DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OPHTHALMIC DEVICES PANEL

96TH MEETING

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Silver Spring Holiday Inn
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C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

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

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

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

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

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

directed through Miss Ann Ree Williams of Miss Latania Williams, who are available at the registration table, and also Shirley Meeks is there today as well.

Those who have requested a reservation for participation during the open public discussion will be seated at the appropriate time. Those who may wish to join them can register inside this room at the designated registration table.

You should know that anyone coming to this now will be seated on a first-come, first-serve basis, with a limit of two participants representing any one group.

For those of you who have brought your laptop computers, there are diskettes from which you may copy the work sheet for the keratome discussion and the outline for keratome 510(k) submissions. They are available at the registration table and need to be returned there after you have transferred the information, for the use of others so that we can all benefit.

For those of you with cell phones and pagers, we ask that you turn them off or put them on the vibration mode.

Lastly, will all meeting participants please speak into the microphone and give your name clearly? This is really important today because we have a lot of people who are going to be speaking into the microphone and probably a

lot of discussion going on, and it will be very important that the transcriber and the summary writer get accurate information.

Now, at this time I would like to extend a special welcome and introduce to the public the panel and the FDA staff, our new panel consultant and our guess discussant who are with us for the first time.

Dr. Leo Maguire is our new panel consultant. He is an Associate Professor of Ophthalmology at the Mayo Medical School, and a consultant to the Department of Ophthalmology at the Mayo Clinic in Rochester. Dr. Maguire currently serves as Chairman of the American Academy of Ophthalmology Committee on Ophthalmic Procedures Assessment, and is on the editorial board of the American Journal of Ophthalmology and Cornea. Dr. Maguire has published and lectured extensively on corneal topography and its application to keratorefractive surgery, on keratoconus, ectatic corneal degeneration and associated optical and public health issues.

Our guest discussant today is Dr. Dan Reinstein, an Assistant Professor of Ophthalmology at the Weill Medical College of Cornell University in New York, and a Professor of Ophthalmology at the University of Paris, France. He has extensive fellowship sub-specialty training in refractive surgery, ophthalmic ultrasound and ultrasound

bioengineering, and combines these in his practice of refractive surgery. Dr. Reinstein has led the development and use of a new 3D very high frequency ultrasound system that provides pachymetry of individual corneal layers with one micron precision. He has pioneered the use of this technology in the assessment of the cornea in Lasik and PRK, with a focus on the study of underlying surgical mechanisms and healing responses within the cornea. His special clinical interests include the assessment and management of the complications of refractive surgery.

I would like to now ask the panel to introduce themselves, the remaining panel, starting with Dr. Marcia Yaross.

DR. YAROSS: Marcia Yaross. I am director of regulatory affairs at Allergan in Irvine, California, and industry representative to the panel.

DR. SUGAR: Joel Sugar, Professor of Ophthalmology, University of Illinois at Chicago; panel member.

DR. MACRAE: Scott MacRae, Oregon Health Sciences University, former panel member and consultant.

DR. BULLIMORE: Dr. Mark Bullimore, Associate Professor of Optometry, The Ohio State University.

DR. MCCULLEY: Jim McCulley, Professor and Chairman of the Department of Ophthalmology, University of

Texas Southwestern Medical School in Dallas.

DR. HIGGINBOTHAM: Eve Higginbotham, Professor and Chair, University of Maryland School of Medicine, Baltimore.

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

DR. JURKUS: Janice Jurkus, Professor of Optometry, Illinois College of Optometry in Chicago.

DR. ROSENTHAL: Ralph Rosenthal, Director, Division of Ophthalmic Devices.

MS. THORNTON: Thank you very much. I would just like to note that we are expecting the appearance of our consumer rep. She is missing from the table, as is Dr. Marian Macsai who is a voting member of the panel. She has had a falling out or a falling off of her bicycle --

[Laughter]

-- and hasn't been able to attend. So I just wanted to note that for the record. But she will be back.

We, in the FDA, would like to extend at this time our appreciation to the panel for the time they have taken from their busy schedules to join us here today. I would like to turn it over to Dr. McCulley. I believe Dr. Rosenthal has asked to follow Dr. Kessler's remarks. So, Dr. McCulley, do you want to take it from here?

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

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

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

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

[Slide]

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

[Slide]

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

[Slide]

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

way we think we work at the Center for Devices from the postmarket world. Most of the action in the medical device world, we recognize at the FDA, happens really out here -- industry, customers, patients, physicians, design modification devices is the vast majority of work that happens in medical device technology.

FDA gets increasingly involved as any product goes from device design, through evolution toward obsolescence, and we get increasingly involved in this tie of a time scale. From the lab and bench testing, definitely to the clinical testing of devices and then, once we start FDA review procedures, there is a long pre- and then a longer postmarket evaluation process at FDA. All of these steps should have frequent and accurate feedback routes, back to the industry, back to the clinical community, etc., and we should have the clinical community involved here, here and also elsewhere in this diagram.

In the postmarket period we have at least five separate regulatory or other mechanisms to monitor product in the postmarket period, and that is as much of FDA's statutory mission as is premarket, to make sure that a device that is placed on the market remains safe and effective.

We have the Medical Device Reporting Program. I will talk to you about that for a few minutes. Then I will

talk for quite a bit about the postmarket surveillance authority that we have at FDA, as well as our post-approval authority which is connected to PMA type products. I will not talk about our epidemiology program nor our very large field inspection program, which are also critical parts of FDA's postmarket evaluation procedures. Time limits me a bit this morning.

[Slide]

Well, why do we care? What questions are interesting in the postmarket period? For many products long-term safety is an issue. Some products get reviewed and passed, approved by panel and by the FDA, after a very brief period of clinical testing but a lot of the products we are talking about are in people's bodies or associated with them for many, many years. So, long-term safety is a critical issue for evaluation in the postmarket period.

Also, performance of a device in community practice and effects of change in user setting. I want to point to this one in particular, not so much for this panel but in general. Most of you know that for the past twenty years hospital stays in the United States and elsewhere in the world have shrunk dramatically. What is happening is that medical technology is being pushed from the hospital to the bedside faster, faster and faster. Increasingly sophisticated technology is at the bedside of you, your

parents, your aunts and uncles, and making sure that products that can be used effectively in the hospital by professionally trained physicians, nurses and other staff can be used at home is a trick, and not all products can be. We discover frequently that products that look safe and effective to you on the premarket side, where you have seen them from highly developed clinical trials with trained staff -- when that product reaches the home, in a home care setting, does not work the same way and patients experience severe, sometimes life-threatening adverse events, and monitoring for effectiveness of technology in settings, in different settings, is important to FDA's postmarket responsibility.

[Slide]

One of the mechanisms we have for looking at those problems is the Medical Device Reporting Program. By law, manufacturers must report deaths and serious injuries to FDA, as well as malfunctions or something called near incidents. Since 1990, all user facilities in the country have similar requirements. All deaths associated with medical devices have to be reported to FDA, and all serious injuries have to be reported, by law, to manufacturers.

[Slide]

Unfortunately, that responsibility of user facilities is observed in the breach. We get 95% of the

100,000 reports we get every year of adverse events from manufacturers, and only 2% to 3% do we get from user facilities. Information in the Medical Device Reporting Program is supposed to include a device specific set of information, event description, event date, etc.

Unfortunately, reports often have very limited information. They provide critical signals to FDA, and I will talk about that in a minute, but in an increasingly litigious environment in the hospital setting, when an adverse event happens with almost any product, the job of the risk manager -- the first job of the risk manager in a hospital setting is to ensure that his facility or her facility doesn't get sued, and then later to think about reporting to the FDA or other authorities. So, we wind up getting a lot of reports that have very limited information from the clinical perspective, and it is hard to deal with that. But, we have a trained staff of about 15 nurse analysts who look at the 100,000 reports we get a year and prompt certain actions in the postmarket period.

[Slide]

Most commonly, we do directed inspections. Several voluntary reports in the last year with ophthalmic products that had to do with comfort issues -- some physicians have reported some concerns, and we have gone and done inspections in facilities to find out if we could support

those concerns.

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

[Slide]

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

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

Both of these authorities are seen as complements

to premarket review, and in some ways even allow us to adjust the pre- and postmarket balance and allow products on the market where we may have some minor postmarket concerns or marketing concerns and allow them to be handled in the post-approval period.

[Slide]

The most essential part of trying to conduct any postmarket surveillance study is to identify the critical public health question, and this can come from "for cause" situations. We may get medical device reports of unusual adverse events or injuries and request that industry conduct a postmarket study to see what is going on.

Also, new or expanded conditions of use or evolutions in technology may cause FDA to require a postmarket study.

Another key question is how will the data be used, and I will come back to that in just a minute.

[Slide]

Originally in the required postmarket surveillance study authorities we used fairly heavy approaches to try and collect postmarket data. A more recent guidance of the kind of designs that we anticipate recommending in the postmarket period is a much wider range of study designs, from detailed and definitive randomized trials or case-control studies in the postmarket period, all the way down to something as

simple as a detailed review of the complaint history or literature that the manufacturer generally keeps, especially under the relatively newly promulgated quality system regulations. That is similar to the GMPs.

[Slide]

But conducting postmarket studies can be very frustrating. Why? First of all, rapid evolution of technology makes studies obsolete. A number of times we have requested a postmarket study, but the time the agency and the industry and the clinical community have decided on doing a study and getting going, we are already on a second or third or fourth generation of product. So, it really lessens the incentive to do a study on a product which already is outdated and not being used very much.

Second, frankly, there is lack of the industry to conduct such studies. Even though we require them, once marketing authority is granted, the news from most postmarket studies are not likely to be, "great! This is a wonderful product." We basically knew that when we approved it. So, the incentive for industry to conduct a postmarket study in trying to address a public health concern can be not so exciting.

There is a lack of clinical interest in the community because the technology, again, is already in use. So, conducting postmarket studies is not so interesting

clinically principally because not so publishable.

Finally, the lack of a clearly specified public health question is the most frustrating thing, and both the FDA as well as panel members have a responsibility to try and figure out what is the right question to ask and that is where I am going to leave you.

[Slide]

When considering post-approval studies, whether it comes from Section 522 authority or from a post-approval study, we need to ensure that the question we are going to ask is of primary important. Do we really need to answer this question in the postmarket period, because the lack of incentives for doing these studies and doing them well are really serious. So we really want to make sure it is an important study that we want to do. We need to clearly specify the public health question, and we want to note the clinical or regulatory relevance of answering the question. What will we do with the data?

