4 I guess then our charge right now is twofold. It

5 is as it was stated, that we should come up with the causes,

6 and maybe as we go down the list, looking for causes, we

7 will find some things in this column that shift over

8 completely. So, let's again take the approach that was

9 recommended to us, which is now to focus this session, to

10 identify the probably causes of each problem, recognizing

11 that some of the things that we have as problems are cause,

12 and to try to group the causes into categories as much as

13 possible, whether equipment related, user/behavior related,

14 or patient or clinical characteristics related, or others if

15 it doesn't fall into one of those columns, and our sheet is

16 laid out that way. Dr. Pulido?

17 DR. PULIDO: Just a question for clarification,

18 are there supposed to be some rows here that weren't put in,

19 for instance under "suction" there is also "decentration of

20 flap." That seems to me a separate row. So, should we first

21 go through and see.

22 DR. MCCULLEY: Actually, decentration of the flap,

23 by and large, is very much determined by how the suction --

24 that determines where the cut is going to be. That is okay.

25 But we can move some of these things around as we come to

1 them. I would propose we start at the top and go down to
2 come up with causes and then we can move, rather than
3 shotgun and scatter gunning it. Let's start at the top and
4 go down.
5 The first is imprecise diameter of flap/hinge. So,
6 let's ask two questions: should that stay in this column? If
7 so, what are the causes? So, imprecise diameter of
8 flap/hinge, that sounds like that should be in this column.
9 What would the cause be? Is it device operator? Patient?
10 Does not the imprecise diameter of flap/hinge relate to free
11 caps and the like?
12 DR. MACRAE: Sure.
13 DR. MCCULLEY: So, should this stand -- I mean, we
14 put everything in here that we could think of so we are
15 going to be x-ing some things off. Do we want to leave that
16 as the heading and move free cap under that? I see some
17 heads nodding. So, under imprecise diameter of flap/hinge,
18 e.g., free cap.
19 DR. REINSTEIN: And short flap, which is the
20 opposite.
21 DR. MCCULLEY: Okay, free cap or -- well, no,
22 wait. Short flap? You mean small flap?
23 DR. REINSTEIN: Diameter smaller than desired.
24 DR. MCCULLEY: Okay, let's see, we have words for
25 that down there where we did it before, and then the extreme

1 was the free cap. Where is it?

2 DR. REINSTEIN: Small cap could be a fully

3 circular small cap.

4 DR. MCCULLEY: But you could also have a small

5 flap and still retain the hinge but the flap be smaller than

6 desirable, and the ultimate of that is a free cap. That is a

7 little artificial but is that not the principle?

8 DR. REINSTEIN: Yes, I think the term short flap

9 is used quite specifically to mean that the bed exposure is

10 not sufficient with respect to the pupil position. So, free

11 cap is an event where there isn't a hinge and that could be

12 in a small or a large flap.

13 DR. MCCULLEY: Right.

14 DR. REINSTEIN: But a short flap is an undesirable

15 small diameter.

16 DR. MCCULLEY: Okay, so whey don't we say it could

17 be -- I understand what you are saying, the way you are

18 using short, but would it fit if we just said small flap,

19 free cap?

20 DR. YAROSS: These are all subsets of flaps that

21 have undesired dimensions.

22 DR. MCCULLEY: Right.

23 DR. YAROSS: So maybe it is undesired flap

24 dimensions as the general category, with then these others

25 being specific examples.

1 DR. MCCULLEY: To use that instead of imprecise
2 diameter? They say the same more or less. Let's leave it --
3 DR. REINSTEIN: Why don't we have the categories
4 as undesirable diameter with or without a hinge? That way,
5 you would have small free caps or large free caps, and you
6 could have small hinged flaps or large hinged flaps.
7 DR. MCCULLEY: Okay, one of the things we often do
8 with this is that we are trying to deliver a message, and we
9 can end up in fine-tuning the exact words of the message ad
10 nauseam. So, as long as we have the message made clear to
11 the FDA, then I think that is our goal. And, I think you
12 have heard us say this and rather than us argue or discuss
13 verbiage, the principle is there and it relates to -- the
14 presence or absence of hinge relates to desired diameter or
15 the varying diameter of the flap or free cap. So, I think we
16 understand this. Do you guys understand that?
17 Now, possible causes -- we have a category, guys,
18 let's go for it. Okay, possible causes: device, operator,
19 patient, other. Clearly, it can be patient related if there
20 is a flat cornea. So, a possible cause under patient would
21 be a flat cornea, flat K.
22 DR. JURKUS: Wouldn't that be operator? It would
23 be up to the operator to determine if the patient has a flat
24 cornea and decide on the appropriate tool to use.
25 DR. MCCULLEY: So there is an operator component,

