

Department of Health and Human Services

Ophthalmic Devices Panel

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CASET Associates, Ltd.
10201 Lee Highway, Suite 160
Fairfax, VA 22030
(703) 352-0091

PARTICIPANTS LIST

R. Doyle Stulting, M.D., Ph.D., Chair

Voting Members:

Mark A. Bullimore, Ph.D.
Eve J. Higginbotham, M.D.
Marian S. Macsai, M.D.
James P. McCulley, M.D.
Richard S. Ruiz, M.D.

P. Sarita Soni, O.D.

Consultant, Deputized to Vote:

Joel Sugar, M.D.
Karen Bandeen-Roche, Ph.D.
Woodford W. Van Meter, M.D.
Mark J. Mannis, M.D.
Michael W. Belin, M.D.
Jose S. Pulido, M.D.
Walter J. Stark, M.D.

Non-voting Discussants:

Eleanor McClelland, Ph.D.
Judy F. Gordon, D.V.M.

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P R O C E E D I N G S

(9:00 a.m.)

Agenda Item: Call to Order

DR. STULTING: I would like to welcome you to the 89th meeting of the Ophthalmic Devices Panel. The first agenda item is introductory remarks by Sara Thornton, Executive Secretary.

Agenda Item: Introductory Remarks

DR. THORNTON: Good morning and welcome to all attendees. Before we do proceed with today's agenda, I have a few short announcements to make, beginning with the break issue. There will be coffee and break things available in the restaurant down there where you have probably all had breakfast already. Any messages for Panel members and FDA participants, information or special needs should be directed to Ms. Ann Marie Williams or Gloria Williams. They will either be standing here in the room or just outside at the table.

We would like all the meeting participants today, sponsors, FDA, and Panel, to speak into the microphone so that the transcriber will have an accurate recording of the comments.

Now, I would like to extend a special welcome and introduce to the public the Panel and FDA staff, Dr. Jose

Pulido, who recently joined the Ophthalmic Devices Advisory Committee as a consultant. Dr. Pulido is Associate Professor of Ophthalmology at the Medical College of Wisconsin in Milwaukee. He specializes in the clinical management of retinal diseases, and associated infectious and inflammatory processes. Welcome to our Panel, Dr. Pulido. To continue, will the remaining Panel members please introduce themselves, beginning with Dr. Gordon.

DR. GORDON: Good morning. Judy Gordon, Chiron Vision and the industry representative to this Panel.

MS. McCLELLAND: Eleanor McClelland, University of Iowa College of Nursing, Associate Professor, Consumer Member to the Panel.

MS. BANDEEN-ROCHE: Karen Bandeen-Roche, Johns Hopkins University, Department of Biostatistics, Consultant to the Panel.

DR. MACSAI: Marian Macsai, Professor of Ophthalmology, West Virginia University.

DR. RUIZ: Richard Ruiz, Chairman and Professor of Ophthalmology, University of Texas, Houston.

DR. STULTING: Doyle Stulting, Professor of Ophthalmology, Emory University.

DR. MANNIS: Mark Mannis, Professor of

Ophthalmology, University of California, Davis.

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

MR. BULLIMORE: Mark Bullimore, the Ohio State University College of Optometry.

MS. SONI: Sarita Soni, Professor of Optometry and Visual Sciences, Indiana University.

DR. HIGGINBOTHAM: Eve Higginbotham, Professor and Chair, Department of Ophthalmology, University of Maryland.

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

DR. BELIN: Michael Belin, Professor of Ophthalmology, Albany Medical College.

DR. VAN METER: Woodford Van Meter, private practice in corneal and external disease in Lexington, Kentucky.

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

DR. THORNTON: Thank you and welcome to you all. The voting member terms of Dr. Richard Ruiz, Sarita Soni, and that of our Chair, Dr. Doyle Stulting, will be completed at the end of this month and we wish to take this

opportunity publicly to thank them for their participation at the meetings, in addition to many hours of review time they have contributed in preparation for our Panel discussions. Their commitment to bringing the best thinking to our deliberations will be missed, however, we are happy to report that they will remain on as consultants to the Panel.

The end of October also brings to a close the terms of the consumer rep, Dr. Eleanor McClelland and industry representative, Dr. Judy Gordon. We have all benefitted from their thoughtful contributions to the Panel discussions and have appreciated their willingness to participate fully in the process. We want you all to know that we applaud your effort. Thank you very much.

Now I think Dr. Stulting will open the public hearing portion of the meeting.

Agenda Item: Open Public Hearing

DR. STULTING: Thank you. This is the portion that is open for public statements. Are there any in the audience who wish to make a presentation before the Panel this morning? It looks like this will be a quiet morning. We will move on to division updates. Dr. Rosenthal.

Agenda Item: Division Updates

DR. ROSENTHAL: I do not have anything specific to say, Mr. Chairman, but I would like to introduce my branch chiefs who will update you appropriately. The first is Dr. Saviola.

Agenda Item: Branch Updates

DR. SAVIOLA: Good morning, everyone. The first item I would like to update everybody about is PMA approvals. I have two approvals to announce this morning. Richard James P950008 for Silikon 1000, which was reviewed by the Panel on January 13, 1997, was approved on September 25.

It is indicated for use as a prolonged retinal tamponade in selected cases of complicated retinal detachments where other interventions are not appropriate for patient management. Complicated retinal detachments or recurrent retinal detachments occur most commonly in eyes with proliferative vitreoretinopathy, proliferative diabetic retinopathy, Cytomegalovirus, giant tears, and following perforating injuries. Silikon 1000 is also indicated for primary use in detachments due to AIDS-related CMV and other retinal infections affecting the retina.

A second PMA for Vitrophage, P910068, the device known as Vitreon perfluorocarbon liquid, which was reviewed

by the Panel back on October 19, 1995, was approved on September 30 of this year.

It is indicated for use as an intraoperative surgical aid during vitreoretinal surgery in patients with primary and recurrent complicated retinal detachments. Complicated cases include, again, giant retinal tear or retinal dialysis, PVR, PDR, tractional retinal detachments and blunt or penetrating ocular trauma.

This PMA was approved for a single batch of product since the company will be changing the raw material supplier. In order to market other batches, the new raw material supplier will need to be identified and FDA will have to approve a PMA supplement to support that change.

I would like to acknowledge the hard work of the review team members who worked diligently with these two sponsors in order to bring these projects to completion. As you can tell from the time frames between Panel review and ultimate approval of the PMAs, there remained a number of pre-clinical issues which needed to be resolved. A special thank you needs to go to the team leaders, Ms. Deborah Falls, and Ms. Eleanor Felton, as well as to the chemistry reviewer, Ms. Ming Shih, for their efforts, as well as to our branch secretary, Ms. Adrienne Burns for her clerical

support on these projects.

The second item I would like to update everyone is regarding the use of the term, All-in-One with multipurpose contact lens solutions. A number of contact lens multipurpose solution manufacturers have submitted trade complaints about a single competitor's multipurpose solution which has at least four private label distributors using the term All-in-One on the product label.

I would like to extend our thanks for bringing this matter to our attention. The firm in question received its PMA marketing clearance prior to reclassification of lens care products. The All-in-One statement was not on the product labeling at that time. They added it after they marketed the device. I want to take this opportunity to assure those interested parties that the Center's Office of Compliance is addressing this situation.

I also want to reiterate that our policy on this topic has not changed. Our view is stated in the May 1, 1997 Guidance for Contact Lens care products. We take issue with firms who use the term All-In-One on their product label, and we plan to do so in the future.

The third item for update is regarding standards review in the 510(k) review process. During the summer, our

branch was one of six pilot branches in the Office of Device Evaluation involved in a project to utilize existing standards in review of Class II medical devices. These would include standards by the American National Standards Institute, the International Standards Organization, as well as standards developed by other groups such as USP.

Our task involved assessing the recently issued May 1 Contact Lens care products guidance to identify standards which could be used to address testing methodology or performance criteria. We also consider the guidance to be a type of standard in terms of certain tests as well.

The idea is that ODE is developing a program where an applicant would have the option to include a declaration of conformance to a particular standard in their 510(k) submission, rather than provide ODE with the actual information covered by the standard. This would translate into reduced review time for staff since they would not invest time in reviewing information covered by the standard. A declaration of conformance format is currently being developed by the office.

The pilot has since expanded to include all of ODE. Each branch will be conducting a series of device reviews to identify applicable standards. In terms of

outcomes, we anticipate that an addendum to the care products guidance will be issued to identify which standards are applicable. As our group continues work on this project, the next device for standards assessment will be daily wear contact lenses.

The last item I want to make a few statements about is orthokeratology, also known as Ortho-K. I would like to take this opportunity to state our working regulatory policy on this alternative refractive correction method. I would like to stress that I am not issuing guidance at this time, only updating the public and the Panel as to where we are on the issue.

As a definition, Orthokeratology is the programmed application of contact lenses to reduce or eliminate refractive error, primarily myopia. This is accomplished by mechanically reshaping the corneal curvature to alter the refractive state of the eye.

The older technique was to fit the lens flat against the cornea, progressively fitting flatter lenses. Newer techniques use reverse geometry lens configurations designed with peripheral curvature made to be steeper than the flat central zone of the lens. This configuration applies pressure to the mid-peripheral cornea as well as to

the center.

The literature does contain information regarding safety and efficacy outcomes for Orthokeratology performed on a daily wear basis with lenses designed to fit with pressure against the central cornea. Safety issues daily wear Orthokeratology addressed by prior research, determined that the older fitting techniques did not raise safety issues beyond those associated with daily wear hard lenses used at that time.

Although Orthokeratology has been practiced since the early sixties, there have not been any contact lenses approved by FDA for that specific intended use since the passage of the Medical Device Amendments to the Food, Drug and Cosmetic Act in 1976.

A contact lens designed for the purpose of Orthokeratology is considered a different intended use, since the Ortho-K lens is intended to correct refractive error by mechanically reshaping the cornea. The basic intended use of a standard rigid lens is the correction of refractive ametropia, achieved by refractive means; specifically, to focus light rays incident upon the contact lens surface to a point on the retina. Although there is some mechanical effect on the cornea as a result of a

standard contact lens design for rigid lens, the intended effect of an Ortho-K lens design is fundamentally different from the intent of a standard lens design.

The Premarket 510(k) Guidance Document for Daily Wear Contact Lenses does contain policy statements within the Clinical section concerning the Expansion of Contact Lens Refractive Powers and Dimensions and Alternate Lens Design Configurations. The alterations of lens power and dimension parameters, such as base curve, optic zone, bevels, edges and peripheral curves as they relate to reverse geometry lenses, or other lenses promoted for Orthokeratology, do not fall within the scope of these policies, since they raise significant questions concerning the safety and effectiveness of these lenses for their intended purpose, to mechanically reshape the cornea in order to reduce or eliminate refractive error. The fitting procedure or efficacy of an Orthokeratology lens designed for myopia reduction are different from those of a standard rigid gas permeable lens.

Some of the newer Orthokeratology lens designs have been discussed for overnight wear. FDA is not aware of any controlled clinical studies incorporating established protocols to investigate Orthokeratology by way of overnight

or closed eye therapy, which have been published in the literature. Corneal reformation while sleeping at night in a closed eye environment raises new safety and efficacy concerns compared to daily wear open eye use of the lenses. The subjects are considered to be at risk for mechanical effects on the cornea, such as warpage and the development of irregular astigmatism.

At this point, the overnight or closed eye use of Orthokeratology lenses is considered within the definition of extended wear, as defined in our device classification regulations. This determination is based upon the indications section of currently marketed extended wear lenses that state lenses may be prescribed from five to seven days between removal for cleaning and disinfection. Although the safety risks of intermittent overnight wear may not be as great as sustained overnight wear, there is still increased risk beginning with the first overnight period.

Therefore, overnight therapy Orthokeratology is considered to be a Class III intended use for a rigid gas permeable contact lens, and subject to premarket approval. Lenses intended for daily wear only are Class II, subject to premarket notification, or 510(k), under Class II.

The clinical studies of overnight Orthokeratology

contact lenses are considered to be significant risk studies, whether or not the lens material has already been approved for overnight or extended wear. Therefore, a clinical study of an Orthokeratology lens designed for use in overnight therapy would require FDA approval of an IDE, as well as IRB approval. The clinical endpoints to be studied are different, compared to rigid gas permeable contact lenses for extended wear, which are refractively correcting a person's vision without the intent of mechanically reshaping the cornea.

There needs to be a distinction made between a licensed practitioner who may prescribe a specific lens design for a particular patient within the scope of his or her practice, versus the promotion and sale of a lens by a contact lens manufacturer. A licensed practitioner who designs, orders, and prescribes a lens with the intent of performing Orthokeratology for a specific patient within his or her practice is doing so as an off label use of that rigid gas permeable contact lens. Practitioners who advertise Orthokeratology in their practice are promoting off label use of rigid lenses. Exaggerated and unsupported claims of safety or effectiveness associated with this technique should not be included in such promotions. FDA

prefers to not intervene in the practice of medicine. However, we exercise regulatory discretion and reserve the right, since we have the authority, to take action when there is a demonstrated risk to public health. At the present time, there are no data available to demonstrate the risk to public health associated with night therapy Ortho-K which would cause FDA to take action against individual practitioners. There is a caveat related to that which I will address in a moment.

A contact lens manufacturer or finishing lab that promotes the sale of specific contact lens designs intended for Orthokeratology are no longer fabricating lenses based on a licensed practitioner's prescription. Promotion of a medical device by a manufacturer for a use which has not been cleared by FDA creates a regulatory issue. In order to come into compliance, the manufacturer would have to file the appropriate marketing application and obtain approval from FDA. Now it is possible for an individual practitioner to cross over into the definition of a manufacturer. That would involve the marketing of predetermined lens geometries, or entering into arrangements with finishing labs to market their lens design to other practitioners.

After 30 years, you may ask why FDA is interested

in Orthokeratology. The advent of refractive laser surgery has moved this issue from the periphery and more into the mainstream. The addition of excimer lasers to the refractive surgery field provided consumers an option beyond radial keratotomy. The promotion of Orthokeratology as a non-surgical option has also increased in the marketplace.