And there is a variety of things we can do -- put out safety alerts or public health advisories. We do those on a routine basis. Change the labeling; change indications; expand indications. There is a variety of things that can be done from a regulatory perspective that help the clinical community and the industry, based on postmarket studies, but only if we figure out ahead of time what we really want to

do and clearly specify the question.

Thanks a lot for your time.

DR. MCCULLEY: Thank you. That was an excellent presentation. One of the things that I think often we get into on the panel is having a tendency to want to deal with a grey area by saying, "well, we'll request a postmarket surveillance study" and that gets us off the hook, on the one hand. On the other hand, I get the sense that we are kind of discouraged from doing that.

I guess it is still not really clear to me where the panel's role should be appropriately in recommending those kinds of studies, along with the warning that we shouldn't abuse it to get ourselves off the hook.

DR. KESSLER: That is a question I have had from panel to panel, and it is the key question. I think we are evolving how this works out. Right now -- let me answer it in two ways. One of the things we are doing is that the Office of Device Evaluation and the Office of Surveillance and Biometrics are going through all of the post-approval studies that have been requested by the panels in the last couple of years. What we are going to start doing in the next year is bringing back that information from studies you have requested in the post-approval arena, try to find out what has happened to them, and has it given us, the FDA, the industry and you, as the panel members, the important

information we want to address those concerns.

I would encourage you to use the postmarket authority not so much to get yourselves off the hook but if you have a relevant public health question you would like to see identified; if you think it is not sufficient to warrant precluding something on the market that you believe would help you, as the clinical community, to understand better how the product can be used in the most safe and effective manner, and FDA may need to make some changes in its regulatory approach, possibly something as simple as a change in labeling, I would encourage you to suggest those; be clear about what you think you want to do with the data when the question is answered, and we will work out the authority and work with the industry to conduct it. So, I would encourage you to use it.

I want to go back to one thing. In postmarket studies we often mistakenly -- and this is in the mid-1990s -- concentrated on asking companies to do very onerous studies, and they found it very difficult. I think there is a lot that can be done at the top end of postmarket surveillance with non-clinical testing of devices or use of existing data sets. For example the Medicare folks have been working with us for the past few years, and we can tap into that and have industry help us work with them to address your concerns. So, I would encourage you to identify those

concerns that are of primary importance, that you think could be helpful to you in the clinical community, and we will work with you to address them in a fast and expeditious manner. So, I would encourage you to continue using that.

If you have a question, Dr. Rosenthal and the exec. sec., they can call us and we can come and sit down and work with you on the kind of designs and approaches that would be appropriate. My postmarket staff will come and attend the panel meetings and help out. So, any time you have something that you anticipate, we will be here.

DR. MCCULLEY: Have we requested any postmarket surveillance studies from this panel in the last few years?

DR. ROSENTHAL: Yes.

DR. MCCULLEY: Do you remember what they were?

DR. ROSENTHAL: You requested repositioning of the toric lens.

DR. MCCULLEY: Right. And, I think we use it very cautiously.

DR. ROSENTHAL: Yes, you do.

DR. KESSLER: And appropriately so. One of the problems that we have had is occasionally some other panels, not this panel, in the past few years have hit a rate of over 50 percent of approvals being recommended with conditions, and many of them postmarket. When the FDA has tried to take action from the recommendations from the panel

and turn it into a postmarket study, when we understood the question, the company and the FDA had a lot of problems. So, we need to really work with you to make sure the question is clearly specified. An unclearly specified question is the best way to a bad study.

DR. MCCULLEY: Sara and Ralph have made that very clear to us, that we need to do that, and I think we have probably responded to it. I still am not 100 percent comfortable with when we should request it and we shouldn't, but I think we will continue to do it carefully.

DR. KESSLER: We will bring you back some findings from some of the studies over the past couple of years. I think that will help you.

DR. MCCULLEY: Well, some of the other panels, it sounds like they have done exactly what I suggested, that the postmarket surveillance studies could be used as a mechanism to get off the hook and not make the decision themselves. Yes, Dr. Higginbotham?

DR. HIGGINBOTHAM: To what extent, if any, does your surveillance cover, I guess, non-United States adverse events or outside of this country?

DR. KESSLER: That is a great question. I will tell you what the law says and then I will tell you what I think is happening.

The law says any event that is reportable under

the medical device reporting regulations, that occurs anywhere in the world, on a product marketable in the United States is reportable here. Okay?

Now, does that happen? Sometimes yes, sometimes no. And I will tell you two stories and then try and get out of your way. The first story: About a year and a half ago we got 13 reports of severe anaphylactic like reactions from chlorohaxine-impregnated catheters in Japan. They worried our analysts quite a bit because they looked unusual. This product had been marketed in the United States seven million times and we hadn't received any reactions. All of a sudden we got 13 from Japan. It just struck us as odd. So we wrote the Ministry of Health and Welfare in Japan and, interestingly enough, in Japan they had only received two reports from their own country.

First of all, this was an international company. They tend to respond better to medical device reporting laws than they do anywhere else. So, we get some reports. But I know that we get fewer than we should.

The second story is to tell you that right now the United States and three countries in Europe, the United Kingdom, Germany and Norway, Canada, Japan and Australia are involved in an international vigilance reporting system, where we are trading on a routine basis adverse events of significant public health importance around the world. We

are trying to build this system so that if something happens with a product in Germany that is of some public health importance we find out about it.

We have had several excellent collaborations over the past couple of years with some of our international partners. The chlorohaxine one is an example. This led to a Japanese based recall. We didn't recall it in the United States because we couldn't find any evidence of any problems, but in Japan they had a recall, sat down with the company and looked at the data, and placed it back on the market after a while. But that is a real success. But some companies are careful, the multi-nationals who understand medical device reporting. Most other companies, even if they market things here, if they are not true multi-nationals don't understand and so we miss things. But that is what the program says. Okay?

DR. PULIDO: Just as a suggestion, when you give us those examples maybe you could write them as case studies, as they do for business school, and show where it was done properly and where it was done improperly. That way, I think we would all learn better how to use this propitiously.

DR. KESSLER: Great! we will have some of both and some of it, in fact, comes from where FDA has done some things improperly. I will be glad to even trot those out. I

am sure the industry will appreciate seeing where we have asked them questions that have not been well done and gives industry headaches. Right?

DR. MCCULLEY: Any other questions?

[No response]

Dr. Kessler, that was excellent. We will welcome you back to come and speak to us any time.

DR. KESSLER: Thank you.

DR. MCCULLEY: I think we are ready now for the Branch updates. Since Dr. Rosenthal isn't here to introduce, we will ask Donna Lochner, Chief of the Intraocular and Corneal Implants Branch, to give us an update.

Branch Updates

MS. LOCHNER: Thank you, Dr. McCulley. And, I would like to thank Dr. Kessler for a wonderful segway into my Branch update.

At the July 23, 1998 panel meeting, the panel recommended that Staar Surgical Company's toric posterior chamber intraocular lenses, Model AA4203TF and Model AS4203T, be approvable with conditions.

The approvable condition was that the sponsor conduct postmarket surveillance of lens repositioning in the first 1000 implants. In the PMA clinical data cohort, there was a 12% rate of lens repositioning. The panel was concerned that the actual rate of lens repositioning, when

the lens was marketed, could potentially be higher than the investigational rate.

FDA approved the sponsor's application on November 4, 1998, with the condition as recommended by the panel. I would like to report to you the results of the postmarket surveillance study.

The first 1029 implants following PMA approval were enrolled in the study. At the time of the firm's submission to FDA, data for 931 patients had been reported. This represents 90.5% of the total number of patients enrolled. Of these 931 patients, 64, or 6.8%, were reported to have had a repositioning of the IOL. There were no reports of adverse events or lens dislocations associated with these repositioning.

It should be noted that the reported rate of repositioning of the IOL is not necessarily the observed rate of misalignments. It only reflects those cases of misalignment that were significant to the patients' visual comfort and/or optimal functioning. As a result of this postmarket reporting requirement, the sponsor has modified their product labeling to include this newly obtained clinical information.

Thank you for your attention. This concludes my panel updates.

DR. MCCULLEY: I am sorry, I think you said it but

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

MS. LOCHNER: Twelve percent.

DR. MCCULLEY: And it dropped to 6%.

MS. LOCHNER: Almost 7%, yes.

DR. MAGUIRE: So, the repositioning rate observed in the initial study wasn't actual repositioning rate; it was clinically significant repositioning.

MS. LOCHNER: Right.

DR. MAGUIRE: So we are comparing apples and apples.

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

DR. MCCULLEY: Dr. Pulido?

DR. PULIDO: For the record, I would like to say I think this was a necessary postmarket surveillance.

MS. LOCHNER: And I think, building on Dr. Kessler's comments, it was focused and directed enough that I think it was able to be done and the firm was able to complete it and basically do exactly what the panel requested.

DR. MCCULLEY: I think you have given us good direction today on how to do these, and kept us from misusing them. Do you have anything further?

MS. LOCHNER: No.

DR. MCCULLEY: Dr. Rosenthal, would you like to introduce the next update -- well, I will. Dr. Beers is

Acting Chief, Diagnostic and Surgical Devices Branch, and will give us a Branch update.

DR. BEERS: Thanks. This will be really a quick update on items from previous meetings of the panel. First, P970001, which is Emory Vision Correction Center's refractory surgery and laser for myopia using Lasik, is still under review.

In fact, all of the following PMAs are still under review. P990010, the CRS PMA using the Visix for Lasik, is still under review.

P980034, Supplement 13, Summit's PMA supplement for Lasik for myopia is still under review.

P980051, the Sunrise laser for laser thermal keratoplasty for hyperopia is still under review.

DR. MCCULLEY: Any questions?

DR. BEERS: Quick, as I said.

DR. MCCULLEY: Thank you. I would like to turn the floor for a moment to Miss Thornton, who has some other housekeeping issues -- administrative issues. Strike housekeeping!

Conflict of Interest

MS. THORNTON: I am sure you have all made your beds this morning --

[Laughter]

The following announcement addresses conflict of

interest issues associated with this meeting, and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government.

Waivers have been granted for Drs. Scott MacRae and Eve Higginbotham for their interests in firms that could potentially be affected by the panel's decisions. A copy of these waivers may be obtained from the agency's Freedom of Information Office, Room 12A-25 of the Parklawn Building.

We would like to note for the record that the agency took into consideration certain matters regarding Drs. Higginbotham, MacRae, Mark Bullimore and Janice Jurkus. These panelists reported current or past interests in firms at issue but in matters not related to what is being discussed today. Therefore, the agency has determined that they may participate fully in today's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse himself or herself from such involvement, and the exclusion will be noted for the record.

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

Thank you, Dr. McCulley.