1 yes. I mean, the issue is flat K. The operator has to deal
2 with that and, within the range of our capabilities, can
3 deal with it within limits.
4 DR. MACRAE: This brings up an important issue,
5 and that is that the operators need some guidance from the
6 manufacturers in terms of what is considered a flat K for
7 that particular device --
8 DR. MCCULLEY: Right.
9 DR. MACRAE: -- and we don't have that. Some of
10 the manufacturers are now starting to produce that, which is
11 very helpful, but we need more guidance in terms of that.
12 DR. MCCULLEY: Okay, so on the patient side it
13 would be flat K; on the operator -- it is going to be device
14 as well. We have to have device capability to account for
15 it. We need larger diameter cuts ability.
16 DR. MACRAE: Also, the thickness. You know, some
17 of the flat corneas that we were very nervous about treating
18 previously we now treat with usually thicker flaps.
19 DR. MCCULLEY: So, under device we would say we
20 need the ability to vary diameter and thickness of flap.
21 DR. REINSTEIN: Imprecise diameter -- the diameter
22 of the flap or cap relates to essentially three issues. They
23 were described by Barraquer 40 years ago: the intraocular
24 pressure at the time of passage, the height of the platform
25 of translation of the plane, of the keratome, the stop gap

1 between the edge of the blade and the edge of the keratome,
2 and the Ks. So, these are the factors, and then we can
3 classify them into the boxes. So, for example, under this
4 box, device elements that would lead to an imprecise flap
5 diameter would be poorly regulated intraocular pressure by
6 the machine during passage; would be obviously improperly
7 machined components so that the predicted diameter is not
8 achieved.
9 Under operator we would have to put all of these
10 issues that Dr. MacRae is referring to. Should there be very
11 specific instructions for the surgeon on how to perform a
12 keratectomy of this depth given the patient's criteria,
13 where a patient has a cornea that is this thick, where a
14 patient has a cornea that has this curvature, you are going
15 to use this ring with this stopper to produce that depth at
16 that diameter.
17 One of the elements that has disappeared from the
18 newer keratomes is an applanation lens, as it was called by
19 Barraquer. That lens was placed on the cornea before passage
20 in order to see beforehand how much of the cornea would be
21 applanated by the keratome head. This determines, before
22 passing the keratome, what the diameter would be. So, there
23 is another piece of equipment that could be used to predict
24 the flap diameter --
25 DR. MCCULLEY: Okay, let me stop you. We are

1 getting into the mitigation, the ways to deal with the
2 problems. Good points but let's try to stay with column one
3 and two. The other thing is you need an effective stop on
4 the microkeratome. That would come under device I think, a
5 specific.
6 So, you have outlined device situations, Scott,
7 operator situations, and we will keep our solutions to this
8 for the next discussion. Well, he had IOP control; it is
9 suction. It is creation and maintenance of effective suction
10 throughout.
11 DR. HIGGINBOTHAM: One of the comments I heard was
12 that IOP control will have an impact on the appropriate
13 diameter of the flap.
14 DR. MCCULLEY: Yes.
15 DR. HIGGINBOTHAM: So, should not IOP be under
16 patient characteristics?
17 DR. MACRAE: The IOP you create with the suction
18 ring.
19 DR. MCCULLEY: Yes, we create it with the suction
20 ring.
21 DR. HIGGINBOTHAM: Okay.
22 DR. MCCULLEY: It is not the patient's normal --
23 DR. HIGGINBOTHAM: So, it should be under device.
24 DR. MCCULLEY: It is under device. It is the
25 effectiveness of the suction ring in creating the right

1 pressure.

2 DR. HIGGINBOTHAM: I understand. Okay, fine.

3 DR. MCCULLEY: It doesn't make any difference what
4 the patient's normal pressure is in this situation. Okay, we
5 have that; we have the causes. Are there any other causes
6 that anyone would like to offer? Mr. Bartell?

7 MR. BARTELL: Yes, the patient I think should be
8 included in this as far as the possible causes simply
9 because of the nervousness of the patient, the tendency to
10 squeeze the eye sometimes. I think you are getting into
11 areas that we are trying to determine but really don't know
12 yet.

13 DR. MCCULLEY: Right. That would probably come
14 under our maintenance of suction, further down. But, I mean,
15 these are going to overlap. Good point. I would worry more
16 about the patient squeezing, not so much about raising their
17 pressures, messing up our suction ring or maintenance of
18 suction. But both could be a problem. Any other comments on
19 this? We will get that under that other category, and we can
20 cross-reference.

21 DR. REINSTEIN: Under operator, we just discussed
22 ring selection, keratome head selection, stopper selection.
23 Those were our operator defined variables -- ring, head,
24 stopper.