Our primary concerns deal with effectiveness and safety. Accurate, well balanced product labeling should accompany these devices to clearly state that Orthokeratology is a temporary effect. The cornea returns to pretreatment status when lens wear is stopped. It is important to communicate reasonable expectations for this procedure to the patients. Orthokeratology has limitations based on the original shape of the cornea. Generally the effectiveness is considered to be limited to around 3 Diopters, and we wanted to be sure that that information is in the product labeling.

From a safety consideration, our concern is primarily directed toward the night therapy approach. Currently there are no good data available in the literature to evaluate this technique. The safety issues for Orthokeratology have generally been addressed by prior research, which determined that the older fitting techniques

did not raise safety issues.

The division has discussed this topic with senior management in the office, as well as with our Center Director. Our branch is currently working with a number of Ortho-K manufacturers to bring them into compliance.

That completes my updates for this morning.

DR. RUIZ: Next will be Dr. Morris Waxler.

DR. WAXLER: Good morning. In fiscal 1997 the Diagnostic and Surgical Devices Branch reviewed more than 65 original investigational device exemptions, IDE, applications, and more than 160 amendments and supplements to IDEs. Almost all of these applications were for refractive surgery lasers. We received several premarket approval applications and supplements, also for refractive surgery lasers.

We have received 11 IDEs for black box lasers. Most of the remaining black box lasers have been seized by FDA or have been discarded by their owners.

We received more than 75 premarket notifications for a variety of Class I and Class II ophthalmic devices.

We will revise our guidance document for refractive surgery lasers, based in part on a consensus reached at tomorrow's meeting, and on the basis of comments

submitted in response to the changes published in the Federal Register. Your comments are welcome.

DR. RUIZ: Finally, Ms. Donna Lochner.

MS. LOCHNER: Thank you. On September 5, 1997, FDA approved PMA P960028 for the model SA-40 and AMO array, multifocal, ultraviolet absorbing silicon posterior chamber intraocular lens.

Please note that FDA did approve the sponsor to continue with the designation, multifocal, in describing their intraocular lens. Not only was a standard found that defined multifocal lenses as those producing more than one focal point, but it was felt that limitation to use of the terminology, bifocal only, would be unduly restrictive.

We have, however, put restrictions on the advertising and promotion of the device, which we believe will address the Panel's concern about promotion of the lens. Thank you.

DR. RUIZ: That completes the update, Mr. Chairman.

Agenda Item: Open Committee Discussion

DR. STULTING: Thank you. We will move now to open committee discussion of a PMA this morning, and I will turn the floor over to Sara Thornton for reading remarks

into the record, and conflict of interest statements.

DR. THORNTON: 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 Panel participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their, or their employer's financial interests. However, the Agency has determined that participation of certain members and consultants, the need for whose services outweigh the potential conflict of interest involved, is in the best interest of the government.

For purposes of today's meeting, Dr. Walter Stark, a consultant on the Panel, is excluded from participating in the intraocular lens premarket approval application, or PMA discussion, however in the absence of any personal or imputed financial interest, the Agency has determined that he may participate in today's discussion of general matters regarding intraocular lenses.

A limited waiver has been granted for Dr. Richard

Ruiz that allows him to participate in the review and discussion of the intraocular lens PMA, and the general matters regarding intraocular lens, but excludes him from voting.

A waiver is on file for Dr. Woodford Van Meter for his interest in firms at issue which could potentially be affected by committees' deliberations. The waiver permits him to participate in all general matters before the committee dealing with these firms.

Copies of these waivers may be obtained from the Agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the Agency took into consideration other matters regarding Dr. James McCulley, Marian Macsai, Eve Higginbotham, and Walter Stark. Drs. McCulley, Macsai and Higginbotham reported financial interests with firms at issue that are not related to the matters before the Panel, therefore the Agency has determined that they may participate fully in the Panel's deliberation.

Dr. Stark reported that he received honorarium and travel fees from firms at issue for speaking engagements that are not related to the issues before the Panel. He

also reported that on several occasions he conducted surgical techniques training for a firm at issue. Since these matters are unrelated to the specific issues before the Panel, the Agency has determined that he may participate fully in the Panel's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which the FDA participant has a financial interest, the participant should exclude themselves from such involvement and their 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.

We would like to note for the record that Eve Lydahl, MD, who is a guest with us today, has reported several professional relationships with the PMA sponsor that are related to the PMA before the Panel, but not directly related to the portion of the meeting in which she was asked to participate. Her professional relationships are in the form of contracts and consulting.

We would like also to note for the record that Dr.

Sverker Norrby, Ph.D., who is also a guest with us today, has acknowledged that he is employed by the sponsor of the PMA before the Panel. Thank you.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27, 1990, as amended April 20, 1995, I appoint the following individuals as voting members of the Ophthalmic Devices Panel for the duration of this meeting on October 20, 1997.

Drs. Karen Bandeen-Roche, Joel Sugar, Woodford Van Meter, Michael Belin, Jose Pulido, and Mark Mannis. For the record, these persons are special government employees and are consultants to this Panel, or consultants or voting members of another Panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

Signed, D. Bruce Burlington, M.D., Director,
Center for Devices and Radiological Health, dated 10-08-97.
Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27, 1990, as amended April 20, 1995, I appoint the following individual as a voting member of the Ophthalmic Devices Panel for the product development protocol recommendation to be taken at

this meeting on October 20, 1997, Dr. Walter Stark.

For the record, this person is a special government employee and a consultant to the Panel, or consultant or voting member of another Panel under the Medical Devices Advisory Committee. He has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting. Signed, Dr. Bruce Burlington, M.D., Director, Center for Devices and Radiological Health, dated 10-08-97. Thank you, Mr. Chairman.

DR. STULTING: Thank you very much. We will now open discussion of PMA P960034 for a Heparin Surface Modified Posterior Chamber Intraocular Lens. I will turn the floor over to Donna Lochner to begin.

Agenda Item: Introduction of PMA P960034

MS. LOCHNER: Thank you. You are being asked to make a recommendation regarding the safety and effectiveness of the Heparin Surface Modified IOLs in PMA P960034 and to assess labeling claims being made for these lenses.

I would like to briefly explain the regulatory difference between statements a sponsor may wish to make in their labeling that describe the results of clinical studies, versus a labeling claim.

As you review the data presented and the conclusions reached, you will assess whether the conclusions made by the sponsor are supported by the data. Once you have agreed upon the conclusion and any modifications to the wording of a labeling statement, you should decide whether the data warrant inclusion of this information as a labeling claim.

Claims are generally reflected in the Indications for Use section of the labeling. The Indications section identifies the target population of the device for which there is valid scientific evidence demonstrating the device's safety and effectiveness.

Approval of a claim in the Indications section of the labeling allows a sponsor to advertise and promote their lens for the particular intended use claimed. It also allows the sponsor to apply to the Healthcare Financing Administration for greater Medicare reimbursement for their IOLs.

While reimbursement issues should not influence your recommendations today, the examples of reimbursement advertising and promotion of lenses are being offered to help you to understand the regulatory implication of approval of a claim.

Your recommendation about the claims should be based upon your assessment of the data provided in support of the claim. Alternately, you may decide that the conclusions are descriptive information concerning clinical studies conducted by the sponsor but do not warrant a claim.

This descriptive information would typically be contained in the Clinical Trials section of the labeling. In other words, if the data does not conclusively provide evidence of the device's use in the target population, but does provide useful clinical information, the labeling statements would not constitute a claim.

We have provided to you the sponsor's revised proposed labeling claims and later on this morning, Dr. Lepri will propose to you our specific questions regarding these proposed claims. I provide this information as background to your discussion of the PMA.

I would also like to thank the review team for this PMA, who worked very hard to bring it before you today. The team leader and engineering reviewer is Claudine Krawczyk, clinical reviewer was Dr. Bernie Lepri, with consulting reviews from Dr. Rosenthal. Statistical reviewer, Dr. Wen(?) Jow(?) Chow, toxicology, Susanna Jones, chemistry, Dr. Kisha Alexander. Microbiology, Susan

Dejai(?), and manufacturing, Sterling Gerrie. Thank you.

Agenda Item: Team Leader Presentation

DR. KRAWCZYK: Good morning. Thank you, Donna, for the introduction. Before I pass the microphone to the sponsor, I would like to quickly summarize for you some important points regarding the premarket approval application for Pharmacia and Upjohn CeeOn Heparin Surface-Modified -- HSM -- which you will probably hear a lot today -- Intraocular Lenses.

The sponsor has requested approval to place the heparin surface modification on all their PMA-approved polymethylmethacrylate, or PMMA, Posterior Chamber Intraocular Lenses. The lenses are the same as those approved under P810055.

You may have noticed in your reviews of the PMA that the foreign studies were performed on PMMA lenses manufactured with ICI's Perspex CQ UV PMMA. The U.S. studies were performed on lenses manufactured with glass(?) flexes(?), UVEX1 PMMA. Engineering and chemistry analyses have determined that the addition of the coating on the firm's different PMMA materials will not result in new safety and effectiveness concerns; therefore, we believe that the submission of the clinical data from both the U.S.

and foreign studies is acceptable.

In addition to the request to add the surface modification to all their PMMA lenses, posterior chamber, the sponsor has also requested approval to include a claim in the Indications section of their labeling regarding the reduction of foreign body reaction associated with the Heparin surface modified lenses.

The sponsor recently proposed a revised claim in the addition of a cautionary statement. A fax received from the sponsor dated October 15, 1997, which includes the revised claim and the proposed caution, has been included in the packet that you received this morning. Specifically, the claim currently reads as follows:

The foreign body reaction measured by cellular deposits and giant cells, is reduced on CeeOn HSM PMMA lenses compared to non-HSM PMMA lenses. This difference is observed during the first postoperative months, but may not be present at 12 months, when the foreign body reaction is less pronounced.

Additionally, information has been included in their draft package insert in the Clinical section, which gives some information regarding the results obtained from the various studies performed to evaluate the lenses and the

surface modification. The following caution statement has been proposed for the labeling as well:

The effectiveness of this Heparin surface modified lens in reducing the incidence of complications or adverse events associated with inflammatory reactions has not been established.

In support of their request, the sponsor has submitted data from several clinical studies. There was one U.S. study of 411 cohort subjects to evaluate the visual acuity and complications with HSM lenses.

To support their claims and the clinical utility of the surface modified lenses, the sponsor has submitted data from eight foreign clinical studies performed by Pharmacia and Upjohn, five published studies, and two U.S. substudies, however one of the substudies was discontinued before sufficient numbers of subjects could be enrolled, therefore these data were not used by the sponsor to support their claim.

FDA continues to evaluate some statistical issues regarding the clinical data. I would now like to introduce Ms. Toni Elliott, of Pharmacia and Upjohn, who will lead off the sponsor's presentation. Thank you.

DR. STULTING: Thank you. While the sponsors are

coming up to the table -- and you may invite any of your personnel that you wish to come up for the discussion. There will be one hour provided for your presentation, and as you present, please introduce yourselves, let us know your affiliation and any conflict of interest that you may have if you are not a company employee. Thank you very much. Go ahead.

MS. ELLIOTT: Good morning. Mr. Chairman, Madam Secretary, Panel members, Panel consultants, and FDA personnel. I am Toni Elliott, Regulatory Affairs, Pharmacia and Upjohn in Kalamazoo, Michigan.

Today we will be presenting information from PMA P960034 for Heparin Surface Modified Posterior Chamber PMMA Intraocular Lenses, otherwise known as CeeON HSM PMMA IOLs. Over 600,000 of these lenses have been implanted worldwide, except in the United States. Presenting today will be Stefan Trocme, M.D., University of Texas Medical Branch at Galveston, Texas.

He will be discussing the postoperative inflammatory response associated with cataract extraction and IOL implantation. Kjell Madsen, Ph.D., Senior Scientist with Pharmacia and Upjohn in Uppsala, Sweden, will be presenting some pertinent preclinical findings. Eva Lydahl,

M.D., Ph.D., from St. Erick's Eye Hospital in Stockholm, Sweden, will present clinical information from some of the international studies which we have conducted.

Finally, Dr. Trocme will return to the podium and will provide data from the U.S. clinical trials. Dr. Trocme.

DR. TROCME: Thank you. Stefan Trocme, Associate Professor at the University of Texas, Medical Branch in Galveston. I am a paid consultant for Pharmacia, and I have no financial interest in the company or the product discussed today.

A large number of PMMA lenses have been implanted in cataract patients worldwide and we know that they have been safe and effective restoring vision to these patients. Although they are well-tolerated, they are not perfectly tolerated. There are reports in the literature suggesting that, indeed, if you study eyes receiving PMMA implants, that there is a foreign body reaction in these eyes, and indeed, this type of reaction may be more common than originally anticipated.

How can that be? This is an artist's rendition of the surgical trauma, and it is hardly surprising that the entry into the eye, the removal of the cataract, and the

implantation of an implant, will cause some initial short-lived inflammation. As surgeons, we know this information to typically be short-lived, however at times this inflammation may be protracted and low grade, and the inflammatory mediators and inflammatory cells, including neutrophils and monocytes may gravitate towards the intraocular lens implant and attach to it.

We may indeed postoperatively at some point, early or late, see the appearance of cells onto the intraocular lens, seen here.

How could this occur? Well, as the blood aqueous barrier breaks down, there is a release of a variety of inflammatory cells as mentioned, including monocytes. Monocytes, when they identify a foreign body in the eye will transform into macrophages, epithelial cells, and into a foreign body multinucleated giant cell.

If such an implant is removed, and studied under the microscope, this is how the multinucleated giant cell can be identified. We know that the presence of foreign body giant cells signify a foreign body reaction. And I will now leave the podium to Dr. Kjell Madsen, who will discuss this in the context of heparin surface modification, and how that can modify this type of response.