DR. MCCULLEY: Thank you. I would now like to turn the floor to Dr. Rosenthal.

DR. ROSENTHAL: Thank you, Dr. McCulley. We have invited you, the stakeholders -- and that includes the clinical community, the companies and, of course, the panel, to this meeting today to help us develop a guidance document for keratomes. By your participation in this process, we hope to develop guidance that will address the pertinent safety and effectiveness issues for all indications for use of keratomes, including making corneal flaps for Lasik.

Recently we approved the first PMA for an individual laser for Lasik. In addition, several PMAs have been presented to this panel for commercially produced lasers seeking the Lasik indication. Keratome manufacturers

have also submitted applications to FDA through the 510(k) process seeking to revise their labeling to include the Lasik indication as well. To date, we have not cleared an application for a keratome with labeling for Lasik.

The outline, which will be provided for you today, identifies the information we currently expect in a 510(k) application for a keratome when indicated for lamellar resection of the cornea. Corneal lamellar resection is considered a general indication for the use of keratomes. This outline, however, does not address data expectations for the specific indication for making corneal flaps for Lasik.

Using this outline, which Miss Hoang and Dr. Beers will present to you, and Mr. Glover, we are seeking input from the panel, from the industry and from the clinical community that would identify additional information, if any, that would be needed to determine the safety and effectiveness of keratomes for the use in Lasik.

As part of this process, we ask that you discuss the risks associated with a keratome when used in Lasik, and the types of clinical and non-clinical information which would be required to assess those risks.

This is being brought to your attention now because in the opinion of the Division there is a major potential public health issue related to the Lasik

procedure. It will be done a large number of times in this country, on a large number of eyes, and we would like your opinion as to how we should approach this issue at this point in time.

Thank you very much.

DR. MCCULLEY: Would you entertain questions if the panel has any relative to that?

DR. ROSENTHAL: Sure.

DR. MCCULLEY: Any panel members have questions or points of clarification for Dr. Rosenthal?

Seeing none, we will now move on to the open public hearing session. There are three individuals who have previously requested time to speak. Each individual, whether by prior arrangement or time allowing to speak following them, will be limited to a maximum of ten minutes. At the conclusion of these presentations, it is my understanding that panel members, if they have questions or points of clarification, may then make appropriate query.

The first person who has requested time is Michael Bartell. I would ask you to come to the podium and remind everyone, please, not only to identify yourself for the record but to state the affiliations and conflicts that would be of note for these discussions.

Open Public Hearing

Formal Oral Presentations

MR. BARTELL: I welcome the opportunity to speak to you today. I appreciate it. I am Mike Bartell, President of Microtech, Inc., a Pennsylvania corporation. We are the exclusive distributors for Moria Microkeratomes product line in both North and South America. We have been involved in the refractive field since the early days of RK, and with the microkeratome market specifically for the past five years.

Microtech has been very closely involved with Moria in the development and evolution of their microkeratome line. We are here today to discuss and define the scope and purpose of the proposed guidelines for microkeratome 510(k) submissions. During the course of these discussions we are going to address the potential concerns related to the Lasik procedure that has evolved in the past years, and we will make an attempt to rank those concerns in their order of priority, determine the possible causes, and look at how we might best eliminate them.

In doing this, we will try to determine and confirm some of the specific responsibilities that fall firmly on the shoulders of the microkeratome manufacturers. In this way, we can agree upon the standards that must be met by a responsible manufacturer prior to the introduction and marketing of new microkeratomes in the United States.

My purpose in addressing this group today is to

make one very important point on behalf of the microkeratome manufacturers. It is extremely important that you protect the integrity of the microkeratomes that have take the time and the effort in proving themselves worthy of obtaining and receiving the 510(k) market clearance by the FDA. Generic microkeratome blades are proliferating in this country at an alarming rate. When a generic blade is substituted in a manufacturer's system, all control, traceability and accountability goes right out the window as far as that manufacturer is concerned.

[Slide]

This slide represents the evolution of the microkeratome system currently manufactured by Moria of Paris, France. It is sold throughout the world. The unit does have 510(k) approval in the United States, and it is manufactured under the strict guidelines established for an ISO-9000 approved marketing facility and manufacturing facility.

[Slide]

A microkeratome is a very sophisticated piece of equipment. When you pop the top off you begin to get a feel for some of the complexities that the surgeon takes for granted.

Dual vacuum pumps serve as a safety backup to each other ensuring an uninterrupted vacuum and the proper

elevation of intraocular pressure for making the cut and creating the Lasik flap.

State-of-the-art power systems ensure power to the unit independent of fluctuating wall current. This unit will continue to operate even if there is a complete power outage, just as we experienced last year up and down the East Coast. This is depicting some of the inner workings of these units.

It has completely computerized circuitry and provides uninterrupted power, ensuring proper functioning and a system of self-checks that prevents a cut from being made even if all systems are not a go at one time. So, there is a complete system of checks and balances in it.

[Slide]

There are actually five different suction rings, two of which are shown here. This selection of five different rings allows the surgeon to select the size of the flap he wants to cut in relation to the specific corneal curvature of the patient. These are very specific specifications.

[Slide]

This little stop ring, here on the left, is actually responsible for creating the hinge in relationship to various size flaps that are created during the Lasik procedure. Again, if they are used properly there should be

no reason for the surgeon to experience some of the free flap complications that have gone on in the past. It has four different settings as far as adjustments are concerned.

[Slide]

The new microkeratome heads that are evolving today are now made out of one solid piece of solid stainless steel. There are no more tiny plates, screws, or cams that need to be assembled. This has basically eliminated the vast majority of the operator error complications that could potentially occur due to omissions or incorrect assembly of the microkeratome.

[Slide]

This is another style of a one-piece head manufactured by Moria that provides a pivoting motion to provide the cut and create the flap. There are three different heads available that give 130, 160 or 180-micron depths of cut. The tolerances within these heads are incredible. They have to be because we are being held responsible for cuts that are a tenth of a millimeter as far as the cutting accuracy.

This particular head depicts the insertion here of a one-piece blade into the side. It is sort of like the old Schick injector razor where it just slips into the side. You can't get it in upside down; you can't get it in wrong. Again, this is going towards eliminating the potential

problems as far as assembly on the part of the medical personnel. The tolerances within the head, as I said, are just very incredible. The blade, one it is put into the system, becomes a part of that total system. Once the blade is inserted in there it has to operate within the absolute tolerances of the head itself. If there is any variance, it can create metal against metal or metal against plastic, creating wear of the head; it can lead to damage of the head, irregular cuts, debris in the inner face, and compromise patient safety.

[Slide]

The head, when it is screwed onto the motor, as shown here, locks the blade into place, fixating it within the area that it must operate on. It is centered on the pivot point of the suction ring and --

[Slide]

-- depicts the motion of the microkeratome as a cut is effected by the surgeon. If you go from the starting position, here, and activate the forward pedal it begins to rotate around towards the stop and, of course, at the stop position is where your flap is created.

My purpose in putting up these nine slides is to convince you of the systematic approach that has to be taken if we are expected to produce incisions in the human cornea within tolerances of a tenth of a millimeter.

[Slide]

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

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

We should like to request that the current FDA policy for generic component products for microkeratome systems be changed. We request that the substitution of generic components to an approved microkeratome system be reviewed by the FDA as an off-label use of that system.

If we are to be held responsible for the function of our system, then we must have control of the components that comprise that system. If the FDA continues to grant 510(k) market clearance to manufacturers of generic components, we feel that the FDA is potentially jeopardizing patient safety and should be willing to assume the product liability for that whole system.

I thank you for your time on behalf of Microtech Moria, and a number of other companies, I am sure, that have spent hundreds of thousands or millions of dollars to bring safe ophthalmic products to the marketplace.

DR. MCCULLEY: Thank you very much. I think you had a very clear message. I am not certain, as a scientific advisory panel, quite honestly -- well, I will stop that sentence that I didn't finish. During the time I have been here, we have never dealt with the specific issues related to regulation of blades, and I think we are probably relatively -- I know I am -- unfamiliar with the FDA's blade regulation process, and that may be appropriate and the FDA may feel that there are no scientific issues related to that

that they would want to bring to us. So, I understand your message. I am not sure what our role in that would be than to hear and understand. I think we can say we have done that, and I guess unless the FDA has any other direction to us as the panel, then I would ask them to provide that. And, these issues may come up subsequently, but our role is as a scientific advisory panel, not a policy advisory panel. Dr. Pulido?

DR. PULIDO: I think though he makes a very cogent argument for the idea that the whole system is a system in and of itself, and I think we and the FDA need to hear that.

DR. MCCULLEY: Right. I agree.

DR. SUGAR: May we ask questions?

DR. MCCULLEY: Yes.

DR. SUGAR: You mentioned tolerances of tenths of a millimeter. A tenth of a millimeter is 100 microns.

MR. BARTELL: That is correct, and --

DR. SUGAR: That seems very broad. And, you are talking about a blade that is specified for 160 or 180 microns. A tenth of a millimeter tolerance is probably unacceptable.

MR. BARTELL: I am referring to the depth of cut of the microkeratome head, not necessarily the blade but the blade, the head, the entire microkeratome system. You need to leave about 250 in the bed to 300 microns, and sometimes

it is very close. So, when we present the head in combination with the blade that is going to give 160 micron depth of cut, not 180 micron depth of cut, we are talking about 20 microns. You put someone else's blade in there, and yet you want to hold me responsible for not giving you a 200 micron cut. That is what our reference is to, the depth of the cut of the head, not tolerance on the blade.

DR. MCCULLEY: Does FDA feel this is the appropriate time to get into these issues or that we should do this subsequently?

DR. ROSENTHAL: I appreciate the issue being brought to our attention, and I think we can certainly address the issue when the final guidance is written. In the process of getting a guidance document, you know, finally completed there will be a lot of opportunity to discuss this issue.

DR. MCCULLEY: I know in the issues that have been brought to us in the matrix that you are wanting us to address the depth of cut is a recurrent theme.

Any other panel questions or comments? Dr. Higginbotham?

DR. HIGGINBOTHAM: I have a question. Is there a shelf life per safety and efficacy for these blades, a period beyond which you cannot actually guarantee their accuracy?

MR. BARTELL: No, it would be more the sterility concern. As long as they are in their protective packages and so forth, I believe there is an expiration date per safety and efficacy but it has to do with the sterility.

DR. MCCULLEY: Other panel questions or comments? Dr. MacRae?