25 DR. MCCULLEY: The stopper also, to me, would be

1 part of the device issue too, if the device had the
2 capability to allow us either to accomplish it, period, or
3 to adjust it.
4 DR. REINSTEIN: And then the operator has to
5 choose the right one.
6 DR. MCCULLEY: Right. Okay, the next is poor
7 precision and reproducibility. The issue here was mean,
8 desired versus achieved; standard deviation; range; maximal
9 thickness, thin, donut, free; AC perforation; ectasia. There
10 is a lot under there but they are all related, one to the
11 other with -- I hesitate to use the word, but accuracy -- a
12 trash basket term -- of our cuts. These are very much device
13 dependent, and they are somewhat patient dependent and
14 operator dependent.
15 DR. MACRAE: And environment dependent. Hydration
16 can be temperature and humidity related too.
17 DR. MCCULLEY: They do with lasering, do you think
18 they do with --
19 DR. REINSTEIN: Yes. They can affect the size. The
20 stop gap can be affected by temperature.
21 DR. MCCULLEY: I know that that is true, but
22 within practical ranges? I assume we are not operating in
23 100 degree temperatures and freezing climate -- within
24 normal range of temperature, this wouldn't be an issue,
25 would it?

1 DR. REINSTEIN: Could we ask Mr. Mastel whether
2 the tolerances and the friction within the narrow range of
3 movement of the blade within the head, could that be
4 affected by temperature changes, operating in Siberia or in
5 the Dominican Republic?
6 MR. MASTEL: I can tell you that with our diamond
7 blade we broke the blade [comment off microphone] and other
8 than that, I don't think it is going to have much effect.
9 But we don't sell it; we are not on the market. Perhaps Mr.
10 Bartell knows.
11 MR. BARTELL: No, I don't think it would.
12 DR. MCCULLEY: Okay. Under this broad category, if
13 we leave this broad category as it is, device-related issues
14 -- we need to know -- I will say it and then you can correct
15 me and you can then expand it, but basically we need to know
16 what our keratomes are going to cut; how reproducible it is;
17 and what the unusual outliers are apt to be. And, we need to
18 know that for the brand of keratome. We need to know what
19 the variability is from one keratome within that brand to
20 another. And probably, the way things are now, we need to
21 know what it is for our individual keratome after the fact,
22 once we get it. Now, how do we put that into terms to help
23 the FDA relative to device issues? Right now there seems to
24 be a good deal of variability.
25 DR. MACRAE: Jim, can I back up?

1 DR. MCCULLEY: Sure.

2 DR. MACRAE: I think in a sense this is the whole
3 point of this meeting, that I don't want to get a
4 microkeratome and have to go back and confirm that my
5 microkeratome is not almost exactly the same as your
6 microkeratome in Dallas, Texas. I think that that is the
7 gist. One of the more important things that we can generate
8 from this discussion so that the agency can go back and say
9 to the manufacturers, we have a problem here. We want to
10 have very alleged accurate -- until we can exactly measure
11 thickness with Dan Reinstein and other type devices, we want
12 to be able to have relative accuracy or alleged accuracy
13 that is very, very good so that we can move forward more --

14 DR. MCCULLEY: With a greater degree of
15 confidence.

16 DR. MACRAE: Yes, with more confidence and start
17 establishing a more scientific way of addressing these
18 problems.

19 DR. MCCULLEY: I think the sense is that we are
20 not sure if our keratome says that it is going to cut 180
21 what it is going to cut, and how do we get at that? What we
22 need to do is not tell the FDA engineers how to do that, I
23 don't think, unless that is what the FDA wants. We need to
24 give them the principles from our side that are of concern.
25 I think Scott has put it very well. This is a major concern

1 for all of us, that is, how reproducibly do our keratomes
2 cut, and how reproducible is one keratome to the other with
3 its cutting accuracy.
4 DR. MAGUIRE: And it should also be established
5 that it is a major concern because of scientific evidence to
6 show that there is a problem, and that is from Dr.
7 Reinstein.
8 DR. ROSENTHAL: May I just suggest, Mr. Chairman,
9 that you put inter- and intra-keratome reproducibility as
10 the device issue? Dr. MacRae is worried that they all do the
11 same thing and you are also worried that they keep doing it.
12 DR. MCCULLEY: Consistently, and I think there is
13 great concern on all of our parts about that. Am I
14 appropriately stating that? Mr. Myers?
15 MR. MYERS: Yes, the way the agency has handled
16 this with other products is having the individual
17 calibration supplied with each unit. This would be possible
18 for a manufacturer to do without too much trouble --
19 DR. MCCULLEY: That is a solution. That comes
20 under our mitigating --
21 MR. MYERS: Okay.
22 DR. REINSTEIN: As Dr. Hoang mentioned at the very
23 beginning when we were discussing accuracy and precision and
24 their relative meaning, in fact, perhaps in the first column
25 we really should be saying poor accuracy, and in the second