DR. MADSEN: I am Kjell Madsen from Pharmacia and Upjohn Uppsala. I am the senior scientist at Creighton(?) Nichol(?) Ophthalmology. And I will today talk about what we have been doing in the preclinical sense, in development of this heparin surface-modified lens, but first I would like to show you another slide on inflammation. It is quite busy, and inflammation is quite complex. I would only like to point out certain lanced(?) points. The complement(?) system, which is a series of proteins, are quite important, and they might be activated by the lens, and attract, recruit, and activate various white blood cells which might attach to the lens surface, stay there, produce other factors, which might contribute to continuing chronic inflammation, which might eventually lead to foreign body reaction, and the lens surface is one important factor in this reaction.

The heparin surface modification is a chemical attachment of heparin molecules at one end to the lens surface. The heparin itself is a polysaccharide with a lot of sulfate groups on it, so it has a heavily negative charge -- that is important.

The three mechanisms that we believe is important in reducing the foreign body reaction is that the heparin

surface modification makes the surface hydrophilic, the surface becomes mobile, and we have the negative charge.

This is an old finding that if you plot the attachment of cells to a surface against hydrophilicity, you get the reverse U-shaped curve, where you have the highest solidation(?) in the intermediate range of hydrophilicity, at extremes both hydrophilic and hydrophobic, you have less solidation(?).

The other two points are illustrated in this cartoon, which are looking in such a 3-D view on a molecular level, and as you can see, the surface is kind of hairy or seagrass-like. You have a lot of heparin molecules sticking out. These molecules can move and they contain a negative charge, which makes the surface similar to a cell surface or other biological surface.

We have done several preclinical assessments in the development of this surface and in the characterization of it, and these are some of the in vitro methods we have been using. The first two are measurements on acute inflammation. The activation of the complement system. The activation of the granulocytes, and the two others are assessments of more chronic inflammation, the attachment of microphages and attachment of fibroblasts.

This slide shows the experiment with complement activation. And it was done in vitro with human plasma, in which we put one intraocular lens, incubated for one hour, measured one component of the complement system, C-3a, which is split from the named C-3, and as you can see on the slide, incubating the plasma for one hour results in some production of C-3a. Incubating with a PMMA lens results in the production of significantly more C-3a, and the HSM lens is similar to the control serum without any lens at all.

For activation of granulocytes, we incubated human neutrophil granulocytes with a lens, and measured the release of oxygen radicals, which you can do with measuring the chemiluminescence, and as you can see, the PMMA surface activates the granulocytes in a time-dependent manner, so you produce oxygen metabolites and in the HSM surface, thus activate the granulocytes very little.

For the cell attachment studies we incubated human monocytes with the lenses for 24 hours and then visualized them with immunohisto chemistry. And as you can see, there are many more cells on the PMMA cells after 24 hours than on the heparin surface. This looks like a different magnification, but it is in fact not. It is probably an out of focus effect because these cells were the only cells seen

in the lens, and they were close to the periphery of the lens.

These are similar experiments with fibroblasts, which were allowed to attach for 24 hours and then the lens was stained with ordinary histological stain, and you see the cells as dark dots in this low power magnification picture, and HSM lenses contain much less cells.

We also did animal in vivo experiments, and I will today present the results from two experiments. The first one is in the rabbit, it is an acute inflammation model. You implant the lens and you count the number of white blood cells in the anterior chamber, and the two other points here is from a monkey study, which 16 monkeys where we implanted one PMMA IOL in one eye, and an HMS IOL in the other eye. It was done close to clinical practice, but with one important difference; we did not use any postoperative anti-inflammatory treatment at all. No steroids postoperatively, but just looking at what is happening.

The next slide shows the results from the rabbit study, the acute study, and as you can see, on Day One, the first postoperative day, there were indeed an accumulation of white blood cells into the aqueous, and with increase in time, the amounts of white blood cells decreased, and as you

can say, there was a significant difference between the PMMA IOL and the HSM IOL. The HSM IOL, again, had almost as few white blood cells as just the surgical removal of the lens produced.

This is from the monkey study where we used a paired approach, with an HSM lens in one eye and a PMMA lens in the other eye, and as you can see, after one month, we could detect cellular deposits on all IOLs in the PMMA eyes, and about 10% in the HSM group, and with increasing time, up to 12 months, the percentages in the PMA group dropped to around 50%, and the HSM stayed more or less the same throughout the period. And this was highly statistically significant. And this study was published in the Journal of Cataract and Refractive Surgery in 1990.

The posterior synechiae were similar. Here you do not see any definite trend on the synechiae over time in the PMMA group, but you had fewer synechiae in the HSM group.

The next slide shows an actual eye in the PMMA group after 12 months, and you can clearly see the cellular deposits, and you can see the synechiae making the pupil uneven. You have an attachment here, for instance. And the corresponding eye, the other eye in the HSM group, is shown in the next slide, which is very clear and you have no

synechiae.

Then I leave the microphone to Eva Lydahl who will discuss the clinical results.

DR. LYDAHL: Thank you. I am Eva Lydahl, I am an anterior segment surgeon at St. Erick's Eye Hospital in Stockholm in Sweden. And I am a paid consultant to Pharmacia and Upjohn. I have no financial interest in the company.

As the heparin surface-modified lens looks exactly like a regular PMMA lens, we have here the unique possibility of doing double-blind controlled, randomized trials, and a large number of trials have been performed -- I am going to present a summary of the results of some of these studies.

The first study was started in 1987 at the Karolinska Hospital in Stockholm, with Professor Bob Phillipson as the principal investigator. Six surgeons participated. There have been two publications from this study, one in the Journal of Cataract and Refractory Surgery in 1992, and one in Ophthalmology in 1990.

The objective of this study as well as of all the other studies that I am going to present was to evaluate the effect of heparin surface-modification of PMMA intraocular

lenses on the inflammatory response after cataract surgery. This is the lens design that was used in this first study.

The study was performed according to the standard FDA protocol. We were examining the standard variables, and the time frames for the follow-up were the standard FDA format. In addition, to meet the objective, we looked at these variables that are all related to inflammation. Iritis, subjective rating at the slit lamp. Synechiae, cell deposits, pigment deposits on the lens. Fibrin light precipitates, secondary cataract, and corticosteroid treatment. The surgical technique was a planned extracapsular cataract extraction, as it was routinely performed in 1987 at the Karolinska.

The postoperative steroid treatment was standardized, and if additional treatment was needed, it was recorded on the case report forms; 129 patients were included in the HSM group and 138 in the PMMA group. You can see that the age, the mean, and the ranges are very similar in the two groups, and also that the patient groups were comparable regarding other baseline data, like preoperative pathologies and other findings.

This is an eye with a PMMA lens where we can see cellular deposits on the surface of the lens. And this is

the variable where we have found a significant difference between the HSM and the PMMA eyes. At three months, this difference is most pronounced. We see that 13% of the patients in the HSM group and 7% in the PMMA group have cellular deposits on their lens surface, and this is significant at this level. Later, this difference decreases.

When this study was halfway through, a paper was published by Dr. Martin Vansil(?) in Aachon(?) in Germany, where he described a method using specular microscopy of this to evaluate the surface of the intraocular lens in vivo in the patient. And he also found that multinucleated giant cells are very common on PMMA lenses, and also concluded that this means that a foreign body reaction to PMMA is very common.

We amended the protocol to the study at the Karolinska and Dr. Vansil taught his technique to the group at the Karolinska, so specular micrographs were taken of the 53 last included patients in the study, 23 HSM and 30 PMMA patients. And micrographs were taken at one week, one month, six months, and three years.

And this is the result at one month. We found foreign body giant cells on 60% of the PMMA IOLs, but not on

any of the HSM lenses. We also see that the frequency of foreign body cells goes down with time, and at three years, this difference is no longer statistically significant, but we only have data from 39 patients here.

Dr. Vansil, whom I mentioned, has written a book about specular microscopy of the lens, and this is a picture from his book. In this area, you can see cellular deposits as we can see them in the slit lamp, and then there is a specular micrograph taken from this area, which shows that what we are looking at is really multinucleated giant cells, so we are talking about the same thing here, it is just two different methods to evaluate the same thing, it is just that specular microscopy is the more sensitive of the methods.

The second study was initiated because we wanted to broaden the examined population. The first study was blond, blue-eyed Scandinavians, and we know that persons with more heavily pigmented eyes tend to react with more postoperative inflammation, so this is a study performed in ten centers throughout the world. There are southern European centers, there are two Asian centers. It has been published in Ophthalmology in 1992; 260 HSM patients and 264 PMMA were included. And this is the lens design.

We see here a very similar picture to the one I showed from the Karolinska study. We see a difference between the two groups that is most pronounced at around three months. We also see that here the level is a little higher than in the Karolinska study, probably reflecting the different population. We had 27% in the PMMA group. In the Karolinska study here it is 44. And also in the study, the difference is statistically significant at three months, but not later.

This study also shows a significant difference regarding posterior synechiae. If we look at the number of patients who have moderate or severe synechiae at any time during a one-year follow-up, we see that there are significantly more in the PMMA group than in the HSM group.

This study is another study where we wanted to look at a different patient population, a group of patients that would react more with postoperative inflammation, and here it is patients with diabetes and glaucoma. It has been published in the European Journal of Implant and Refractive Surgery in 1995.

This is the lens that was used. There were four surgical centers. Dr. Vansil was involved here to teach the technique and he also evaluated all the photographs that

were taken. The primary variables were giant cells, evaluated from specular microscopy photographs, and cell deposits seen at the slit lamp; 118 HSM patients and 121 PMMA patients were enrolled.

We can see that there was a fairly even distribution between diabetes and glaucoma. We also see that the duration of the disease was similar in the two treatment groups.

These are the results regarding cell deposits seen with a slit lamp. As in all the previous studies, the difference is most pronounced at around three months because the level of the problem on the PMMA lenses is at its highest at three months, and here we are just under 60%. We see that the PMMA group improves with time, but the HSM group stays on approximately the same level, around 20% throughout the study, and in this study, there is a significant difference, also, at one year. This is the giant cells seen with specular microscopy, very similar picture. We see that almost 80% have giant cells in the PMMA group at three months.

Another patient population with more reactive eyes seems to be patients with heavily pigmented eyes, and this study was performed in two Asian centers, one in Malaysia

and one in Singapore, and this is the results looking at cell deposits with a slit lamp, and it confirms that the level is high here. We see a significant difference between the two groups at three to six months and it is still significant at a year. That is just under 100 patients in this study.

In summary, the results are very consistent from study to study. We see less cell deposition on the HSM lenses at the slit lamp. We see foreign body giant cells on the lens surface with specular microscopy. I have now only presented percentages of patients who have deposits, but if we look at those who have cell deposits, and compare PMMA and HSM, we find that the number of deposits is much higher on PMMA lenses than HSM lenses, and that is just as consistent from study to study, and highly significant in all studies.

We do not see a difference regarding iritis. We have not been able to detect a difference in posterior capsular passification, whether we look at the aggrates(?) or whether we look at Elschnig Pearls and fibrosis on intact capsules. We have not seen the difference in the need for additional corticosteroid treatment.

We have information from some studies, some of

them I have not reported here. There is one study that shows less breakdown of the blood aqueous barrier with HSM lenses at six months. The blood aqueous barrier is reestablished in the HSM group, but not in the PMMA group in the study that was performed by Professor Korniyavas(?) in Quinbrane(?), Portugal. There are a couple of studies that show less posterior synechiae. There are studies that show less pigment deposition on the lens surface.

In conclusion, in a standard evaluation of safety and effectiveness, HSM is not different from unmodified PMMA, so there are no additional safety concerns. But our studies have shown that a foreign body reaction to PMMA is very common, that is not new, but all these studies have confirmed that finding, and we have seen that it is most pronounced at around three months.

We also have seen that in certain patient groups, such as patients with glaucoma, diabetes and heavily pigmented eyes, this foreign body reaction is more common and it persists later than in the normal cataract population. And we have also demonstrated that this foreign body reaction can be significantly reduced by heparin surface modification of PMMA IOLs. Thank you. I will now leave the word to Trocme for a presentation of the U.S.

clinical data.

DR. TROCME: Thank you. Stefan Trocme, University of Texas, Medical Branch. I will report results from two U.S. clinical trials. The first U.S. clinical investigation tested safety and effectiveness of the heparin surface-modified PMA IOLs. First is grid values. There were three lens values tested. I will show you their design. Model UV89H. Model 720H. And Model 810H.

The best case final visual acuity at one year of 20/40 or better exceeded grid values for every age group. All sight-threatening complications within grid values, with the exception of the cumulative hyphema.

In terms of adverse events, eight patients were reported with adverse events. None were deemed to be lens-related. All adverse event rates were within grid values. This led us to conclude that the first U.S. clinical study demonstrated that there was a reasonable -- there is a reasonable assurance that the HSM IOLs are safe and effective for the visual correction of aphacia.

Now to the second study, the U.S. claims study. This is the lens used, Model 815HS. The objective of this trial was to evaluate the effectiveness of the CeeOn HSM PMMA intraocular lens in reducing postoperative inflammation

following cataract surgery in routine patients and in defined risk groups, namely, diabetic patients and glaucoma patients. This was a parallel, double masked, randomized multi-center investigation including eight study sites.

These are the inclusion criteria. Routine patients with visually significant cataract requiring surgery and justifying primary implantation of a posterior chamber IOL to diabetic patients with significant cataract requiring medical treatment with either insulin treatment or tablet treatment for the diabetes, but patients without significant retinopathy.

A third group is the glaucoma group that required a diagnosis of primary open angle glaucoma, including pseudoexfoliation. These patients were required to have a glaucomatous optic disc cupping(?) or a characteristic visual field defect.

Here we have the postoperative follow-up schedule. One week, one month, three months, six months, and twelve months. At each postoperative visit, these patients were subjected to a routine postoperative exam, but in addition to that, they had a dilated slit lamp examination in order to enable the investigator to scan the entire intraocular lens in order to determine presence or absence of cell

deposits. This was an investigator determination at the slit lamp.

There was also specular microscopy with the dilated pupil, with a standardized protocol for photography. First, a low power survey photograph of the intraocular lens, then followed the high-power specular micrographs at these given locations. These photographs were submitted to a reading center with one single certified reader at the Jones Eye Institute at the University of Arkansas.