DR. MACRAE: I just want to thank the presenter and also acknowledge that these systems aren't always being used the way the manufacturers recommend, such as, I think the use of generic blades is an extremely common phenomenon now and it brings out the issue of if there are problems occurring, are they occurring as a result of the device being used in a way that it wasn't really originally designed to be used, yet holding the manufacturers accountable to that. So, I do think that you have a very legitimate concern and, yet the panel has difficulty assessing that. We are not engineers and we have very limited data in terms of that. But I acknowledge sort of both sides of this issue. It is a difficult issue and I suspect as time goes on it will be more explored.

DR. MCCULLEY: Thank you very much.

MR. BARTELL: Thank you.

DR. MCCULLEY: The next speaker is Douglas E. Mastel, President, Mastel Precision.

MR. MASTEL: It is going to get me a minute to get

this --

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

MR. MASTEL: Thank you. Doug Mastel, from Rapid City, South Dakota. I will try not to overpower you with this microphone. My wife complains I am too loud all the time; says I don't listen to her.

[Slide]

Our company is located in Rapid City, South Dakota. It is a fitting tribute to be here, in Washington, D.C. We have the distinction of having Mount Rushmore in the Black Hills. We also have a more dubious distinction, the Sturgiss motorcycle rally. If any of you are Harley riders, you can come sometime and watch all the people from all over the world riding hogs, chasing cattle.

[Laughter]

[Slide]

I have a little bit different perspective, I suppose, and I really appreciate Mr. Bartell. They are a quality company, and I appreciate what they are suggesting. As a metallurgical engineer though, I would come from a little bit different angle, and I want to look at the science behind the blade, being a diamond blade manufacture.

[Slide]

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

underexposed here but these blades were cut on the edges with electron discharge machining.

[Slide]

In a different perspective now you can see the sputter, which we look at under a different magnification now.

[Slide]

If you are looking at interface debris and various problems with the blades, I think that the blade has to be the most important consideration of the whole event. You are sectioning the cornea.

[Slide]

What is the microstructure of the material properties of these blades? Should we be using Rockwell? Should we be using indentation, hardness characteristics? What is the actual alloy that the manufacturer is using? They are buying ribbon stock, most of them. Some people are making their own, but what is that steel? That would be a question I would have for you.

Should we be doing tensile testing? Should we be doing testing at all? What is the microstructure? I can guarantee you after that blade was heated with that electron discharge machining that the blade was distempered -- thin cuts, buttonholes -- you name it.

What is the surface finish of the blade? Should we

be using RMS characterization, common manufacturing principles that seem to be not applied to this industry? And what about the cleanliness of the blade? We talk about sands of the Sahara and all the things that are going on and everyone says it is multifactorial, and I will get into that in a minute.

[Slide]

This is that same blade. You can see the molten appearance here. Electron discharge machining works like a reverse arc welder. It just simply burns and dematerializes the stuff that is there like a laser goes through. But the heat here is the problem.

[Slide]

Another blade. It was not quite heated to the same level.

[Slide]

Here is another manufacturer and you can see that it is an entirely different morphology. In my estimation it could be better but it is pretty good.

[Slide]

You can see the granular appearance of the microstructure, indicating that it has had minimal thermal input.

[Slide]

Again, at 10,000 times magnification. I find

oftentimes, having had some scanning electron microscopy training personally, SEMs are used in a way to make something look unreal, unrealistic.

[Slide]

What is edge sharpness? First of all, the edge profile, the angle alpha is normally around 33 degrees in diamond technology and in steel. So, the edge bevel has to be a primary consideration in the effectiveness of the microkeratome. It cannot be refuted. What are the included angles on the blades of the manufacturer? This should be a prime determinant.

Are there secondary bevels and tertiary bevels? Should safety and efficacy be using optical microscopy and, if so, what magnification? Should we be using scanning microscopy, which is impractical in a manufacturing environment? What is the edge radius? Should we be looking down at the angstrom range? In environment blade technology we can get down to atomic bevel edges, which is in the anagstrom range. Steels are not quite capable but still you can generate a very good edge on steel.

What about physical testing? We have no testing to determine how effective a blade is going to be. It seems to me that we should come up with some sort of a standard. You make a cut. How much pressure is used -- pascals, whatever, newtons, whatever we are going to be looking at -- and find

out how effective a cut is in a standardized material.

[Slide]

This is another blade. You have a primary, a secondary and a tertiary grind on this particular blade. It was sent to us because it was problematic, several years ago. Here you have an edge of 1000 X. It looks fine.

[Slide]

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

[Slide]

This is not.

[Slide]

Now, here is one with a primary and a secondary grind. You can see the first grind angle here and the second here. Now, what is this profile here? That is that angle out that we talked about.

[Slide]

Here we have a primary, secondary and that tertiary grind again.

[Slide]

That is this blade, and it is masked because of the radically pathetic surface finish here on the edge.

[Slide]

But this has an entirely different sharpness --

[Slide]

than this. This is much more acute, and this blade was much better.

[Slide]

Now, we talk about interface debris. That is those grinding lines that are posterior to the blade. The blade runs this way. That is going to be sandpaper to the stroma. It is also a dirty surface. What we found in our research was -- first of all, this is going to also carry epithelium into the interface and lay it down. A slick surface is a clean surface.

[Slide]

So we did some x-ray diffraction on some blades just to find out what they were.

[Slide]

We found out that the best material is 440C. This is a couple of years ago.

We wanted to find out what is the stuff we are seeing here because x-ray diffraction does not look for organic materials? We were seeing sulfur, chlorate, silicone -- we were wondering what the heck we were seeing on the surfaces versus a clean scan.

[Slide]

So, prior to Dr. Bobby Maddox who was the first to present -- or he called me personally because we don't sell microkeratomes. We have been a developer of a microkeratome

for nearly four years now -- still not available. And, he called me because he had these stromal interface problems; a couple of stromal melts -- a disaster. Now it is common today to talk about sands of the Sahara. Where is it coming from?

Well, he sent us some of his blades after having this problem. We submitted them to a company in California that did FTIR spectroscopy. That is how you look for hydrocarbons. We found polyamides, benzenes and esters -- common machining lubricants used in electron discharge machining, or whatever. And, we looked at the surface finish. It is going to be hard to clean these now. How are the blades being cleaned? The doctor is looking with a surgical microscope, going, "that's clean and that's not." I see it all the time. That can't be in this business. It needs to be a factory finish. Okay?

Then Dr. Maddox sent another one, with silicone oil. Talk about sand -- you bombard silicone, you are going to get silica and free radicals.

[Slide]

So we tore a microkeratome apart recently and I was expecting to look at the O-rings that were sealing the drive because Dr. Maddox said that is coming out of the gear boxes and I was looking for the O-rings. There were none. What is in the gear box, and how is it isolated from the

cornea?

Thank you.

DR. MCCULLEY: Thank you. Could you tell us what Mastel Precision is, what kind of business you are in and what your specific interest is in this so that we know how to put your comments in perspective relative to the overall?

MR. MASTEL: We have been manufacturing instruments for nearly two decades. We have been in development and Dr. Stulting did the research at the microkeratome face-off. We have been in development for four years of a diamond keratome, using a diamond blade. I personally elected not to put a microkeratome on the market because I was confident it was going to be safe and effective, and it has almost killed us. We were almost there but Dr. Stulting would say, "it looks pretty promising; you'll never make it work." So, we hope to have a microkeratome some day, but it was a matter of coming here and trying to share some information I have had for several years. If we can be of assistance, we would like to do that.

DR. MCCULLEY: I appreciate your information. I am sure that the FDA engineers really appreciate your information, and I think that is at the level where those issues would be.

Any other questions or comments?

[No response]

Thank you very much.

MR. MASTEL: Thank you.

DR. MCCULLEY: The next presentation will be by George H. Myers, Consultant, Hawken Industries.

MR. MYERS: Thank you. You will have to excuse my hoarse voice today. Dr. Dibbs, who is the president, unfortunately, couldn't be here today.

Hawken makes a disposable microkeratome which has received 510(k) clearance. It just occurred to me, it completely avoids all these problems of blade replacement because you have to replace the whole microkeratome.

My comments are split into two parts. One is what measures might be taken with tests of 510(k) submissions to get information to see what is actually necessary in a microkeratome for Lasik. Most of them are actually used for that, but when the original device was made nobody had even heard of it.

Some of the questions -- I have to apologize for not having slides -- are how smooth does the stroma have to be? How well defined should the edges be? How thick a flap is needed? All that is known now is that if the flap is too thick greater than 250 microns one had problems. What effects do corneal curvature and geometry have on the flap? What is the intraocular pressure necessary for a good flap? And, what is the difference between nasal and superior

hinges?

So, what we are suggesting -- now, the question is whether FDA can actually require this -- is that certain data be included with the 510(k) even though clearly there is no way of establishing substantial equivalence from it, and this eventually would be used with a registry to try and find out what makes a good microkeratome for Lasik.

For example, we suggest animal tests to establish flap thickness, with the intraocular pressure recorded and the flap dissected measured. Some human tests to substantiate the animal tests. Scanning electron microscope of the stromal beds and edges on the animals. Of course, then you would have to have some criteria for the SEMs.

But we think if enough data is acquired, then we are sort of proposing using the 510(k) as a process for requiring the data and eventually we will find out what makes a microkeratome suitable for Lasik since the FDA cannot itself carry on research.

The rest of my comments, having just completed a 510(k) clearance with Ms. Hoang, who is sitting here -- some things occurred to us which are not on the outline. There are presently guidelines for the maximum pressure used for the device -- the suction used to hold the device onto the cornea. We actually had a clinical evaluation and we just reported whatever the investigator used and we were told

that this was much higher than the accepted standard. Well, it was accepted but our fellow who did the clinical studies said he thought that the level cited was way too low, and maybe that can be corrected.

This is not exactly a scientific thing but applicants, for example us, have been asked to submit test results and specifications on a lot of the complements of the device. This is, to me, the case that should be specifically mentioned in the guideline. It is very easy to do these beforehand. When one gets the comments, with 30 days to answer, and when one requires all these tests it can be very difficult.

That question is really related to Lasik. There are a great many different devices called microkeratome, from old hand-operated ones to completely automatic ones. Are all these really suitable for Lasik?

Then related to this, we have been told that there are some devices that have been cleared by the agency which have actually not succeeded at all in the market. The suspicion is that there are not too well suited for Lasik but they are probably very good microkeratomes. Is there any knowledge as to why this might be the case? Is there any way of learning about this?

Thank you very much.

DR. MCCULLEY: Thank you. Any questions or

comments for Mr. Myers? Dr. Higginbotham?

DR. HIGGINBOTHAM: Just a point of clarification, I am sure you didn't mean human tests but tests on cadaver eyes.