1 column we should say poor precision and reproducibility as a
2 device cause because those are the only things we can
3 control, the precision and reproducibility. The accuracy is
4 the problem.
5 DR. MCCULLEY: Okay.
6 DR. REINSTEIN: In that column, keratome aspects
7 which would lead to poor reproducibility of the thickness of
8 the flap include, again, control of the intraocular pressure
9 during suction --
10 DR. MCCULLEY: Let me interrupt you just a second.
11 You are changing as individuals are talking, on the screen.
12 Please don't do that. Wait until we reach a consensus. Can
13 you back up to where you were, just as a matter of how we
14 are going to do that?
15 DR. REINSTEIN: Intraocular pressure control and
16 stability during passage of a keratome is a device element
17 which leads to poor reproducibility, poor tolerances of the
18 elements as purchased by the use, i.e., height of the plate,
19 stop gap within the keratome that is manufacture.
20 DR. MCCULLEY: Let me ask you something. Ralph
21 said something I thought was really very good, that, to me,
22 so far has covered everything, and that was inter- and
23 intra-keratome device consistency. Does that not cover the
24 whole thing from the device standpoint? There are lots and
25 lots of things under that, but does that not encompass it?

1 DR. YAROSS: I think that is, again, the result
2 and that underneath that, as Dr. Reinstein said, you have
3 the issues of calibration and tolerances.
4 DR. MCCULLEY: Okay. So, consistent calibration
5 and tolerance.
6 DR. YAROSS: Accurate calibration --
7 DR. MCCULLEY: Accurate calibration.
8 DR. YAROSS: -- and consistent tolerances, and
9 appropriately specified tolerances.
10 DR. REINSTEIN: But if we are going to get down to
11 the elements, then there are so many.
12 DR. MCCULLEY: Let me ask the FDA. Do you want us
13 to go, from that standpoint, to that degree of detail, the
14 elements that would be in this? Ralph?
15 DR. ROSENTHAL: I think Quynh said yes, but can
16 you do it quickly?
17 [Laughter]
18 DR. MCCULLEY: Yes, see, that is the problem. So,
19 Dan, would you -- I will tell you what let's do. Can you
20 rattle those off right now or do you need a minute to think
21 about them.
22 DR. REINSTEIN: I will do my best and I will get
23 help from other uses.
24 DR. MCCULLEY: And no embellishment.
25 DR. REINSTEIN: No. Intraocular pressure control

1 and suction control; ring dimension tolerances; applanation
2 lens dimension tolerances; blade dimension tolerances; head
3 dimension tolerances; keratome head translation speed
4 tolerances; blade oscillation rate.
5 DR. MAGUIRE: How about blade wear? At ARVO there
6 is a paper that suggested that using it in the second eye
7 gives thinner thicknesses than pass after the first eye.
8 DR. REINSTEIN: That is very true. This is a
9 characteristic that hasn't been -- this has not been studied
10 properly, actually --
11 DR. MCCULLEY: Either say yes or no, that you
12 accept that, blade wear as an issue.
13 DR. REINSTEIN: Yes.
14 DR. MCCULLEY: Okay. Any other? Marcia?
15 DR. YAROSS: From a blade wear issue, that gets
16 into the whole operator standpoint of perhaps reuse of
17 single-use products.
18 DR. MCCULLEY: Okay.
19 DR. YAROSS: Or appropriate handling of reusable
20 devices -- operator processing of the device. So, I think
21 that impacts that under the operator.
22 DR. MCCULLEY: Do you have any others under device
23 tolerance issues?
24 DR. REINSTEIN: We said blade dimension tolerances
25 but we should really also mention what Mr. Mastel presented

1 to us, issues such as edge quality and --

2 DR. MCCULLEY: How about blade characteristics,

3 period? And let it be all-encompassing, and surely you guys

4 can fill in the fine points under that.

5 DR. MACRAE: Under that I think we could also lump

6 in generic blades and then just leave it to the agency to

7 sort out whether the generic blades are compliant relative

8 to the manufacturers blades. That is not an issue we can

9 sort out but I think it is an important issue.

10 DR. MCCULLEY: Okay, so please put that there as

11 well. Any other device tolerance or device characteristics

12 that would relate? If you think of them, you can still bring

13 them in.

14 DR. STULTING: I have another one, Jim.

15 DR. MCCULLEY: Identify yourself.

16 DR. STULTING: Doyle Stulting, American Academy of

17 Ophthalmology. Another one is device design. We have AC

18 perforation up there, and probably the most common reason

19 that is caused by is not there, and that is a device design

20 that permits an operator error.

21 DR. MCCULLEY: Good point. So that becomes an

22 issue with ability to vary the plate and the operator having

23 to put the plate in. Thank you, Doyle. Any other issues

24 under device?

25 [No response]