These are the primary efficacy assessments. Determination of occurrence of giant cells on the lens surface, by specular microscopy, and second, determination of presence of cell deposits by slit lamp examination on the intraocular lens.

Safety assessments. Presence of postoperative complications were recorded. The presence of postoperative ocular pathologies and adverse events were also recorded.

We enrolled 220 routine patients, 58 glaucoma patients, and 89 diabetic patients into this study.

Demographics. HSM and non-HSM treatment groups were comparable in each of the three patient populations.

Operative characteristics. A vast majority in both treatment groups in the routine, glaucoma, and diabetic

patients, had phacomulsification, utilized visco-elastics, and the lens was placed in the back.

Sight-threatening complications comparable between HSM and non-HSM patients in each of the three patient populations. Adverse events. None reported in the routine patient group. One reported in the glaucoma group. Two reported in the diabetic group. And none were deemed to be lens-related.

Here we have the bar graph depiction of the results, and occurrence of giant cells in routine patients. Note the considerable difference in favor of HSM lenses in terms of occurrence of giant cells, and here at three months -- sorry, at one month -- we have a 52% occurrence on PMMA versus a 7% occurrence on the heparin surface-modified lens. From one week through six months, this difference was statistically significant in favor of HSM lenses.

Looking at cell deposits, we again see this difference in favor of HSM lenses. This difference achieves statistical significance at the three-month study visit.

Occurrence of giant cells in glaucoma patients, again, the same pattern of difference in favor of HSM lenses. Here we have 10% versus 48% at the three-month time point. This achieves statistical significance.

Cell deposits. Similar pattern. The difference between HSM and the PMMA achieves statistical significance. The pattern is seen throughout the evaluation period. Giant cells occurrence in diabetic patients, again, less occurrence of giant cells in the HSM group at all time points, and in this group, this achieves statistical significance at all time points evaluated.

A similar pattern with the exception of the one-week evaluation period for cell deposits in diabetic patients. The difference is seen here, achieves statistical significance in favor of HSM at the three-month evaluation time.

Subjecting these findings to a simultaneous -- that is, evaluating all time points at once, evaluation, a longitudinal data analysis shows statistically significantly less occurrence of giant cells in the HSM group for routine patients, glaucoma patients, and diabetic patients.

Looking at cell deposits, a difference in favor of HSM, achieves statistical significance in the routine patients and glaucoma patients.

The findings from all clinical trials lead us to conclude that there is a reasonable assurance that the CeeOn HSM IOL is a safe and effective lens for the visual

correction of aphakia. Two, that the CeeOn HSM IOL reduces the foreign body reaction as measured occurrence of deposits in giant cells on the intraocular lens surface.

These findings together support the claims statement that clinical studies demonstrate that foreign body reaction, measured by cell deposits and giant cells, is reduced in the CeeOn HSM, PMMA lenses, compared to non-HSM PMMA lenses. This difference is observed during the first postoperative months, but may be present at 12 months, when the foreign body reaction is less pronounced. Thank you.

DR. STULTING: Does that conclude the presentation? Okay, thank you very much. It is now 10:25, roughly. I would like to take a 15-minute break. If we could reconvene here in 15 minutes, we will begin the discussion of this PMA.

[Brief recess.]

DR. STULTING: I call the meeting to order once again. We would like to hear the clinical reviews, then the primary Panel reviewers and after that we will ask the sponsors to return to the table for a question and answer session before we vote. So, the floor now belongs to Dr. Lepri for presentation of a clinical review.

Agenda Item: Sponsor Presentation:

Clinical Review

DR. LEPRI: Thank you, Mr. Chairman. I am going to limit my comments today to the issues that will present information to the Panel that should be considered in the placement of claims and clinical information in the labeling.

This PMA is comprised of the reports of 15 studies, two conducted in the United States and 13 conducted internationally. The two United States studies consist of the primary study and substudy Model 815HS. The primary study was for a duration of approximately two years with 686 patients enrolled and a 411 cohort.

The substudy Model 815HS had a duration of greater than two years with 367 patients enrolled and recorded. There was no cohort.

The primary U.S. study satisfactorily meets current grid guidelines as discussed by Pharmacia in their presentation, and demonstrates the performance of the IOLs for the correction of aphakia, but do not address the clinical utility of heparin surface-modification.

Study 815HS was a randomized, controlled 12-month study comparing HSM and non-HSM IOLs for the presence of giant cell and cellular deposits. It was discontinued in

October of 1996 for administrative purposes.

The study enrolled 367 patients, there was no cohort reported. Of these 367 patients, 220 were routine cataract patients, 15 had glaucoma, and 89 were diabetic. There were eight sites and eight investigators.

Visual acuity is the primary efficacy endpoint of any IOL study. Even though the IOLs studied in this PMA have already been proven to be safe and effective for the correction of aphakia, visual acuity still bears mentioning in consideration of heparin surface modification.

This first slide depicts the visual acuity of those patients having 20/40 or better, who were routine patients. At 12 months postoperatively, 90% of the non-HSM patients have visual acuity of 20/40 or better, and 91% of the HSM patients have visual acuity of 20/40 or better. The glaucoma patients, 94% of non-HSM and 82% of the HSM had a visual acuity of 20/40 or better at 12 months. For the diabetic patients, at 12 months, 83% of the non-HSM and 83% of the HSM diabetes patients had visual acuity of 20/40 or better.

The visual acuity results clearly reflect that visual acuity is not affected by applying this heparin surface modification to these IOLs. Statistically

significance testing was conducted for substudy Model 815HS. Each population was analyzed separately and adjusted for potential center effects, and all analyses were conducted at the .05 level of significance.

There were no statistically significant differences detected between HSM and non-HSM patients for the categories of age, race, or gender within the individual groups of routine, glaucoma, and diabetic patients.

This next chart depicts -- somewhat graphically, and I will explain my codes to you -- the presence of giant cells on the lenses. Yes stands for, yes, there was demonstrated statistical significance. No means no. Demonstrated statistical significance. RG&D stands for the patient's subgroups of routine glaucoma and diabetes.

You will see that there is clearly a trend in the routine patients of some demonstrated statistical significance for week one, month one, month three, and month six. The diabetic patient showed and demonstrated statistical significance for all postoperative periods. Glaucoma, however, only demonstrated some statistical significance at the three-month interval.

For cellular deposits, the only demonstrated significance that was consistent was at three months for all

three pathology groups, and for glaucoma there was also some demonstrated statistical significance at the sixth-month postoperative interval. What we need to look at is, what is the clinical significance of these findings, and that is one of the questions that is posed to you today in the remainder of this presentation.

Moving onto the international data sources, Pharmacia conducted eight international studies, distinguished as Group I and Group II with four in each group. Group III studies were published reports by independent authors.

Group I studies included over 1100 patients for investigations ranging anywhere from one to two years in duration, and you can see it there with the clinical variations that were evaluated.

Group II studies were for three to twelve months in duration and report results for a total cohort of 239 patients.

Group III was comprised of five studies ranging from 3 to 16 months in duration with a total cohort of 249. Three studies were uncontrolled and two studies used historical controls of PMMA and comparable patients.

The first European study that I will review is the

Karolinska study, and it was a controlled double-blind study comparing HSM with PMMA in patients having undergone extracapsular cataract extraction with IOL implantation. The postop inflammatory responses evaluated by Pharmacia were giant and cellular deposits, and also, a comparison of iritis will be made.

The population was 267 patients for enrollment at which 248 were cohort, 127 assigned to PMMA and 121 assignment to HSM. Patients also had two milligrams of betamethasone via subconjunctival injection, in addition to topical steroids for four weeks in this particular study.

The early postop period showed no major differences between HSM and PMMA lens groups. There was a notable increase in percentage of giant cells and cellular deposit for three months and later, being statistically significant at three months, which was the first postop exam after steroids had been discontinued. This comment is not a conclusion but rather a note of curiosity for your consideration in evaluating the labeling claims.

At two to three years, little difference was seen. Iritis was evident in both groups early on and not at all at the six-month exam. In the study, the sponsor states, Consequently, there is no reason to believe that the

difference is an effect of heparin surface modification.

The next international study was also from Group I, and it was a randomized double-blind study in a patient population characterized by having diabetes and/or glaucoma. Its duration was one year; 239 patients were enrolled and 188 were cohort. In the cohort, 89 received PMMA and 99 received HSM lenses. Once again, giant cells and cellular deposits were evaluated.

In this particular study it is noted by the sponsor in their presentation, 64 patients of the 239 enrolled were not included in the analysis; 7 for operative complications, and 57 because there was uncertainty of photo identity for the specular microscopy results.

At three months, giant cells were observed in 73% of the PMMA and 22% of HSM patients. At one year, it was reduced to 32% in PMMA, and 17% in HSM. For cellular deposits, at three months we have 54% in the PMMA population, and 19% in the HSM population. At one year, 38% in the PMMA and 18% for the HSM patients. There were no observable differences in visual acuity function, and no observable differences between disease groups.

The last study is a Group II study which was a double-blind, parallel randomized study, also. Its duration

was six months, and its purpose was to evaluate the recovery of the blood aqueous barrier in postop patients by using anterior segment fluorophotometry; 64 patients were enrolled, and 61 were cohort; 27 had the PMMA IOLs, and 34 had the HSM IOLs.

At six months, the HSM patients had reestablished the blood aqueous barrier, and the PMMA patients' blood aqueous barriers were still elevated. There were no statistical differences shown at one week or one month for either cell deposits or synechiae.

Summary comments. The early postop periods show no major differences between HSM and non-HSM groups. The general trend observed is that statistically significant differences are established at the three-month postop interval, no major differences at one year or in the patient function as measured by visual acuity performance. Some variation in results occurred between pathology groups.

HSM shows a clear trend of reduced inflammation. This is obvious at three months when steroids have been discontinued for about eight weeks, and adverse events and complications meet current grid values for IOLs for HSM and non-HSM IOLs in this study.

In preparation for presentation of the questions,

I have this note to the Panel members. The purpose of Question 1 is for the Panel to provide their opinion on the placement of the claim in the proposed labeling. The information is as follows:

Giant cells and cellular deposits were the efficacy variables of Study 815HS in Routine, Diabetic, and Glaucoma patients. Statistical significance of differences between HSM and PMMA IOLs showed variable results between patient groups and over time.

Question 1A. Do the clinical data measured in this PMA support the labeling claim that "The foreign body reaction, measured by cellular deposits and giant cells, is reduced on CeeOn HSM PMMA lenses compared to non-HSM PMMA lenses. This difference is observed during the first postoperative months but may not be present at 12 months, when the foreign body reaction is less pronounced."? Or

Question 1B. Is this statement more appropriately placed in the "Clinical Trials" section of the labeling?

Question 2. Do the clinical data in this PMA provide reasonable assurance of the safety and efficacy for the visual correction of aphakia with heparin surface-modified PMMA intraocular lenses?

Question 3. Do the clinical data in this PMA

support the proposed Caution Statement: "The effectiveness of this heparin surface-modified lens in reducing the incidence of complications or adverse events associated with inflammatory reactions has not been established."?

Thank you, and I would like to particularly thank Pharmacia and Upjohn for the very thorough and exhaustive job they did of presenting all of the data so that it was very legible and understandable and easy to find in such a large study. Thank you.

DR. STULTING: Thank you very much. Primary Panel reviewers for this PMA were Joel Sugar and Martin Mannis. I will ask Dr. Sugar to present his comments.

Agenda Item: Primary Panel Reviews

DR. SUGAR: I would like to thank the sponsors and Dr. Lepri for their excellent presentation of data and Dr. Lepri's excellent review. I have little to add.

I was distressed by a few things, one, the preoperative pathology was a supposed exclusionary criteria for entry into the study, yet 25% of the cohort patients had preoperative pathologic conditions listed as exclusionary criteria. That does not alter the final conclusion.

I was distressed in Study 90IE01 which looked at patients with glaucoma and diabetes -- this is one of the

European studies -- and found less cells on the HSM lenses, more fibrin and fibrin-like deposits on the HSM lenses, but they did not look at clinical iritis in these patients.

It raises the question in my mind whether looking at cellular deposits on the lenses really says something about the ability of the lenses to introduce inflammation, or merely says something about the electrostatic resistance of the lenses to adherence of macrophages and giant cells.

My conclusions are that the data provided by the sponsors support approval of this lens for correction of aphakia. The package insert lists the indications with the Indications statement -- and this has already been partly dealt with -- that the CeeOn HSM lenses have been shown to reduce foreign body reaction to the lens surface and therefore increase biocompatibility of the intraocular lens, following implantation in both routine and high risk patients, particularly during the first postoperative months.

The data certainly support the development of fewer deposits on these implants. Overall, however, they do not support or refute in any way, except earlier reestablishment of the blood aqueous barrier, a higher "biocompatibility" of the lens.

It would probably be preferable for the statement be made that these lenses have been shown to induce less lens deposits, and to allow more rapid reestablishment of the blood aqueous barrier without a specific statement about biocompatibility.

Another concern -- minor one -- in the package insert is the statement that YAG laser capsulotomy, it is recommended that it not be performed on patients implanted with HSM-modified lenses earlier than six months postoperatively.

The support for this recommendation is uncertain, and it is of concern to me that, if there is adverse effect associated with earlier capsulotomy, that has not been presented, and many if not most surgeons are likely to do capsulotomies earlier in their patients.

In summary, I agree with approval of the lens for correction of aphakia with the modifications discussed above, and the answers to Dr. Lepri's questions are 1A, yes; 2, yes; 3, yes.

DR. STULTING: Dr. Mannis.

DR. MANNIS: Thank you very much, Dr. Stulting. First, I would also like to thank the sponsors for a lucid presentation of their data, and particularly to Dr. Lepri

and his team for providing us with very good information on which to base our summaries.

To save time for everyone, I would say that I agree almost completely with Dr. Sugar's assessment in looking at the U.S. studies. I believe that the study design, the number of participants in the study, provided us with good information that HSM lenses demonstrate safety and efficacy equal to unmodified lenses. And that the safety data suggests there is no increase in complications or adverse reaction when using these modified lenses.