MR. MYERS: Well --

DR. HIGGINBOTHAM: I don't want the public to think that we are doing human tests.

MR. MYERS: Well, our device -- this may be a special situation but our device was used on human tests. The investigator had a PMA actually for Lasik for the surgery but he needed a keratometer. Obviously, this was described in his PMA. Yes, we are suggesting human tests. This is the typical thing, that they are first used in animals to demonstrate the safety and then used in humans. We suggested animal studies first.

DR. ROSENTHAL: I think we should clarify that there is an issue of clinical testing, a clinical trial for the use of a keratome. Ultimately you would have to use it on humans but there is pretesting on animals and cadaver eyes. So, I think we should actually think about what is required from a clinical standpoint and the use of humans if the panel feels that it is an appropriate think to include in this guidance document.

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

DR. SUGAR: Can I just ask you, you have a marketed device? Is that correct?

MR. MYERS: Yes, that is right.

DR. SUGAR: 510(k) approved. What kind of marketing surveillance do you do? Not FDA required, but do you do any follow up on the efficacy of your device?

MR. MYERS: Good Manufacturing Practices require certain procedures with all complaints, with all communications provided to the manufacturer. That is kept up, is followed up. Also, the device has a CE market that is sold in Europe which requires its own pooling of the complaint file and the manufacturer is kept informed -- there haven't been any, I might add -- of any complaints overseas. But aside from that, there has not been a attempt to actually reach out, as far as I know, to the users.

DR. SUGAR: Thank you.

DR. MCCULLEY: Any other questions or comments by panel members?

[No response]

Thank you very much.

MR. MYERS: Thank you.

DR. MCCULLEY: The next thing scheduled is actually a break. The next thing after that is unusual formatting that we have, or different formatting, for a broader opening of discussions. So, I think it is probably

wise for us to go ahead and take our break now rather than trying to break once we get that ball rolling. So, let's take a 15-minute break.

[Brief recess]

Open Public Discussion

DR. MCCULLEY: Let me call the panel session back into order. We are now going to begin an open public discussion period, which is, in my experience, a new phenomenon. Hopefully, we can keep this reasonably well organized. I will remind people again that any time an individual speaks, please state your name. If it is the first time you are speaking, please indicate your affiliations and any conflicts that would be germane to the discussion.

Now I would like to ask Dr. Beers and Ms. Hoang to introduce this session and maybe lay down some ground rules and directives.

Session I: Problems Associated with Keratomes

DR. BEERS: Everette Beers, Acting Branch Chief for the Diagnostic and Surgical Device Branch. We are moving into the guts of this session today.

My sole function here is to introduce the next session and to introduce the presenters for FDA. Quynh Hoang is a scientific reviewer in the Division of Ophthalmics and Diagnostic and Surgical Devices Branch. She is an electrical

engineer. She has been with us five or six years -- almost ten years in FDA but five or six years in our Branch. She has been intimately involved with keratomes.

Also, I wanted to recognize Joe Glover, who is also a scientific reviewer. He is a biomedical engineer and he is going to help Quynh present this.

At this time, I am going to relinquish my seat to Mr. Glover and I am going to turn this over to Quynh, who will give you an outline and some indication of how to proceed, and direct you through this process.

MS. HOANG: Thank you, Dr. Beers. Dr. McCulley, panel members and participants, we envision this open public discussion period as a brainstorming session in which all problems associated with the use of keratomes can surface, as well as the causes of the problems and, most importantly, the ways to mitigate the problems.

The discussion period is divided into three sessions that correspond with the above topics, as you can see from the agenda. We have provided you with a work sheet that will be used to capture the points brought up during the discussion. The work sheet will be displayed on the projection screen and modified concurrently with the discussion, but only at the direction of the panel chair. So, please, ensure that Dr. McCulley acknowledges your point and directs us to either add or delete from the work sheet

as appropriate.

As you are aware, this is the first time that we have tried this format, and Joe and I will be trying to input the data expeditiously. Please bear with us if we encounter any difficulties. Thank you.

DR. MCCULLEY: Thank you. Do you have any further directive to us up front, before we start on the charge?

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

DR. MCCULLEY: Let me point out again, everybody please look at the agenda. We have three different sessions or sections to this. The first is to enumerate the problems and to add to or take from this list. The second charge, in the second hour, is to discuss the possible causes. The third charge is to try to determine why these occur and how we might avoid repeats of the problem.

It is going to be difficult for us to keep things pigeon-holed and we are going to have a potential problem to get ahead of ourselves and, therefore, not have time to deal with some of the issues per charge. So, the first hour will be devoted to the list -- adding to, taking from and not a lot of editorial comment about causes, how to prevent, and so on and so forth, unless the comment relates to "this should come off of the list," or "this is why it should remain on or be added to it."

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

those of you in the audience who are participants also have a copy of the list. I guess the first question would be is there anything on this list that should be removed? Does anyone have any thoughts about that? Things that should be added to the list? I certainly have a long list of things. Are there other issues?

You guys who are out there, you are equal participants in this portion of the discussions so please join in, including those of you who participated in the formal open discussions. So this, in effect, is an expanded group for discussion, with the panel only being a part of the group.

Anyone have any other issues that they would like to add to this list?

DR. MAGUIRE: Yes, I think there is a number of things that relate to the clinical problems that come up. One would be variability in flap thickness from case to case and issues related to that.

DR. SUGAR: You can look at it as accuracy.

DR. MAGUIRE: More likely to call it consistency of cut.

DR. SUGAR: Reproducibility.

DR. MAGUIRE: Correct, and also the kind of standard deviation reproducibility. Dr. Reinstein can talk to this very well, and he has done elegant work. We don't

have good scientific basis for saying that 250 microns is, in fact, the place where we see an increased risk of ectasia, and certainly corneal ectasia should be on this list.

DR. MCCULLEY: So that is one to add, corneal ectasia.

MS. HOANG: Did you want to add corneal reproducibility?

DR. MCCULLEY: You need to get to a mike.

MS. HOANG: I am sorry.

DR. MCCULLEY: There are a number of things up here and I don't know how we are going to put them together, but we have accuracy of cut. We have too thick; too thin; irregular thickness. We have those issues there and I am not sure how we are going to want to state them or maybe group them together, but those are there. But a specific problem, as Dr. Maguire is stating -- a specific outcome is ectasia or progressive corneal ectasia, however, one wants to state it. But I think that there would be agreement that that should be added to the list.

DR. REINSTEIN: We should really use the terms as per engineering definitions. Accuracy is the conformity between the measured and the actual thickness. Precision, or colloquially known as reproducibility, is the concordance between repeated measurements of the same point or object.

So, if we are going to define accuracy of cut, which is a colloquial term for what we really want to know which is the mean and the standard deviation for that specific keratome. II think that is really what we should be defining.

DR. MCCULLEY: And what term do you want to use for reproducibility?

DR. REINSTEIN: We could use either reproducibility or precision.

DR. MAGUIRE: And what Dan is saying is that accuracy has both to do with the mean and the standard deviation of the cut, and it is important that both of those components of accuracy be looked at separately because they are both extremely important in preventing one of the catastrophic complications of Lasik, which is progressive corneal ectasia. So, there are two different components. In other words, a 180 micron keratome, does it consistently create, or does it have a mean thickness of 180, or 160, 200? That is important. The other thing that is important, if 180 micron keratome has a standard deviation of plus/minus 30 microns versus plus/minus 60 microns, that is extremely important too. And, so they have to be looked at separately.

DR. REINSTEIN: Of course, the standard deviation is an experimentally derived number from a series of points

in an experiment, and they describe a statistical chance of another cut being at a certain distance from the mean. I think a separate descriptor which may or may not be important for a specific keratome would be the thickest possible flap observed in an appropriate number of cuts by experiment, this being because a standard deviation only describes the probability of being thicker than the mean. It is not a description of an outlier or of an event where different clinical characteristics of a patient and the surgeon and the environment would cause the keratome to cut deeper than the standard deviation probability curve would have predicted. So, the deepest cut may be a factor that would give us an indication as to the safety of the keratome.

DR. MCCULLEY: Leo, could I ask you to -- let me please remind you again, each time you speak -- I am not going to do it because I keep jumping in, but will everyone else, please, at least say something that allows the transcription people to know who is speaking? If I could ask Leo maybe to -- we have accuracy of the cut; we have too thick, too thin, regular thickness; we have donuts up there; free cap should be up there. All of those things that are issues, and then the corneal ectasia is one of the secondary events related to some of those things. Can you possibly put all of that together in a category that unifies that issue

that relates to the accuracy, precision, outlier?

DR. MAGUIRE: I think what we are interested in is trying to avoid all complications in refractory surgery as much as possible, paying particularly attention to more catastrophic complications. What happens is that a lot of these things are related to each other. So, I think one way of looking at the problems is to start with the more catastrophic complications observed in Lasik and work down. Certainly the most catastrophic complication in Lasik I have seen is guillotining of the anterior segment, leading to loss of the eye and light perception. That is catastrophic, and that can happen. And, I have one patient who I take care of for somebody else where something equivalent to that has happened.

DR. MCCULLEY: Let me ask Scott. What we need to try to do now, we need to create our list. Right now we need to try to get this list so that -- you know, the first thing up there is accuracy. The last two things relate to the same thing. We need to try and get this in reasonable logic. Scott is real good at this. Let me ask Scott if he can.

DR. MACRAE: Let me just suggest that we use cut accuracy and precision, or reproducibility, as one category and that will take care of thin flaps, thick flaps. Dan, you may want to refine that in terms of the way that we described it, but I think that is one category. We want a

consistent flap that is of a reproducible depth that we know. And, one of the problems that we are having with the manufacturers is they have a number on their plate but it doesn't correspond to the type of data that Dan and other people are generating.

DR. REINSTEIN: I think we should stay away from the word "accuracy" because we can't define accuracy. We don't know the actual thickness of a flap; we only know how thick we measured it. So, strictly speaking, we should only be talking about the reproducibility or the precision of depth, central depth.

DR. MCCULLEY: Let me try this then -- I don't want to end this discussion, but if we had a heading that was cut mean and standard deviation with thickest outlier -- not elegant, under that we have the issues of thick, thin, free, donut, AC perforation, ectasia.

DR. MACRAE: Can you go through those again?

DR. MCCULLEY: Okay. The heading would be cut mean and standard deviation with thickness outlier. It says it but not elegantly. Then the list would be thick, thin, free, donut, AC perforation and ectasia. Irregularity would come under a different heading, regular, irregular.

DR. SUGAR: I would suggest the word range instead of thickest outlier. The range is always going to be 100 percent --

DR. MCCULLEY: Well, it is for the keratome, but okay. Standard deviation and range. Dr. Pulido?

DR. PULIDO: Dr. McCulley, I think that is reasonable. How about if we just look at it in groupings -- characteristics of the keratome, characteristics of the keratome flap? That would include reproducibility, etc. Corneal complications, anterior chamber complications. Other ocular complications, for instance intraocular pressure monitoring isn't up there.

DR. MCCULLEY: There are a lot of different grouping possibilities. It could be blade; blade plate; interaction; mechanical oscillation; translational speed related to such and so forth. Your proposed overall categorization was -- say that again.

DR. PULIDO: Characteristics of the keratome; characteristics of the keratome flap. You can change that. Under that would be reproducibility, etc. Then corneal complications; anterior chamber complications; other ocular complications. Included under that would be intraocular pressure.

DR. MCCULLEY: Okay, let's keep that in mind as maybe a final unifying approach that we could take. Mr. Mastel?

MR. MASTEL: Thanks, Dr. McCulley. I believe that the proper way to go about this would be to establish flap

tolerances which are the deviation from the standard. Tolerances are what you are willing to accept as the variance. Then other complications would, I think, be a separate grouping.

DR. REINSTEIN: The heading of that column says keratome problems. Are we defining the criteria that a keratome should have?

DR. MCCULLEY: The approach we are taking is problems associated with the keratome. I think that one thing we are going to have to be careful with here -- and there is overlap and I am not sure how that is going to be dealt with, and that is the clinical problems associated with the use of the keratome, and the other relates to the engineering issues and tolerance of the instrument. And, we are not an engineering advisory panel. Some of us, like Dan and Mr. Mastel, have obviously engineering backgrounds and expertise. How much we get into that, I am not sure. I think our expertise is going to be going at it, as Dan suggested, from the keratome-related problems. We will get into causes of how they can be dealt with, and some of that will relate to recommendations about engineering issues.

DR. MAGUIRE: I think you might want to change that heading, like Dan says, instead of blaming it on a keratome to say clinical problems associated with lamellar flaps because some of these are multifactorial, or their

etiology remains unclear or controversial. So, if we just say clinical problems because that is what we are really after, and this is problems associated with these procedures. What we can do is then bring in the keratome-related problems. I think that is really the right way to work on it because a lot of these things are interrelated.

DR. MCCULLEY: You need to put in that first category, as suggested, ectasia as well.

DR. REINSTEIN: The mean and standard deviation or range are not a clinical problem. They are descriptors that are going to help us avoid problems.

DR. MCCULLEY: You know, we can have some really major semantic discussions here. I think as long as we know what we are talking about, we can let the FDA subsequently, if they want to have consistency in semantics, deal with that.

MS. HOANG: Dr. McCulley, I am sorry to interrupt. The reason why we put down accuracy is that it is relative to the specification for the device. For instance, if the physician keys in 160 microns, is he getting the 160 microns? That is what we meant by accuracy.

DR. MCCULLEY: We know that, and that is what we are trying to get at, and trying to refine it a bit more than using as loose a term as accuracy, even though that might end up being the best term for the average clinician

to be faced with. We will leave, you know, the final wording to you. But I think the important thing here is that we use words that we understand, and that we stay to the points.

DR. MACRAE: I would like to suggest that rather than sort of being directed by the computer that we use this as a brainstorming session, and that what Dan says and what we say just kind of be thrown into the pot and then at the end we can come to a clear consensus about the verbiage because it seems like the computer, and Quynh having to do that, is going to be -- in a sense, it is sort of going to lead us rather than --

DR. MCCULLEY: That was the format laid out, that we would work from that and continually upgrade it. I understand your point but we are going to end up needing to create this, and I think probably in terms of trying to manage it within the time frame, we ought to still try to work with this, add or take from it, and not get too much caught up in word usage. Then we can fine-tune the word use as long as we know what we are talking about.

DR. MACRAE: I would like to add just one thing that Jose mentioned, and that is intraocular pressure and the reproducibility of the intraocular pressure system because of the potential damage to the optic nerve. I got a letter from Jack Hertzman, that was sent to the FDA, basically talking about the concerns with intraocular

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

DR. MCCULLEY: We could put that maybe under -- would it be appropriate to put that under suction?

DR. MACRAE: Actually, that is what I did. I put it under intraocular pressure and suction loss.

DR. MCCULLEY: Yes, if we put suction we could have suction, suction loss, consistency of suction of IOP created, and one of the major problems under that is going to be ischemic globe issues. So, if we could add that: consistency, maintenance of, and potential ischemia.

DR. MAGUIRE: IOP.

DR. MCCULLEY: Then after suction, put in parentheses IOP. I think if we are discussing clinical problems, the clinical problems that arise as a consequence of that, we can say central artery occlusion --

DR. MAGUIRE: That is the ischemic globe.

DR. MCCULLEY: Yes.

DR. MAGUIRE: You could have pupillary abnormalities; you can have retinal damage; you can have central artery occlusion.

DR. YAROSS: I would like to make a suggestion. What we are actually trying to do is a risk management exercise, and in risk management there are some tools -- obviously, we don't want to get into engineering tools here but one of the things that one does is to identify both the

hazards and the failure modes and the consequences. And, one of the things that is confusing us a little bit is that we are mixing failure modes, hazards and consequences.

What I would suggest is that, using the outline that we have there for clinical problems, is focus first on what are the clinical events, for example, an undesired flap thickness. That is really a clinical event. Then we can go back and the next column is possible causes, and we can get into the failure modes such as improper tolerance.

Then also, in considering what are the clinical issues, use the clinical knowledge of this group to look at what are the consequences, such as ischemia, things of that sort, to come up with what are the failure modes that we are worried about.

But I think part of the issue is that we are trying to do all three of these at once, and we may want to try to take them one at a time.

DR. ROSENTHAL: May I also say we know what the possible clinical problems are. We don't need this panel to enumerate them for us, unless you feel that it is important to.

DR. MCCULLEY: Your first charge to us was to enumerate, add to and subtract from your list. I am trying to do what you asked us to do. If you want us to do something else then, okay, tell me what.

DR. ROSENTHAL: No, it is just that we don't need a discussion of frequency --

DR. MCCULLEY: No, I agree. But you need on your list ischemic globe.

DR. ROSENTHAL: We need IOP, yes.

DR. MCCULLEY: Yes.

DR. ROSENTHAL: And its consequences.

DR. MCCULLEY: Right, and that is what we are trying to do. I don't disagree that there may be much better approaches and more sophisticated approaches. What we have been presented with is a charge that I think we need to stay with and not reinvent.

DR. YAROSS: No, I am not suggesting that. What I am saying is some of these things, which are the failure modes, really belong in the next column.

DR. MCCULLEY: Right.

DR. YAROSS: So, in terms of some of these tolerance issues, if they are fairly simple in terms of what are the clinical issues in terms of irregular cut or an undesired depth -- those are really, I think, simple ways of formulating what are the clinical issues.

DR. MCCULLEY: I understand.

DR. YAROSS: And then we can come back to causes.

DR. MCCULLEY: Okay. I think probably what we will end up doing -- I will try to do that as we go -- but what

we may end up doing is creating a longer list here and moving some of those over to be certain we don't miss some of the issues. But I will try to keep it as clean as possible.

Okay, so we just had the suction issues. Another suction issue, to my mind, is decentration of the flap. So, under suction issues we have consistency of, maintenance of, ischemic globe, decentration of flap.

DR. MACRAE: That is a separate issue from suction.

DR. MCCULLEY: Decentration is? It is the suction ring and its placement and where it sits that determines a lot of decentration. So I put it there. So humor me for a minute.

DR. PULIDO: What is the difference between that and flap [comment off microphone].

DR. MCCULLEY: They are postop. Flap dislocation is a postop event.

DR. MACRAE: I would like to add partial flap.

DR. MCCULLEY: Partial flap, to me, Scott, is not just -- I would put that somewhere with irregularity because a partial flap can be because of malfunction of the machine or obstruction of the pass. It isn't so much a depth related issue.

DR. MACRAE: It can be if it is --

DR. MCCULLEY: If you amputate it.

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

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

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

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

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

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

Pulido?

DR. PULIDO: Dr. McCulley, I am not a cornea doctor, nor do I play one on TV, but --

[Laughter]

-- Dr. Sugar and Dr. Thu have shown a few cases of Lasik to me where you can see some metal shavings in the flap. Do we want to include that?

DR. MCCULLEY: I think another category that isn't up there has to do be interface debris.

DR. HIGGINBOTHAM: That was exactly my question, considering the debris we saw on scanning electron microscopy on those blades. I would think from a very innocent standpoint -- I too am not a cornea specialist and don't plan to be -- that you could get trapped debris in the interface.

DR. MCCULLEY: So, interface debris is a major heading. Dr. Reinstein?

DR. REINSTEIN: Under the chatter lines, perhaps we could make the heading of that box quality of the bed because the bed may contain chatter lines. It may contain a nick in the blade. It may contain a step due to a change in the depth during the passage of the keratome.

DR. MCCULLEY: Thank you. A good point.

DR. REINSTEIN: A second point, I thought I saw edge -- is there an edge box?

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

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

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

DR. SUGAR: It could be perimeter characteristics.

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

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

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

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

epithelial defects over the flap, despite the fact that they are not intended at all.

DR. MCCULLEY: I think that should be a category as well, epithelial defects.

DR. REINSTEIN: Then we could maybe separate them into central and peripheral --

DR. MCCULLEY: Put in parentheses central versus peripheral. Mr. Bartell, I saw your hand.

MR. BARTELL: I was going to bring up epithelial abrasions.

DR. MCCULLEY: Okay, we got it.

DR. REINSTEIN: Can I ask, on our outline of content of keratome 510(k) submissions, Part 5, Section A2(b)(7), methods and components used to produce variable hinge diameter or thickness. May I suggest that that not be a fifth order subdivision.

DR. MCCULLEY: Well, wait. If you are getting to a point that relates to this, all right; if you are talking about something down there, that is way on in the afternoon.

DR. REINSTEIN: Well, the thing is that it is --

DR. MCCULLEY: Relate it to our list.

DR. REINSTEIN: It is related, as Marcia pointed out, to the next columns --

DR. MCCULLEY: No, we are on this column. Put something in this column. If you want to put a reminder in

this column that doesn't necessarily go, I think that is okay but we don't want to get into -- right, we will do that later.

Any other things relating to this list to add or subtract? I think, you know, just by way of the interstitial keratitis -- I mean, that is the sands of Sahara; that is the diffuse lamellar keratitis. Interstitial keratitis is probably not the best term. The one that I have seen that is probably the best, and I have asked for help from everybody else, is diffuse lamellar keratitis. There are some nods. Doyle, how do you feel about that?