Looking at the non-U.S. studies as a conglomerate, I think the assessment is somewhat more complex, and that has to do with the fact that these studies are really quite heterogeneous in terms of sample size and adequate controls. And what we can conclude from them, then, cannot be quite as expansive.

Taken cumulatively, I felt that the non-U.S. studies did suggest that HSM lenses are not associated with increased morbidity, even in eyes with Uveitis, but did not conclude that the data suggested that they were superior to unmodified lenses.

I think that the data particularly as presented this morning suggests that HSM lenses do cause a decrease in

cellular deposition, but as suggested by Dr. Sugar, the jump from cellular deposition to whether or not that is truly beneficial in terms of mitigating inflammatory response, clinically, is yet a second jump. So, my conclusion would be consistent with Dr. Sugar's and that is that we recommend that these HSM lenses appear to be safe and effective for the visual correction of aphakia, and that the labeling be altered as suggested by Dr. Lepri's team.

DR. STULTING: Thank you. Last, the sponsor and anyone you would like to come to the table for questions and answers. And the floor is open for discussion. Perhaps we could we begin with the question posed by Dr. Sugar about the recommendation for a six-month wait before performing YAG capsulotomy. And for the record, once again, please state your name before you speak so that the transcriptionist can get that information accurately.

MS. ELLIOTT: I will attempt to answer Dr. Sugar's question. The Caution Statement in the labeling is there because it was requested to be there. The Agency, because we had not done a specific YAG laser study, determined, if the heparin effect was compromised in any way by the YAG laser, they recommended that we put this cautionary statement in the labeling.

We do have a YAG laser study that shows the damage done by a YAG laser and HSM lens is no different than that that you see on a non-HSM PMMA lens. I have some transparencies if you would like to see the results of the damage. Because the lens is surface-modified, there is no additional cracking or phasing or anything like that that you see. It looks just like a PMMA lens.

The company is in the process of providing a rationale to the Agency in order to be able to do away with this particular cautionary statement.

DR. SUGAR: The implication from your statement is that the laser removes the surface modification. Is that accurate or inaccurate or unknown?

MS. ELLIOTT: At this point, we do not think it does; it is unknown because we have not done that particular type of study, although the pitting that you normally see is such that it is so small that we really do not think it does affect that, but we cannot state that, scientifically.

DR. STULTING: Any other comments on this issue?

MS. McCULLEY: I have one that ties to it, maybe. I maybe missed it. What is the life of the heparin on the lens and so how long is it present in a heparin-like form, where one would expect it to continue to have its activity?

And then another question is the eludibility of the heparin. And this may be really ignorant, but I remember from medical school, heparin is an anticoagulant and your hyphema rate was higher than the grid, so is there any possibility of any cause and effect there?

MS. ELLIOTT: I think we have like a two-part question here.

MS. McCULLEY: You do,.

MS. ELLIOTT: If we could have slide number 43, please. And Dr. Madsen will address this question, the first part of it.

DR. MADSEN: Okay. Kjell Madsen. This is the results of a stability study in vivo in the rabbit, where we compared -- yes, in this study, we implanted HSM lenses into a rabbit, and then took them out at various times and compared them with chemical analysis how much of the heparin remains on the lens surface? And as you can see, there is essentially no difference throughout the period of two years. And there as no difference between the lenses taken from the shelf or taken from the eye. We conclude that the heparin surface layer is stable for at least two years in the rabbit eye.

DR. STULTING: I do not know the protamine method,

and I am not certain how you did this. You could have heparin-like material still on the lens, do you know that it is still heparin?

DR. MADSEN: We are not absolutely certain that it is chemically unmodified, but it is similar enough to bind the protamine, which is a fairly specific method.

DR. STULTING: Would that -- my impression of what you have shown with this lens is that cells do not adhere to it, just as Dr. Sugar said, so that it is not -- the principle benefit is that cells do not adhere, so monocytes, macrophages do not adhere. They then are not there then to become giant cells, and that that is what you have shown. Is how I interpret your data.

DR. MADSEN: Yes.

DR. STULTING: Do you know that the protamine binding site and the cell -- or the tendency not to bind or allow cells to bind, are the same?

DR. MADSEN: We have no information on that.

DR. STULTING: So you do not know that you still have an active molecule over time, for the initial benefit that you have demonstrated.

DR. MADSEN: No.

DR. STULTING: And that initial benefit that you

have demonstrated could very well be only the binding of cells during the initial, early postoperative period, and everything else that you have shown is simply an epiphenomenon related to that.

DR. MADSEN: That is a possibility, yes.

DR. STULTING: To me it looks like it is a probability, but --

MS. ELLIOTT: As to the second part of your question concerning the hyphema patients -- Toni Elliot. In the original U.S. study, there were 18 patients reported with hyphema. Of those patients, all were reported at Form 1 or 2, with the exception of one patient that was reported at Forms 1, 3, and 4.

That particular patient had preoperative pathology, operative complications, and postoperative complications, which would have contributed to the reporting of hyphema.

The reports were felt to be related to the surgical procedure rather than any type of inflammatory reaction to the lens.

DR. LYDAHL: Eva Lydahl. If I may add, the amount of heparin is also so small, and as we have shown, the heparin stays on the lens surface. There is no reason to

believe that the heparin would cause the bleeding in the eye.

DR. STULTING: Dr. Higginbotham?

DR. HIGGINBOTHAM: I have a series of questions just to really clarify in my mind some of the aspects of your data.

DR. STULTING: Excuse me. Are you going to get onto another subject besides the YAG capsulotomy issue?

DR. HIGGINBOTHAM: Yes, I am.

DR. STULTING: Could we bring that to closure? I have one more comment of my own to add about that and that is that the labeling as it now stands may have medical legal implications and implications in patient care.

I do not see any strong reason to label this lens, not for -- in such a way that capsulotomy is precluded before six months, and I can imagine that if a physician determined that this was necessary and performed a capsulotomy and there were some complication, then the labeling might be used in a court of law to show that he had done something that was outside of the standard of care, and that raises some concern in my mind.

I would like to see, were there other comments from the Panel that might support that statement.

DR. McCULLEY: In complete agreement with you.

DR. STULTING: So, would it be the Panel's feeling that this statement should be changed to be more consistent with clinical care? I am seeing head-nods and hearing yeses, so we should then probably remember to put this as a condition with our recommendation at the end. I am sorry, Dr. Higginbotham, please proceed.

DR. HIGGINBOTHAM: Thank you. Regarding your glaucoma patients, as a glaucoma surgeon, it is not unusual to see these deposits on lenses postoperatively, however many of my patients really have no complaints, and I wondered if you did any other questioning besides just measuring visual acuity, glare testing, surveys, etcetera, just to really determine if there was any clinical benefit to providing an intraocular lens that may not have these deposits.

My other questions relate to whether or not you actually could determine if there was any correlation between previous types of antiglaucoma meds and the greater prevalence of monocytes and giant cells on the lenses, perhaps pilocarpine-treated patients may have had greater numbers of these giant cells.

Another question relates to the inclusion of

pigmentary glaucoma patients in your cohort. In the United States study you indicated that you included exfoliation patients, but I wonder if pigmentary glaucoma patients were also included.

Also -- and this is my last question -- whether or not you could identify, particularly in the glaucoma cohort, if manipulation of the pupil was related to the more resistant cases of patients that did not seem to respond to your lenses in terms of the routine as well as the diabetic? I think that is it for me for now. Thank you.

DR. TROCME: Stefan Trocme. With regards to the first question regarding further tests, the answer is, no glare test was done, nor were there any questions regarding patient comfort provided through the U.S. clinical trials, although this might have been of considerable interest, obviously it was not a part of the protocol, to my knowledge.

In regards to the second. Question about inclusion of pigmentary glaucoma. Toni, correct me if I am wrong, this may have been considered M.D. and not included, it was primary open -- yes, but pigmentary -- yes.

I do not believe that any pigmentary glaucoma patients were included in our study population, correct?

MS. ELLIOTT: For the most part -- and I would have to go back and check -- I would say probably 99% of the patients did not have exfoliation, they were strictly open angle glaucoma with visual field defects or glaucoma optic discomfort.

DR. TROCME: The third question regarding medication -- Dr. Trocme -- and manipulation of iris. This is actually a very good question, and was not part of the original protocol to explore, however it is information available through our record. I would like to remind you, though, that the glaucoma group was the smallest group that we had. And this may introduce some additional statistical difficulties in making certain determinations of subcategories.

DR. LYDAHL: Eva Lydahl. If I could add regarding the European study, which was larger, almost 250 glaucoma patients, patients with pseudoexfoliation glaucoma were included. There were a substantial number of pseudoexfoliating glaucoma, but no pigmentary glaucomas were included.

In that study, there were no attempts to measure visual function in any other way than visual acuity. And we did not look at manipulation of the pupil. It is definitely

probably the most -- well, it is probably one of the reasons that we see lots of dispersion of pigment in cells but it has not been looked at.

MS. ELLIOTT: Toni Elliott. Regarding your question concerning the medications that the glaucoma patients were on. We have not done that type of analysis, however those data are available and with a small patient population, we would be able to put together some information for the Agency within the next two weeks to possibly answer that question.

DR. McCULLEY: Is it fair to say that you have not shown -- you have shown a phenomenon that there are fewer deposits, but you have not demonstrated any clinical relevance.

DR. TROCME: That statement is true -- Dr. Trocme -- that statement is true if you look at the standard perimeters of efficacy, it is a correct statement.

DR. McCULLEY: But you show no harm, either.

DR. TROCME: Correct.

DR. McCULLEY: And you did show the phenomenon.

DR. STULTING: Any other comments? Yes.

MS. BANDEEN-ROCHE: Karen Bandeen-Roche. I would like to follow-up on Dr. Higginbotham's satisfaction

question. In particular, I noticed that there was more than a 25% prevalence of post-capsular haze, persistent haze, so my two questions: Is this consistent with non-heparin treated lenses? Could it have been caused by the heparin treatment, and is there information on whether patients were bothered or not?

MS. ELLIOTT: Toni Elliott. We saw no differences between the HSM and the non-HSM patients in regards to the occurrence of posterior capsule passifications. The percentages were very stable between the two treatment groups in all three patient populations.

I have a chart here if you would like to see it I will be glad to put it up for you.

DR. PULIDO: Jose Pulido. I agree with Drs. McCulley and Sugar, that what you have shown is that the amount of cellular deposit in giant cells is reduced, but that does not necessarily mean that the foreign body reaction is reduced. And what I would like to know is, if you are trying to show that it has anti-inflammatory capabilities, why fluorophotometry data was only from the European centers, and there were actually two centers that had fluorophotometry data.

You did not mention the results of the other

center, which really did not show much difference, correct?

DR. LYDAHL: No, that is correct. There was a study performed at St. Thomas' Hospital in London by Mr. David Sporton(?). That study -- it was not possible to demonstrate any difference in the breakdown of the blood aqueous barrier. There was a large variation of the risk cells. You could not demonstrate a difference.

DR. PULIDO: And so you did not progress with those studies in the United States, correct?

MS. ELLIOTT: That is correct.

DR. PULIDO: So that means that you have some questions about the breakdown of the blood aqueous barrier and the efficacy of breakdown of the blood aqueous barrier with HSM lenses?

DR. LYDAHL: Eva Lydahl. Well we are two scientific studies, one shows the difference and the other one does not, so it is up to interpretation. What we know is that the study that demonstrated a difference was performed by the father of the method, Professor Kunyavas(?) and so he was very well acquainted with the method, and that possibly could be a factor, that results were better and less a variation of the results. Could be.

DR. PULIDO: Speculation.

DR. LYDAHL: Speculation, I agree.

DR. STULTING: Dr. Macsai, you had a question.

DR. MACSAI: Yes. It seems that this lens does indeed have less cells deposited on its surface, so one would presume that if there are inflammatory cells in the anterior chamber, that those cells might gravitate towards the trabecular meshwork, and in the U.S. study you only reported one patient with persistent secondary glaucoma, but I am wondering if you looked at whether or not there was an elevation of intraocular pressure in these patients postoperatively, who received this lens, of even a small level, and in the glaucoma patients, was there any need for additional glaucoma medications? For example, if they were on a beta blocker, was an alpha agonist needed in addition?

MS. ELLIOTT: The answer to your first question -- now I forgot your first question.

DR. MACSAI: It involved the monitoring of the intraocular pressure, postoperatively in these patients.

MS. ELLIOTT: I am sorry, yes. Thank you. We did not monitor -- we collected that data, we have not analyzed that data. We would be glad to do that and, again, provide that information to the Agency. Now, as far as postoperative medications for the glaucoma patients, we

looked at all the concomitant medications that were taken by both groups. We found no differences in any of the patient groups regarding the additional medications that were required for their conditions, whether that be glaucoma or diabetes, postoperatively.

DR. MACSAI: Do you agree that there would be the same inflammation postoperatively in the hands of the same surgeon, using the same technique in different intraocular lenses, so that those inflammatory cells are still within the anterior chamber somewhere, and reasonably could be affecting the facility of outflow in those patients?

DR. MADSEN: While we do not have any hard data on this, it is known from the behavior of microphages that to become fully activated, they have to stick to some surface, and in order to be transformed into foreign body giant cells, they certainly have to have a foreign body to react to.

If there is no sticking to the lens, presumably the cells drift away, probably most of them through the trabecular meshwork, where they might stay for awhile, with their colleagues, taking up various dust and debris in the trabecular meshwork, and then eventually leave the anterior chamber to universal circulation, as the other macrophages

in the trabecular meshwork.

MS. ELLIOTT: Excuse. Dr. Macsai, we have found some IOP data. Dr. Lydahl?

DR. LYDAHL: We have looked at IOP in the European glaucoma study, and there was no difference between the two treatment groups regarding postoperative IOP at any time in the postoperative course, and at visit one, which is the first postoperative day, 15 -- no, it is not the first. It is one week, sorry, 15.2 in the PMMA group and 15.1 in the HSM group. Mean values.

DR. STULTING: Dr. Ruiz.

DR. RUIZ: Well, it is a little bit off the focus, but just of interest. You can recall early on in the intraocular lens uses, before visco-elastics, there were devastating mechanical effects on the endothelium of the cornea, if there was contact with the PMMA. Have you-all gained any data as to whether or not this heparin surface modification affects that?

DR. LYDAHL: Yes, we have. We are just getting a couple of slides up. Endothelial cells were done in two studies, the Karolinska study, we have data from 76 patients, preoperatively and at three years. And the cell loss(?) at three years is 17.3% in the HSM group, and 20.8%

in the PMMA group. So there is no significant difference between the treatment groups.

The other study that looked at endothelial cell counts is the study by Edson Thomas' Hospital with 54 patients, a comparison between preoperative and three-month data; 7.5% versus 6.8%, which is also not different. So, there is no sign that the heparin would be harmful to the endothelium.

DR. RUIZ: Actually, I was addressing it from the other standpoint, that is, with mechanical touching of the endothelium, does the heparin protect it?

DR. LYDAHL: It is hydrophilic, so if you actually touch it, there have been studies performed with touching the lens to the endothelium, and you rip off the cells with the naked PMMA surface, but not with heparin surface-modified. But in a clinical situation with the use of visco-elastics, we do not see it.

DR. RUIZ: Fine, no, I was actually -- so there have been some experiments actually done where you bring the heparin-treated surface in contact with the endothelium and it does not tear it off.

DR. LYDAHL: Oh. Okay.

DR. RUIZ: No, I am asking.

DR. MADSEN: Yes, we have been doing that, others have been doing it also, and the results are essentially that HSM does not rip off the corneal epithelium, however, the clinical significance of this is doubtful.

DR. RUIZ: Well, I -- it is still protective.

DR. MADSEN: Yes.

DR. RUIZ: Thank you.

DR. STULTING: Dr. Pulido.

DR. PULIDO: One other question. There was one study where there was an increase in the amount of patients with moderate iritis. There was another study, a European study, where there was an increase in the number of patients with severe iritis in the HSM group, is that correct? In comparison to the PMMA group?

MS. ELLIOTT: Was that -- do you recall, was that in one of the international studies, because I --

DR. PULIDO: Yes, they were both international studies.

[Pause while physicians review notes]

MS. ELLIOTT: I apologize because of the number of studies, we are having difficulty finding that.

DR. RUIZ: 901E02 more severe iritis. 871E02, when reported at any time, 14.2% PMMA patients compared to

27.3% HSM patients were reported with moderate iritis, 90 PMMA patients compared to 80 HSM patients were reported with mild iritis. The difference between groups was statistically significant.

DR. STULTING: Let's take a look at these one at a time and, Dr. Pulido, if you could give us the page and volume number so we can all be looking at the same data, maybe that would be helpful.

DR. RUIZ: Volume I, page 358.

DR. LYDAHL: Yes, we do, it is correct, that on the first postoperative day, there was more moderate iritis reported in the HSM group than in the PMA group, but after the first day, there was no -- that difference was gone.

DR. RUIZ: But it says, when reported at any time.

DR. LYDAHL: Yes, but that -- that is cumulative from the first day, which means that these that were reported on the first postoperative day, will be included at any time. So, it is only first postoperative day, and the significance of this -- I do not know, but we do not believe that it is related to the heparin surface modification. It has not been seen in any other studies, it is just this study.

DR. PULIDO: There was one other study where there

were more severe cases of iritis with the HSM lenses, and that was 901E02.

DR. STULTING: What is the volume and page on that?

DR. PULIDO: I am finding it right now. Page 655 of Volume II; 4.7% of HSM patients had severe iritis, versus 2.4% of the PMMA lens group. Granted, they were small numbers, but --

PARTICIPANT: Just one patient and two patients, so it is --

MS. ELLIOTT: Yes, there were just one and two patients, and unfortunately when you are working with small numbers like that, you will get skewed percentages. Again, they were reported only at Form 1, and when you look at the data as a cumulative effect, you include those patients at Form 1, so I do not know that it was a big red light.

DR. PULIDO: Well, there are two different reports now where there were maybe more cases of iritis with the HSM group than with the PMMA group, reported at any time. Does that raise concern about the possibility that it is actually more inflammatory?

MS. ELLIOTT: No, again, with these -- Study 901E02, you are talking about one patient and two patients,

and only at Form 1. Because we state, we are looking at a cumulative iritis, we have to look at it from the very beginning, from the very first postoperative visit, all the way through. So, I think mainly it is at the Form 1 that skews the information where we stand at any time during the study.

DR. STULTING: Dr. Banded-Roche.

MS. BANDEEN-ROCHE: I just think it is worth reiterating the point that for subgroup-specific comparisons and for long term outcomes, as you have noted, the sample sizes are not great, there is some selection, and so we should be bringing a lot of biologic knowledge to bear to evaluate safety in those cases.

DR. STULTING: Are there other comments or questions?

DR. VAN METER: Mr. Chairman, following up on what Karen just said, many of the parameters that appear in this study are largely variable to surgical technique, and in many cases I think the surgical technique probably has more bearing on the clinical outcome than the intraocular lens itself.

For example, clear cornea versus sequel(?) tunnel(?) is going to have a far greater effect on hyphema

than probably what lens is used. A patient that has been on chronic myotics may have a much greater prostaglandin release, and many patients that have their pupil forcibly dilated for cataract surgery will have more deposits and cells than a patient that might not have been on chronic myotics preoperatively.

Fluorites and ultrasound time may have a lot more to do with corneal edema, and then there are other complications that are listed, such as macular degeneration, and posterior capsular passification that have to do with cortical clean-up and are not related to the lens.

Interestingly, two of the patients in your study that actually got worse had a reason given that they had posterior capsular passification, and when I finish, I would like an answer, is this just because the study terminated -- these patients ended before they could have their YAG laser done within the six months, or was there another reason why the YAG was not done?

MS. ELLIOTT: Could you tell me which study you are speaking of?

DR. VAN METER: Look on -- and this is in Appendix I provided by you and it is patient's number 665, who is between 60 and 69 years of age. And the other is patient

351, who is over 80.

MS. ELLIOTT: Is this in the 815HS study, Doctor?
Up at the top of that page, in the table?

DR. VAN METER: It does not say. This is Table
24.

DR. STULTING: That is the Appendix -- isn't that
the Appendix --

DR. VAN METER: This is the Appendix --
[simultaneous discussion]

DR. STULTING: That is the FDA Appendix, not the
sponsor's.

DR. VAN METER: Okay. Well -- okay, it -- but I
would like to get back on this, that in trying to track down
the clinical evidence that is provided here, I agree with
the reviewers that it is pretty clear that this lens is safe
and effective as a correction of aphakia, but I have a hard
time making the jump between cellular deposits on the lens
and clinical inflammation when all of these other surgical
parameters are largely unidentified and clearly can weigh
more on the outcome than the type of lens.

DR. STULTING: Maybe you could look up the exact
reference, if you want to pursue that, or if you would
rather drop it, having made your point that you made --

MS. ELLIOTT: I just wanted to make a statement on this. That particular study was an open label study. We did not have a dual population, if I am thinking -- if it is the right -- if it is the study I am thinking of. If it is the original U.S. study, all patients in that study received an HSM lens.

DR. VAN METER: Okay, but I mean, were you consciously avoiding doing capsulotomies on these patients?

MS. ELLIOTT: No, we were not, and it is very possible that that patient did not undergo YAG capsulotomy until after the study was done.

DR. VAN METER: Okay, that is perfectly plausible.

MS. ELLIOTT: I can -- if you -- I can find out for sure when and if the patient did have --

DR. VAN METER: It is patient 351 and patient 665.

MS. ELLIOTT: I can provide that information after the break.

DR. VAN METER: Okay. Thank you.

DR. SUGAR: One point in what he made -- is that there were 40 investigators accruing the 411 available patients, which is I think a bit of a problem with inter-center variability. Somewhere -- is it in the PDP where you talk about there being a minimum of 25 available patients

per center?

PARTICIPANT: Yes. That is right.

DR. SUGAR: So that is prospective, okay. In the future I think that would be an appropriate issue for us as a Panel to discuss.

DR. STULTING: Are there other comments? By my count, we have two people who have not made any comments. Three, excuse me.

DR. McCULLEY: I have a question if no one else has one.

DR. STULTING: Dr. McCulley, go ahead.

DR. McCULLEY: This is from a completely different perspective. You did bilateral intraocular lens or cataract intraocular lens surgery on monkeys. What power intraocular lenses did you put in those monkeys?

DR. MADSEN: I do not -- really, I do not have the data there [simultaneous discussion and laughter] -- but the lenses were rather special. Since human intraocular lenses do not fit into the monkey eye, we made special scaled-down versions of the posterior -- the power I do not recollect at the moment, but --

DR. McCULLEY: But did you determine power appropriately for those monkeys so that they could function

visually?

DR. MADSEN: I do not think so.

DR. McCULLEY: My question was not frivolous and you know the monovision -- I mean, that aside. You do not think -- yes, it is funny, but this is not a funny issue, I am sorry. You then put intraocular lenses in monkeys without determining the appropriate optical power -- we have a human advocate here -- that did not necessarily allow those monkeys visual function?

DR. MADSEN: Yes, I believe so. I am not certain at this moment.

DR. MACSAI: That would never pass the IRB in the United States nor any --

DR. McCULLEY: Well, this is animal rights, and I think that if you did not determine appropriate optical power for those monkeys, and you did bilateral surgery, I do not know what the FDA's position and philosophy is on this, but for my personal philosophy, I think that is terrible. And that there should be insurance that things like that do not happen, if indeed that is what you did, which was in effect blind the monkey.

DR. MADSEN: Yes. Okay.

DR. LYDAHL: I would like to comment on that. I

saw those monkeys. I did the surgery. And they functioned -- I mean, you could see them in their cages and that they were functioning just as well after surgery as before, so I am completely convinced that we did not blind the animals, and the study was of course approved by the IRB before initiation.

DR. McCULLEY: Well, I mean, by the Animal Rights -- or the Animal Committee. I think that you may have lucked into it. Your assessment of their visual function may not be accurate, it may be accurate, but I would think that it should be required that when bilateral surgery is done on animals, especially a primate, although it could be argued that it should be any animal, that the surgery is done in such a way that the power of the implant that is put in will leave the monkey visually functional.

MS. ELLIOTT: We will certainly keep that in mind the next time we have need to perform an animal study. Thank you very much.

DR. STULTING: Dr. Higginbotham.

DR. HIGGINBOTHAM: Thank you, Mr. Chair. I wonder if the primary reviewers could maybe respond to my concern that I have been mulling over for the last several minutes, and that is this issue about glaucoma patients.

I wonder as we contemplate the answer to Question 1A, considering the fact that we do not really have a lot of data on glaucoma patients and this population, at least in the review of the studies by the FDA, there was only a statistical difference in the number of cell deposits at three months, so it is not an overwhelming response in this population of patients.

I wonder if there might be some added, not necessarily caution, but added statement that the benefit of these lenses in glaucoma patients has not been clearly indicated by data. I mean, you certainly have reviewed the data in much more detail than I, but based on what I have heard this morning, I do not really see there is much of a difference, generally.

DR. SUGAR: Do you want me to respond, or do you want --

DR. STULTING: If you would like --

DR. SUGAR: The request was for implantation for correction of aphakia, other diseases not discussed. And the data do not support or refute you using this lens in any other disease, including iritis. And there is no evidence in any of the data presented that I can see that this lens is any better or any worse in the long run for patients who

have correction of aphakia, including glaucoma patients.

DR. MANNIS: I would agree, I think the data suggests parity, not superiority.

DR. STULTING: Dr. Belin.

DR. BELIN: If we look at the fax on October 15 from the company, I know we are dwelling on this for a long time, but the company has not asked for labeling that shows clinical superiority. I think what they are asking for is what we have been discussing.

I just kind of want to make a comment that I realize we are talking about a very small thing, we are talking about it at three months, at six months, at one year, there is less giant cell formation, but occasionally - - I am not saying that this is the case -- improvements in medical care occur at very small steps along the line.

If we look at cataract surgery in general, when we switched from intracap to extracap, the comment back then was, well, there was really no difference between the two, and then from extracap to phaco(?), again there was, initially, no difference between the two. And then from standard lenses to foldable lenses. But if we go back to intracap now, to clear corneal foldable, I think we can see that there has been an improvement.

I do not have a problem with what they are asking for. I think it is safe and effective, but I think we do have to, in the back of our minds, remember that sometimes changes occur with very, very small steps. And that is all, just a comment.

DR. RUIZ: May I say something, Mr. Chairman?

DR. STULTING: Yes, Sir.

DR. RUIZ: My experience has been that these deposits on the lens rarely cause much difficulty, but I have had probably four cases over the years in which they caused a lot of difficulty, and this was a chronic, long-standing thing, where we actually used the YAG laser to blow them off the surface of the lens because they really interfered with vision. So that the long term results on this lens may be much better than the -- more impressive than the short term results. Thank you.

DR. STULTING: Alright. We had diverse comments. I would like at this point to try to move on. Let's restrict our comments to significant concerns and issues of labeling. Are there any other questions at this point of the sponsor? Alright, I would like to ask the sponsors to return to their seats at this point so we can complete our discussion. I would like to give you an opportunity later

to respond to any issues that may occur during this portion of the proceedings, that you would like to comment on, just to allow you a fair chance to speak, if you need to.

There is one other issue that I had that I would like to bring up for discussion before we move toward a vote, and that is the issue of Uveitis. The sponsor, at least in this instance, has made some effort to present some data about eyes with Uveitis that have been transplanted, and this is different from the usual PMA that we receive for an implant, where patients with Uveitis are specifically excluded.

If you look at the standard labeling, this appears to be the standard labeling that we normally see with an intraocular lens. On page 246 of Volume I, there is a caution there. Patients with anterior segment inflammation of unknown etiology -- And on page 247, at the top, there is another mention, the safety of the intraocular lens implantation has not been substantiated in patients with preexisting ocular conditions, and among those listed is iritis.