DR. STULTING: It is a reasonable term but it is not always diffuse. I would call it non-specific interface keratitis.

DR. MACRAE: I would say lamellar keratitis, and then we can talk about diffuse versus focal.

DR. MCCULLEY: Okay.

DR. MACRAE: I have seen a number of cases now --

DR. MCCULLEY: But we don't want to use interstitial. So, lamellar keratitis is our term for this.

Under the flap dislocation we have slippage and poor alignment that probably need to be added to that as additional terms so that we can potentially deal with those.

DR. REINSTEIN: On slippage, I don't know where we would want to categorize it but, clearly, microfolds and

Bowman-layer cracks, which can be visually significant, should be mentioned on a list of problems. I don't know how they relate to the keratome necessarily. They might be more to do with surgical technique.

DR. MCCULLEY: Yes, we want to put that in. I have that on my list too -- flap wrinkles resulting --

DR. REINSTEIN: Microfolds, cracks.

DR. MCCULLEY: Whatever -- wrinkles, microfolds, cracks will be all-inclusive, and the potential clinical issue there is irregular astigmatism. So, put the irregular astigmatism as well.

Have we dealt effectively with the perimeter of the flap? Where is that? Scott, as I understood, what you were talking about was amputation of the flap. Was I following you or not?

DR. MACRAE: Right, where you kind of have a skipping type microkeratome pass where you are relatively superficial on a flat cornea, you get a little cornea and then essentially the microkeratome bounces out a little bit and then comes back in again. So, you have a donut shape or a partial, just little --

DR. MCCULLEY: Slivers.

DR. MACRAE: -- slivers of cornea.

DR. MCCULLEY: We can put that under irregular flaps.

DR. MACRAE: Right.

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

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

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

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

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

everything included that we would want to include and we can move categories. But are there any other problems? Yes, Mr. Bartell?

MR. BARTELL: I think you mentioned free flap and I don't believe it was put up there.

DR. MCCULLEY: Is free flap not up there?

[Multi-member discussion]

DR. MCCULLEY: A free cap is intraoperative. Where do you have donuts? There is free. Thank you. It is there. What you might want to put is free cap, not just the word free. Now, initially this all fit on the screen.

DR. REINSTEIN: I am sorry to interrupt, free cap is related to an unwanted diameter because the stop is beyond where the diameter actually occurred, and donut is a function of the thickness.

DR. MCCULLEY: Right, and pressure and curvature and all sorts of things. So, how would we split those? Why don't we put free/small -- free cap or small flap?

DR. REINSTEIN: Unwanted thickness, unwanted diameter are headings really.

DR. MCCULLEY: Okay, let's get all the concepts up there, and we want to add the concept of a small flap, with the ultimate in that being a free cap.

DR. MAGUIRE: I think what you are looking at is some unwanted width. That would be another way of going

about it because a free flap occurs when a hinge fails to present itself --

DR. MCCULLEY: Okay, rather than trying to argue which is which, let's add to this in that same area, undesired hinge width. And, we are going to work on these things. Right now, quite honestly, my goal is to get everything up there that we need. Mr. Mastel?

MR. MASTEL: How about free donuts?

[Laughter]

DR. MCCULLEY: Any combination of anything up there is assumed as a possibility. We have irregular and the slivers, so I put that under the irregular and the slivers.

Any other things that need to be on the list for us to be all-inclusive?

DR. REINSTEIN: Infections.

DR. MCCULLEY: I think that is already there, isn't it?

MS. HOANG: Yes.

DR. MCCULLEY: We have other things we have not mentioned.

[Multi-member discussion about the lost screen]

DR. MCCULLEY: If you lost it all we are going to kill you!

[Laughter]

MS. HOANG: Well, let's see.

DR. MCCULLEY: We are assuming that the other things that are on here that we have not mentioned are still there -- epithelial ingrowth, infection. Somebody had better have been taking notes.

MS. HOANG: We have been taking notes.

DR. MCCULLEY: A question to you, you did still have on the list the other things we have not mentioned. Epithelial ingrowth should still be there. We have not talked about that. Infection should still be there; we haven't talked about that. Everything else we have talked about. So we are assuming that those things are still there, that nothing was taken from the list.

While they are looking to recoup, are there any other additions to this list that anyone can think of? Not that things will not be move to another column, but anything that should not be on this list? I assume no.

DR. REINSTEIN: We sometimes cut the lids -- we sometimes inadvertently cut the lid of the patient. Perhaps that might be included.

DR. MCCULLEY: Lid lacerations? Do we want that? I mean that is an issue with one type of keratome compared to another.

DR. MAGUIRE: And, I think lid laceration is something -- again, these things interact -- that can relate to risk of infection. So, it probably should be included.

And, it also can relate to interface debris and effects on the blade before it actually enters the cornea. So, I think that is appropriate.

DR. MCCULLEY: Right.

DR. REINSTEIN: And on that topic, there are keratomes that are difficult to place, difficult to get suction ring placement --

DR. MCCULLEY: That is going to come potentially under ischemia and those kinds of things, things that add time to the suction time.

DR. MACRAE: We get into a whole sort of category of complications like pain, ptosis from the pressure. These are all relatively non-critical areas in terms of the public health issue.

DR. MCCULLEY: I don't know where they fit here. So, thanks for bringing it up. I don't think that would fit here.

DR. MAGUIRE: One other one is complications in patients who have had previous refractory surgery.

DR. MCCULLEY: I think that is a different issue.

DR. MAGUIRE: Well, it is an issue with the keratomes.

DR. MCCULLEY: Right, but it is a clinical setting issue. I think it is a point well taken that it is a concern for us but I don't think it fits into this, as I see it.

DR. MACRAE: What I would suggest is that we kind of put that on the back burner for now. That comes with the patient issue later on, the third column.

DR. MCCULLEY: Mr. Bartell, you have had your hand up back there. Do you still want to speak, Mr. Bartell?

MR. BARTELL: No, he brought up the eyelid cutting.

DR. MCCULLEY: Okay. Any other issues? And, there is nothing that we want to take off the list. We have a long list up there that covers more than the screen. From a functional standpoint, what I would like to see is all of us have a printout, a hard copy of that now for the next step.

MS. HOANG: If you don't mind, could we have a break first though? We have to hook up the printer to print it out.

DR. MCCULLEY: Okay. You have recovered it, I take it from that.

MS. HOANG: Not --

DR. MCCULLEY: We are confident you will. You are going to produce everything that has come out of our brain and our mouth so far on a hard copy, and why don't we take a break for you to accomplish that, of ten minutes, fifteen minutes?

MS. HOANG: Fifteen minutes.

DR. MCCULLEY: Fifteen minutes.

[Brief recess]

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

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

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

Does the list look complete relative to what we

said before? Anyone see any omissions?

[No response]

Session II: Probable Causes

I guess then our charge right now is twofold. It is as it was stated, that we should come up with the causes, and maybe as we go down the list, looking for causes, we will find some things in this column that shift over completely. So, let's again take the approach that was recommended to us, which is now to focus this session, to identify the probably causes of each problem, recognizing that some of the things that we have as problems are cause, and to try to group the causes into categories as much as possible, whether equipment related, user/behavior related, or patient or clinical characteristics related, or others if it doesn't fall into one of those columns, and our sheet is laid out that way. Dr. Pulido?

DR. PULIDO: Just a question for clarification, are there supposed to be some rows here that weren't put in, for instance under "suction" there is also "decentration of flap." That seems to me a separate row. So, should we first go through and see.

DR. MCCULLEY: Actually, decentration of the flap, by and large, is very much determined by how the suction -- that determines where the cut is going to be. That is okay. But we can move some of these things around as we come to

them. I would propose we start at the top and go down to come up with causes and then we can move, rather than shotgun and scatter gunning it. Let's start at the top and go down.

The first is imprecise diameter of flap/hinge. So, let's ask two questions: should that stay in this column? If so, what are the causes? So, imprecise diameter of flap/hinge, that sounds like that should be in this column. What would the cause be? Is it device operator? Patient? Does not the imprecise diameter of flap/hinge relate to free caps and the like?

DR. MACRAE: Sure.

DR. MCCULLEY: So, should this stand -- I mean, we put everything in here that we could think of so we are going to be x-ing some things off. Do we want to leave that as the heading and move free cap under that? I see some heads nodding. So, under imprecise diameter of flap/hinge, e.g., free cap.

DR. REINSTEIN: And short flap, which is the opposite.

DR. MCCULLEY: Okay, free cap or -- well, no, wait. Short flap? You mean small flap?

DR. REINSTEIN: Diameter smaller than desired.

DR. MCCULLEY: Okay, let's see, we have words for that down there where we did it before, and then the extreme

was the free cap. Where is it?

DR. REINSTEIN: Small cap could be a fully circular small cap.

DR. MCCULLEY: But you could also have a small flap and still retain the hinge but the flap be smaller than desirable, and the ultimate of that is a free cap. That is a little artificial but is that not the principle?

DR. REINSTEIN: Yes, I think the term short flap is used quite specifically to mean that the bed exposure is not sufficient with respect to the pupil position. So, free cap is an event where there isn't a hinge and that could be in a small or a large flap.

DR. MCCULLEY: Right.

DR. REINSTEIN: But a short flap is an undesirable small diameter.

DR. MCCULLEY: Okay, so whey don't we say it could be -- I understand what you are saying, the way you are using short, but would it fit if we just said small flap, free cap?

DR. YAROSS: These are all subsets of flaps that have undesired dimensions.

DR. MCCULLEY: Right.

DR. YAROSS: So maybe it is undesired flap dimensions as the general category, with then these others being specific examples.

DR. MCCULLEY: To use that instead of imprecise diameter? They say the same more or less. Let's leave it --

DR. REINSTEIN: Why don't we have the categories as undesirable diameter with or without a hinge? That way, you would have small free caps or large free caps, and you could have small hinged flaps or large hinged flaps.

DR. MCCULLEY: Okay, one of the things we often do with this is that we are trying to deliver a message, and we can end up in fine-tuning the exact words of the message ad nauseam. So, as long as we have the message made clear to the FDA, then I think that is our goal. And, I think you have heard us say this and rather than us argue or discuss verbiage, the principle is there and it relates to -- the presence or absence of hinge relates to desired diameter or the varying diameter of the flap or free cap. So, I think we understand this. Do you guys understand that?

Now, possible causes -- we have a category, guys, let's go for it. Okay, possible causes: device, operator, patient, other. Clearly, it can be patient related if there is a flat cornea. So, a possible cause under patient would be a flat cornea, flat K.