Furthermore, physicians considering lens implantation in such patients should explore the use of alternative methods of aphakic correction and consider lens

implantation only if alternatives are deemed unsatisfactory to meet the needs of the patients.

I am wondering whether with the data in front of us today, these are appropriate labeling -- this represents appropriate labeling for this lens, since most ophthalmologists are looking for lenses that can be implanted in Uveitis, and in fact that is what we do frequently, as a matter of practice today. Yes, Dr. Rosenthal?

DR. ROSENTHAL: May I comment? As you know, in Europe, this lens has been touted as being respectable to use in patients with Uveitis, and in fact, in England, where I worked for many years, it was taken as dictum that the lens was superior to the routine PMMA lens in patients with Uveitis.

I think there is nothing more that the Agency would like to have demonstrated in the appropriate study, than that in fact this lens is superior to PMMA lenses in patients with various forms of intraocular inflammation, but unfortunately, the study has not been done in which they have taken a group of patients with Uveitis and studied the two different types of lenses. Only the single type of lens has been studied.

I should like to, with your encouragement, encourage the company to do a study of that sort, following the decision made here today, so that some claim could be made, or some decision could be made, about a claim relating to its superiority in patients with Uveitis.

DR. STULTING: I agree. It is unfortunate that the data presented were completely uncontrolled. Comments from the Panel about this issue?

DR. MACSAI: Perhaps if such data could be obtained in a cohort future study, the labeling could be modified in the future.

DR. STULTING: Would the information from that single uncontrolled study be included in the labeling as part of the clinical data that is presented in the back portion, just for information?

DR. LEPRI: Mr. Chairman, no, it is not included in the study. The sponsor has not indicated that they wish to target any specific pathology groups for which this heparin surface-modified lens is indicated, and that includes Uveitis patients, also.

DR. STULTING: Okay. Any other comments from the Panel? As best I can summarize what has gone on so far, it would appear that no one has any major concerns about the

safety and efficacy of the lens, compared with its PMMA equivalents, and the issues mainly center on the labeling at this point.

Let me give the sponsor one opportunity to make any comments that they would like to make.

MS. ELLIOTT: As you know, we did begin a study of Uveitis patients, and we did provide the FDA with basically a data listing from that particular study. The study was discontinued after two years.

We had originally planned to enroll 80 patients in the study, and at that two-year time point, we had only been able to enroll 28 patients. Because of the complexity of the protocol, we had difficulties with the randomization procedure. We had difficulties keeping certified photographers available for the patients, and we just basically had difficulty enrolling patients.

The final numbers that we ended up with were 28 patients, nine of whom received HSM lenses, 18 of whom received PMMA lenses. So we have a disproportionate number.

I have taken the time to summarize the data from those patients, and have found that in the Uveitis population, there were no significant differences in the visual results, visual outcomes, or in the complication

rates for those patients. However, there is a remarkably -- I cannot say significant -- because we have not run statistics on it, but a remarkable difference in the amount of giant cells on the lenses in favor of the HSM patients.

There has also been a study done in France using Uveitis patients, whereby they used the same lens, certain patients received HSM, and others received the non-HSM lens.

DR. LYDAHL: As well, I would like to comment on that French Uveitis study. We have some slides. That was another attempt --

DR. ROSENTHAL: Has that been submitted in the PMA? I am sorry, but as you know, we cannot present data at this meeting that has not been submitted in the PMA.

DR. LYDAHL: Sorry, I -- okay --

MS. ELLIOTT: I am not sure that article was -- I think that article was submitted. It is the Jones article.

DR. ROSENTHAL: Jones article from France?

MS. ELLIOTT: Yes, it is. Yes.

PARTICIPANT: Jones is included.

DR. ROSENTHAL: Jones is from England.

MS. ELLIOTT: The article was written by Jones.

DR. ROSENTHAL: Nick Jones from Manchester? Well, I am not sure. Certainly, that article was included with

serachromic(?) keratocyclitis(?), in which there were no controls used, in which they said that the lens could be used, but I am sorry. If --

DR. LYDAHL: No, that -- that is not the right paper. The Jones article is -- that is a non-controlled study, but the publication --

DR. ROSENTHAL: I am sorry, but unless it was presented --

MS. ELLIOTT: That is fine, I am sorry.

DR. STULTING: Okay, well, thank you. I will ask the sponsor to return to their seats. And so the message is, we would like to have controlled studies for these kinds of claims, and I think the ophthalmic community would certainly appreciate that as well, because there is a desire to have an implant that is demonstrated to do better in these patients.

I would like to call your attention to the questions that we have so kindly been given by the Agency, that is in the back of your hand-out containing the agenda for today. It is labeled Clinical Questions for Panel Discussion. They are also up on the screen for you to look at, and we are required to provide an answer for this to the FDA.

The first question is,
Giant cells and cellular deposits were the efficacy variables of Study 815HS where Routine, Diabetic, and Glaucoma patients were studied. Statistical significance of the difference between HSM and PMMA differed between patient groups and over time.

Given these differences, do the clinical data measured in this PMA support the labeling claim that "The foreign body reaction, measured by cellular deposits and giant cells, is reduced on CeeOn HSM PMMA lenses compared to non-HSM PMMA lenses. This difference is observed during the first postoperative months but may not be present at 12 months, when the foreign body reaction is less pronounced."?

Or, alternative B, Is this statement more appropriately placed in the Clinical Trials section of the labeling?

Those of you who believe that A is the correct answer to this question, please signify by raising your hand. There should be 11 hands for voting members.

DR. McCULLEY: I do not understand, what is the relevance of the placement, I do not -- I do not know.

DR. STULTING: We are answering questions that have been posed to us by the Agency, and we are required to

do this.

DR. ROSENTHAL: May I comment? May I comment --

DR. McCULLEY: In order to answer it, I would like to know the relevance of the placement.

DR. STULTING: Oh, I am sorry. The relevance was given to us once before, during the -- Donna, didn't you mention it?

DR. McCULLEY: She did, but I did not understand it, I am sorry.

DR. STULTING: Alright, let's do it again, just for clarification.

DR. ROSENTHAL: Donna, would you like to mention it once again, since you do it more eloquently than I would?

MS. LOCHNER: I think the question is speaking to the issue of whether the sponsor has provided evidence to support a labeling claim, which is something that would go into the Intended Use section of the labeling. It means that the lens has been shown to have a purpose that is indicated for a particular population.

A claim has different implications to the sponsor in terms of how they may advertise and promote their lens, potentially in terms of reimbursement they may receive for the lens.

One way to think of it, sort of on a practical basis is, does the statement -- if you believe the conclusion has been adequately supported, do you believe it belongs in the Indications for Use section of the labeling?

DR. STULTING: The bottom line is, can a detail man come and tell you this, and can they put it in their print advertisement, am I correct?

MS. LOCHNER: That is an implication.

DR. STULTING: Okay.

DR. PULIDO: Dr. Stulting?

DR. STULTING: Yes, Sir.

DR. PULIDO: Point of clarification. What if one does not agree with the first part, the foreign body reaction measured by, but rather it should say, the amount of cellular deposits and giant cells is reduced on CeeOn?

DR. STULTING: Well, that was actually in my mind. We are free, as I understand it, to modify the wording so that it can then be placed where you think it would be appropriately placed. Am I correct? Okay.

DR. PULIDO: I would propose changing that.

DR. STULTING: Alright, so there is a proposal that we keep it in the Claims statement, but modify its wording slightly?

DR. McCULLEY: Well, those are two different questions. I like the wording change, but from the evidence presented and the absence of clinical relevance, I would rather see it in the Clinical Trials section rather than in the Claims section.

DR. STULTING: Okay, I propose that we work out the wording and then figure out where it goes.

DR. McCULLEY: Alright.

DR. STULTING: Is that acceptable?

DR. McCULLEY: That is acceptable.

DR. STULTING: Dr. Pulido, would you like to suggest your alternative wording?

DR. PULIDO: The amount of cellular deposits and giant cells is reduced on CeeOn HSM PMMA lenses compared to non-HSM PMMA lenses.

DR. STULTING: Okay, does everybody understand that proposal? In other words, we are just removing the foreign body reaction portion of it -- [simultaneous discussion] --

DR. SUGAR(?): Just cellular deposits and giant cells are reduced.

DR. STULTING: But are you proposing to delete the second sentence in that, or leave that in?

PARTICIPANT: No, you want to leave it in.

PARTICIPANT: Leave it in.

DR. PULIDO: No, and continue with the next --

DR. STULTING: He is fine with the rest of it, but wants to get rid of the foreign body --

DR. McCULLEY: Right, and I would suggest adding another sentence that is in effect, the clinical relevance of this is uncertain, as a third sentence in that.

DR. STULTING: Is that materially different from the Caution Statement?

DR. McCULLEY: It seems to be the same as Number three.

DR. STULTING: Let's see. Well, the Caution Statement that was proposed then in this --

PARTICIPANT: Yes, in the fax -- [simultaneous discussion] --

DR. STULTING: What is it, three here? I believe those are all the same now, am I correct? All the materials we have the same statements, the slides and the letter and the program are the same, correct?

DR. McCULLEY: I still would propose it there. It is not as strong in Number Three as the clinical relevance of this is uncertain. And it puts it in proximity.

DR. STULTING: Okay, well, let's get the content correct and then we will do the placement, because if it moves to a different place then it will all be together. Oh, Dr. Lepri.

DR. LEPRI: Excuse me, Mr. Chairman. As a point of information for all the Panel members, the quote placed here in Question -- I am talking about Question 1A, is that, the sponsor proposed on their labeling, their modified labeling -- it begins with, clinical studies demonstrate, have demonstrated that the foreign body reaction as measured by cellular deposits is reduced.

We changed that in our proposal to, the foreign body reaction, rather than clinical studies demonstrate, because of the implications for the labeling.

DR. STULTING: So, this is the correct statement that we are --

DR. LEPRI: This is what the Agency is proposing, yes. Thank you.

DR. PULIDO: I would also like to delete, the foreign body reaction is less pronounced at the end, as well. But may not be present at 12 months. Period.

DR. STULTING: When the differences are less pronounced, so when -- Dr. Belin.

DR. BELIN: I want to reiterate. I think what Jim was saying is, I would want to -- and since we are talking about this, we cannot not talk about the second part -- but would want to have the Caution -- what is now called the Caution Statement incorporated into this statement, maybe for different reasons, because I think a Caution Statement alerts a physician of a potential medical problem.

What we are doing here is we are taking something that says, it is not any better, but clearly not any worse, and saying, that is a caution. I think that is the inappropriate use of a caution statement.

I think this all needs to be in one statement, whether it ends up being in Trials or Claims, I would rather see it as one complete statement.

DR. STULTING: Okay. Let's see, Dr. Pulido, did you by chance jot down --

DR. MACSAI: I have it.

DR. STULTING: Marian, fantastic. Could you read what you jotted down?

DR. MACSAI: As point of clarification, Dr. Pulido has recommended deletion of the following words from 1A:

Foreign body reaction, measured by -- and in the second line, is, and changing it to read as follows:

The amount of cellular deposits and giant cells are reduced on CeeOn HSM PMMA lenses compared to non-HSM PMMA lenses. This difference is observed during the first postoperative months, but may not be present at 12 months. Period. Deleting, when the foreign body reaction is less pronounced.

DR. PULIDO: Thank you, Dr. Macsai.

DR. STULTING: Okay. Is everyone comfortable with that statement? Are there any other comments or recommendations?

DR. McCULLEY: I still would like to see the sentence, The clinical relevance of this is uncertain, following those two sentences that Marian just redid.

DR. STULTING: Okay, well, let that be the next issue. Does anybody have any problem with what has been read, so far? Okay, let's go on and work out the content of this third one, and then we will deal with where it is placed as the final issue, alright?

DR. MACSAI: So, then, Jim, what you would like to do is just add the statement made in Number Three --

DR. STULTING: No. No, actually --

DR. MACSAI: -- to be part of this statement?

DR. McCULLEY: I like my statement better than the

other one. The other one can be used somewhere else. Mine is real simple. The clinical relevance of this is uncertain. Fewer words and pretty clear.

DR. STULTING: Okay. You need to have another word other than this, and you might want it to read, the clinical relevance of this reduction, which refers back to the previous sentence.

DR. McCULLEY: Agree.

MR. BULLIMORE: Relevance seems a little strong. How about ramifications -- [simultaneous discussion] We all understand relevance.

DR. STULTING: The proposed statement is, The clinical relevance of this reduction is uncertain. I hate to get into the grammar and the exact wording, but it is probably appropriate here because we are dealing with some issues that are the major concern for this Panel --

DR. McCULLEY: Well, the only thing there is that the reduction that we would be referring to could be the reduction in the first sentence, or the reduction in the second, the absence of the phenomenon. So, I mean, I think the meaning is there, and I would rather let the FDA play with the grammar.

DR. STULTING: Is the Agency clear about what it

is that is being recommended, and can you take care of the grammar and structure okay?

MS. LOCHNER: Okay, I think we are clear of the words. We are clear of the words, we still need your recommendation regarding the placement.

DR. STULTING: Okay, I want to go back to the recommendation by Dr. Belin and Dr. McCulley, that the statement that we have just considered be placed immediately after the two sentences that we have already decided upon. Is there general consensus that that is appropriate?

PARTICIPANT: Yes.

DR. STULTING: Any dissension? Okay, I see no dissension, and so the recommendation is that the three sentences we have just constructed be presented together, and now we should move onto the issue which was originally presented to us as to whether these are appropriately put in the Claims portion or the Clinical Trials portion of the labeling. Dr. Belin?

DR. BELIN: I just want to get back to the issue -
- I just want to make a comment. I actually prefer the proposed wording supplied by the company over what Dr. McCulley said. Not that there is a big difference, but I think we are getting into an area where -- to give an

analogy -- if we have a lens that turns out to be much easier for a physician to insert in an eye -- much easier. Night and day difference -- but, the patients still turn out to have the same 20/20 rate, same complications rate, are we going to have a statement saying, this has no advantage?

It does have an advantage. I think they showed an effect. Period. I think to say it is not clinically relevant to me is a little strong. I think what they say here is, they have not shown a statistically significant reduction in the incidence of complications or adverse events associated with inflammatory reactions.