DR. JURKUS: Wouldn't that be operator? It would be up to the operator to determine if the patient has a flat cornea and decide on the appropriate tool to use.

DR. MCCULLEY: So there is an operator component,

yes. I mean, the issue is flat K. The operator has to deal with that and, within the range of our capabilities, can deal with it within limits.

DR. MACRAE: This brings up an important issue, and that is that the operators need some guidance from the manufacturers in terms of what is considered a flat K for that particular device --

DR. MCCULLEY: Right.

DR. MACRAE: -- and we don't have that. Some of the manufacturers are now starting to produce that, which is very helpful, but we need more guidance in terms of that.

DR. MCCULLEY: Okay, so on the patient side it would be flat K; on the operator -- it is going to be device as well. We have to have device capability to account for it. We need larger diameter cuts ability.

DR. MACRAE: Also, the thickness. You know, some of the flat corneas that we were very nervous about treating previously we now treat with usually thicker flaps.

DR. MCCULLEY: So, under device we would say we need the ability to vary diameter and thickness of flap.

DR. REINSTEIN: Imprecise diameter -- the diameter of the flap or cap relates to essentially three issues. They were described by Barraquer 40 years ago: the intraocular pressure at the time of passage, the height of the platform of translation of the plane, of the keratome, the stop gap

between the edge of the blade and the edge of the keratome, and the Ks. So, these are the factors, and then we can classify them into the boxes. So, for example, under this box, device elements that would lead to an imprecise flap diameter would be poorly regulated intraocular pressure by the machine during passage; would be obviously improperly machined components so that the predicted diameter is not achieved.

Under operator we would have to put all of these issues that Dr. MacRae is referring to. Should there be very specific instructions for the surgeon on how to perform a keratectomy of this depth given the patient's criteria, where a patient has a cornea that is this thick, where a patient has a cornea that has this curvature, you are going to use this ring with this stopper to produce that depth at that diameter.

One of the elements that has disappeared from the newer keratomes is an applanation lens, as it was called by Barraquer. That lens was placed on the cornea before passage in order to see beforehand how much of the cornea would be applanated by the keratome head. This determines, before passing the keratome, what the diameter would be. So, there is another piece of equipment that could be used to predict the flap diameter --

DR. MCCULLEY: Okay, let me stop you. We are

getting into the mitigation, the ways to deal with the problems. Good points but let's try to stay with column one and two. The other thing is you need an effective stop on the microkeratome. That would come under device I think, a specific.

So, you have outlined device situations, Scott, operator situations, and we will keep our solutions to this for the next discussion. Well, he had IOP control; it is suction. It is creation and maintenance of effective suction throughout.

DR. HIGGINBOTHAM: One of the comments I heard was that IOP control will have an impact on the appropriate diameter of the flap.

DR. MCCULLEY: Yes.

DR. HIGGINBOTHAM: So, should not IOP be under patient characteristics?

DR. MACRAE: The IOP you create with the suction ring.

DR. MCCULLEY: Yes, we create it with the suction ring.

DR. HIGGINBOTHAM: Okay.

DR. MCCULLEY: It is not the patient's normal --

DR. HIGGINBOTHAM: So, it should be under device.

DR. MCCULLEY: It is under device. It is the effectiveness of the suction ring in creating the right

pressure.

DR. HIGGINBOTHAM: I understand. Okay, fine.

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

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

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

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

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

part of the device issue too, if the device had the capability to allow us either to accomplish it, period, or to adjust it.

DR. REINSTEIN: And then the operator has to choose the right one.

DR. MCCULLEY: Right. Okay, the next is poor precision and reproducibility. The issue here was mean, desired versus achieved; standard deviation; range; maximal thickness, thin, donut, free; AC perforation; ectasia. There is a lot under there but they are all related, one to the other with -- I hesitate to use the word, but accuracy -- a trash basket term -- of our cuts. These are very much device dependent, and they are somewhat patient dependent and operator dependent.

DR. MACRAE: And environment dependent. Hydration can be temperature and humidity related too.

DR. MCCULLEY: They do with lasering, do you think they do with --

DR. REINSTEIN: Yes. They can affect the size. The stop gap can be affected by temperature.

DR. MCCULLEY: I know that that is true, but within practical ranges? I assume we are not operating in 100 degree temperatures and freezing climate -- within normal range of temperature, this wouldn't be an issue, would it?

DR. REINSTEIN: Could we ask Mr. Mastel whether the tolerances and the friction within the narrow range of movement of the blade within the head, could that be affected by temperature changes, operating in Siberia or in the Dominican Republic?

MR. MASTEL: I can tell you that with our diamond blade we broke the blade [comment off microphone] and other than that, I don't think it is going to have much effect. But we don't sell it; we are not on the market. Perhaps Mr. Bartell knows.

MR. BARTELL: No, I don't think it would.

DR. MCCULLEY: Okay. Under this broad category, if we leave this broad category as it is, device-related issues -- we need to know -- I will say it and then you can correct me and you can then expand it, but basically we need to know what our keratomes are going to cut; how reproducible it is; and what the unusual outliers are apt to be. And, we need to know that for the brand of keratome. We need to know what the variability is from one keratome within that brand to another. And probably, the way things are now, we need to know what it is for our individual keratome after the fact, once we get it. Now, how do we put that into terms to help the FDA relative to device issues? Right now there seems to be a good deal of variability.

DR. MACRAE: Jim, can I back up?

DR. MCCULLEY: Sure.

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

DR. MCCULLEY: With a greater degree of confidence.

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

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

for all of us, that is, how reproducibly do our keratomes cut, and how reproducible is one keratome to the other with its cutting accuracy.

DR. MAGUIRE: And it should also be established that it is a major concern because of scientific evidence to show that there is a problem, and that is from Dr. Reinstein.

DR. ROSENTHAL: May I just suggest, Mr. Chairman, that you put inter- and intra-keratome reproducibility as the device issue? Dr. MacRae is worried that they all do the same thing and you are also worried that they keep doing it.

DR. MCCULLEY: Consistently, and I think there is great concern on all of our parts about that. Am I appropriately stating that? Mr. Myers?

MR. MYERS: Yes, the way the agency has handled this with other products is having the individual calibration supplied with each unit. This would be possible for a manufacturer to do without too much trouble --

DR. MCCULLEY: That is a solution. That comes under our mitigating --

MR. MYERS: Okay.

DR. REINSTEIN: As Dr. Hoang mentioned at the very beginning when we were discussing accuracy and precision and their relative meaning, in fact, perhaps in the first column we really should be saying poor accuracy, and in the second

column we should say poor precision and reproducibility as a device cause because those are the only things we can control, the precision and reproducibility. The accuracy is the problem.

DR. MCCULLEY: Okay.

DR. REINSTEIN: In that column, keratome aspects which would lead to poor reproducibility of the thickness of the flap include, again, control of the intraocular pressure during suction --

DR. MCCULLEY: Let me interrupt you just a second. You are changing as individuals are talking, on the screen. Please don't do that. Wait until we reach a consensus. Can you back up to where you were, just as a matter of how we are going to do that?

DR. REINSTEIN: Intraocular pressure control and stability during passage of a keratome is a device element which leads to poor reproducibility, poor tolerances of the elements as purchased by the use, i.e., height of the plate, stop gap within the keratome that is manufacture.

DR. MCCULLEY: Let me ask you something. Ralph said something I thought was really very good, that, to me, so far has covered everything, and that was inter- and intra-keratome device consistency. Does that not cover the whole thing from the device standpoint? There are lots and lots of things under that, but does that not encompass it?

DR. YAROSS: I think that is, again, the result and that underneath that, as Dr. Reinstein said, you have the issues of calibration and tolerances.

DR. MCCULLEY: Okay. So, consistent calibration and tolerance.

DR. YAROSS: Accurate calibration --

DR. MCCULLEY: Accurate calibration.

DR. YAROSS: -- and consistent tolerances, and appropriately specified tolerances.

DR. REINSTEIN: But if we are going to get down to the elements, then there are so many.

DR. MCCULLEY: Let me ask the FDA. Do you want us to go, from that standpoint, to that degree of detail, the elements that would be in this? Ralph?

DR. ROSENTHAL: I think Quynh said yes, but can you do it quickly?

[Laughter]

DR. MCCULLEY: Yes, see, that is the problem. So, Dan, would you -- I will tell you what let's do. Can you rattle those off right now or do you need a minute to think about them.

DR. REINSTEIN: I will do my best and I will get help from other uses.

DR. MCCULLEY: And no embellishment.

DR. REINSTEIN: No. Intraocular pressure control

and suction control; ring dimension tolerances; applanation lens dimension tolerances; blade dimension tolerances; head dimension tolerances; keratome head translation speed tolerances; blade oscillation rate.

DR. MAGUIRE: How about blade wear? At ARVO there is a paper that suggested that using it in the second eye gives thinner thicknesses than pass after the first eye.

DR. REINSTEIN: That is very true. This is a characteristic that hasn't been -- this has not been studied properly, actually --

DR. MCCULLEY: Either say yes or no, that you accept that, blade wear as an issue.

DR. REINSTEIN: Yes.

DR. MCCULLEY: Okay. Any other? Marcia?

DR. YAROSS: From a blade wear issue, that gets into the whole operator standpoint of perhaps reuse of single-use products.

DR. MCCULLEY: Okay.

DR. YAROSS: Or appropriate handling of reusable devices -- operator processing of the device. So, I think that impacts that under the operator.

DR. MCCULLEY: Do you have any others under device tolerance issues?

DR. REINSTEIN: We said blade dimension tolerances but we should really also mention what Mr. Mastel presented

to us, issues such as edge quality and --

DR. MCCULLEY: How about blade characteristics, period? And let it be all-encompassing, and surely you guys can fill in the fine points under that.

DR. MACRAE: Under that I think we could also lump in generic blades and then just leave it to the agency to sort out whether the generic blades are compliant relative to the manufacturers blades. That is not an issue we can sort out but I think it is an important issue.

DR. MCCULLEY: Okay, so please put that there as well. Any other device tolerance or device characteristics that would relate? If you think of them, you can still bring them in.

DR. STULTING: I have another one, Jim.

DR. MCCULLEY: Identify yourself.

DR. STULTING: Doyle Stulting, American Academy of Ophthalmology. Another one is device design. We have AC perforation up there, and probably the most common reason that is caused by is not there, and that is a device design that permits an operator error.

DR. MCCULLEY: Good point. So that becomes an issue with ability to vary the plate and the operator having to put the plate in. Thank you, Doyle. Any other issues under device?

[No response]