I think that is actually -- [simultaneous discussion] -- I like the wording of the company, that is all --

DR. MACSAI: I agree. I agree with Dr. Belin. I would rather see that statement put in.

DR. STULTING: Okay. State your recommendation once again, please?

DR. BELIN: That the two statements be joined -- my recommendation is that the wording in the, quote, proposed Caution Statement, which is not how I would like to see it, remains the same. The effectiveness of this heparin

surface-modified lens, in reducing the incidence of complications or adverse events associated with inflammatory actions, has not been established.

DR. STULTING: Okay, so essentially, we have two proposals for the third sentence, is that correct? Are there comments -- would anyone like to speak for or against those two proposals? Okay, let's try to come to an agreement.

The first proposal is that the third sentence be, The clinical relevance of this reduction is uncertain -- or similar wording. The second proposal is that the wording remain as included in the letter from Pharmacia under proposed Caution Statement.

Those in favor of the first proposal, please raise your hands. That is one, two [counting] -- that is five. And those in favor of the statement as presented by the sponsor, please raise your hand.

PARTICIPANT: You get to break the vote.

DR. STULTING: No, that is six, as I count them. Okay, there were six votes for the proposed Caution as included in the letter from the sponsor, and five for the proposed change. So, the sense of the committee is that it remains as stated here.

[The motion to accept the proposed Caution statement as included in the letter from the sponsor was approved by a vote of 6 to 5.]

DR. STULTING: I think we still have not been clear about whether we are comfortable having those two -- I tell you what, let's first consider whether the first two statements belong as Claims statement or as Clinical Trial statements.

DR. ROSENTHAL: Could I just clarify --

DR. STULTING: Sure.

DR. ROSENTHAL: That you are happy with removing the first three words of the first statement, everyone is happy with that?

PARTICIPANT: Yes.

PARTICIPANT: Yes.

DR. STULTING: That is my interpretation, we will clarify it. Understand that the first phrase, Clinical studies demonstrate that -- are not included in the wording as we are voting on it so far. Fully understood?

DR. SUGAR: No, no, no. The foreign body reaction measured by is deleted.

DR. STULTING: And the foreign body reaction measured by is also deleted.

DR. ROSENTHAL: Have you all agreed that it will start -- the amount of cellular deposits and giant cells is reduced on --

PARTICIPANT: Yes.

DR. ROSENTHAL: Followed by, this difference is observed during -- followed by, Number Three question.

DR. MACSAI: You want me to read that into the record?

DR. STULTING: Are there any questions? Marian, go ahead.

DR. MACSAI: Can I just make a motion?

DR. STULTING: Sure, you can make a motion any time that you have the floor, and you now have the floor.

DR. MACSAI: I would like to move that the following statement be placed in the Claims section. The amount of cellular deposits and giant cells are reduced on CeeOn HSM PMMA lenses, compared to non-HSM PMMA lenses. The difference is observed during the first postoperative months, but may not be present at 12 months.

The effectiveness of this heparin surface-modified lens in reducing the incidence of complications or adverse events associated with inflammatory reactions has not been established.

PARTICIPANT: Seconded.

DR. STULTING: Is there a second for that motion?

PARTICIPANT: Seconded.

[The motion was duly seconded.]

DR. McCULLEY: Point of clarification. Marian has taken our statement that we were working on agreeing on, and placing it, all in the same --

DR. MACSAI: Yes. Yes. Let's move along --

[simultaneous discussion and laughter] --

DR. McCULLEY: Well, but what if I agree with half of you but not the other half?

DR. STULTING: Well, you can speak for or against the motion at this point.

DR. MACSAI: Then vote against it -- [simultaneous discussion] --

DR. McCULLEY: I would like to see us decide, unless we want to go ahead now -- I think there are two issues. We need clarification that the statement as read is what we want. And I am in favor of that.

Then we need discussion about where it is going to be placed. So if we can -- you know, I am not still completely certain of the appropriateness of the placing. My gut instinct is that it should go more in Clinical Trials

than in Claims, but I am not 100% sure of that. But I do like the statement.

DR. STULTING: That is an appropriate comment, since her motion includes the placement, so we will just continue that discussion, if that is alright with everybody. Go ahead, Michael.

DR. BELIN: I would leave it in Claims. I think these are -- prior to the surface modification -- correct me if I am wrong -- these are basically lenses that are already approved, right? So, the company has done a large number of studies, not to put something in Clinical -- I mean, it is a claim. They have done a lot of them. A lot of work. And the reason they did the work, is to get a, quote, Claim. And their claim was proven.

We have addressed the fact that it may not be clinically relevant -- going back to your word -- but it does belong in the Claims section, in my opinion.

DR. SUGAR: I agree with Dr. Belin.

DR. STULTING: Could the Agency clarify for us -- I think I know the answer to this -- but, if we pass the motion as recommended, would that mean that they can now advertise this, but they have to have a footnote that has the third statement in it, or something to that effect?

MS. LOCHNER: Whatever words you agree to, if it includes this third sentence, if you recommend that those words be included in the Claim, that is then what the firm is limited to in their advertising. So in other words, it would have to carry through all the statements in their advertising.

DR. STULTING: Okay. Is there further discussion on the motion on the floor? Judy.

DR. GORDON: Just a brief comment. I do think that the placement in Claims has medical legal implications for the users of these lenses and of other PMMA lenses. I will limit my comment to that, but I think it is worth consideration.

DR. MANNIS: What do you mean?

DR. STULTING: I am not sure what that means.

DR. MANNIS: What do you mean by that?

DR. GORDON: I think it relates back to the comments made before, relative to identifying, for example, a certain population and implying that, then if you -- what does it translate into if you do not use this lens in that population? I think having it as a claim raises those sorts of issues.

DR. STULTING: Oh, I see. I have to have stuff in

real basic English, I am a southern boy, here. You are worried because people will get in trouble for not putting this lens in people, is that correct? Alright.

DR. GORDON: Yes.

DR. MACSAI: But the statement that was previously a caution is now a claim.

DR. SUGAR: It is saying that relevance is unknown.

DR. MACSAI: Saying that the relevance is not clear, so how could that become a medical caution?

DR. GORDON: And that may be adequate. I am just raising the question -- I do not have an answer.

DR. STULTING: Yes, it is probably a good issue to bring forward. In other words, would everybody feel comfortable defending their decision not to use this lens, based on the labeling? Am I saying that correctly?

DR. GORDON: I think that is exactly the issue that is worth addressing.

DR. MACSAI: If I may comment, though I know we practice in a very medical legal society, we have been asked here, on the basis of our scientific opinions, and not necessarily our legal ones, so I would leave that to the lawyers at the Agency to --

PARTICIPANT: They do not always watch out for us, though.

DR. STULTING: Is there further discussion of the motion on the floor? I see no further discussion, would you please repeat it, Dr. Macsai?

DR. MACSAI: The motion?

DR. STULTING: Yes, Ma'am.

DR. MACSAI: I move that the following statement be placed in the Claims section of PMA P960034:

The amount of cellular deposits and giant cells are reduced on CeeOn HSSM PMMA lenses, compared to non-HSM PMMA lenses. This difference is observed during the first postoperative months, but may not be present at 12 months. The effectiveness of this heparin surface-modified lens in reducing the incidence of complications or adverse events associated with inflammatory reactions has not been established.

PARTICIPANT: I would like to second that.

DR. STULTING: It has already been seconded, and we are ready to vote, unless there is further comment. Those in favor of the motion as stated, please raise your hand. That is 11 for. Those opposed -- there should be none. And there are none opposed.

[There was a show of hands and the motion was approved unanimously.]

DR. STULTING: So the motion passes, and we have now commented on points one and three of the questions that we were submitted. I interpret Question 2 to be approval, recommendation for approval or not, am I correct about that?

PARTICIPANT: That is correct.

DR. STULTING: So, we have addressed these comments. Are there any other questions from the Agency that Dr. Rosenthal or anyone else would like to bring up, that we should address here during this discussion, before we move to a vote?

MS. BANDEEN-ROCHE: I just want to know if the Panel is happy with the visual acuity data that appear in the Clinical part of the label, particularly, it is a best case visual acuity.

My concern arises from the fact, both that the cohort acuity was noticeably better than the non-cohort acuity, and that there was noticeable variation among providers in the acuity that was achieved, and so, I would propose that both overall and best case acuity be presented, and that a description of precision of the estimate be developed that include the design which was a very

imbalanced split among providers.

DR. STULTING: I believe that, overall and best case are always presented, am I incorrect about that? Is that right?

MS. BANDEEN-ROCHE: Did I just miss it?

MS. LOCHNER: No, actually, currently, usually just the best case is presented.

DR. STULTING: Okay, I stand corrected, then. What would the Agency's reaction be to that recommendation? In other words, it seems to me that if we are going to do that, it should be standard for all implants.

MS. LOCHNER: Yes, I think we would want that point of clarification. We certainly can recommend it for this PMA, but we would be interested in the clarification whether you want this across the board.

DR. STULTING: In other words, those kinds of things are wise all the time, and I think it -- in my opinion, at least, would be that it is unfair to require it of one manufacturer and not another, so it would be a generic recommendation for the Agency, I think. Maybe we should -- would it be appropriate to discuss that in the Guidance document?

MS. LOCHNER: Yes.

DR. MANNIS: Yes, exactly.

DR. STULTING: Alright, let's move that discussion to later today.

DR. MACSAI: I have a second issue before approval. Are we going to address Dr. Sugar's concern about YAG at six months, in labeling or -- what are we going to do about that?

DR. STULTING: Let's see, it has been discussed already. I think there was a consensus. Maybe it would be included in the recommendation for approval or not approval.

DR. MACSAI: That that be modified, correct?

DR. STULTING: Okay, is there any other discussion? Alright, I will turn the floor over to Ms. Thornton for comments before we move to a vote.

DR. THORNTON: Your recommendation options for the vote are as follows: Approval, there are no conditions attached. The Agency action, if the Agency agrees with the Panel recommendation, an approval letter will be sent to the applicant.

The second option is approvable with conditions. You may recommend that the PMA be found approvable, subject to specified conditions, such as resolution of clearly identified deficiencies which have been cited by you or by

FDA staff. Prior to voting, all of the conditions are discussed by the Panel and listed by the Panel chair.

You may specify what type of follow-up to the applicant's response to the conditions of your approvable recommendation you want. For example, FDA response or Panel homework assignment. Panel follow-up is usually done through homework assignment to the primary reviewers of the application, or to other specified members of the Panel. A formal discussion of the application at a future Panel meeting is not usually held.

If you recommend post-approval requirements to be imposed as a condition of approval, then your recommendation should address the following points:

The purpose of the requirement. The number of subjects to be evaluated. And the reports that should be required to be submitted. The Agency action. If the FDA agrees with the Panel recommendation, an approval with conditions letter will be sent.

The third option is not approvable. Of the five reasons that the Act specifies for denial of approval, the following three reasons are applicable to Panel deliberations:

The data do not provide reasonable assurance that

the device is safe under the conditions of use prescribed, recommended or suggested in the proposed labeling.

Reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or suggested in the labeling.

Based on a fair evaluation of the material facts and your discussions, you believe the proposed labeling to be false or misleading.

If you recommend that the application is not approvable for any of those stated reasons, then we ask that you identify the measures that you think are necessary for the application to be placed in an approvable form.

If FDA agrees with the Panel's not approvable recommendation, we will send a not approvable letter. This is not a final Agency action on the PMA. The applicant has the opportunity to amend the PMA to supply the requested information.

The amended application will be reviewed by the Panel at a future meeting, unless the Panel requests otherwise.

Tabling. In rare circumstances, the Panel may decide to table an application. Tabling an application does not give specific guidance from the Panel to FDA or the

applicant, thereby creating ambiguity and delay in the progress of the application, therefore we discourage tabling of an application.

The Panel should consider a not approvable or approvable with conditions recommendation that gives clearly described corrective steps. If the Panel does vote to table a PMA, the Panel will be asked to describe which information is missing and what prevents an alternative recommendation.

Following the voting, the Chair will ask each Panel member to present a brief statement, outlining the reasons for their vote. Thank you, Mr. Chair.

DR. STULTING: Dr. Sugar.

DR. SUGAR: I would like to recommend approval with the modifications in the labeling that we have already discussed.

DR. STULTING: It has been moved and seconded that we recommend PMA P960034 for approval with the modifications in labeling that we have discussed and those include the one referencing YAG laser capsulotomy, and the one that we have discussed regarding the claim.

DR. THORNTON: Am I to understand that he is proposing an approvable with conditions?

DR. STULTING: That is correct. Well, it is

approvable with labeling changes, there are no conditions being imposed on the sponsor.

DR. SUGAR: Yes, I think it is full approval with changing the wording. That is not really conditions. They do not have to come back to us with anything. Is that correct?

DR. STULTING: It is unconditional approval with recommendations for labeling. Any further discussion?

DR. MACSAI: I second the motion.

DR. STULTING: It has already been seconded, I believe, but we will take another second. We will take a third --

DR. ROSENTHAL: Excuse me, Mr. Chairman, I am informed that that is actually a conditional approval, but we understand the sense of the motion and --

DR. STULTING: Okay, I stand corrected.

PARTICIPANT: Call the question.

DR. STULTING: Okay. Those in favor, please raise your hand? I count 11 for. Those opposed, please raise your hand.

[There was a show of hands and the motion was approved unanimously.]

DR. STULTING: There are no hands raised, so now

we have to poll those voting, and we are required for you to make a statement as to why you voted for it. In this case, none against. And that statement may be very brief, so we will begin over here.

DR. VAN METER: The data showed it to be safe and effective. I think that the surface modification is helpful. The clinical relevance is yet to be determined.

DR. STULTING: Thank you. Dr. Belin.

DR. BELIN: I agree.

DR. McCulley: Couldn't have said it better.

DR. HIGGINBOTHAM: I agree.

MS. SONI: I agree, too.

DR. SUGAR: Same.

DR. MACSAI: I agree.

DR. STULTING: Dr. Bullimore, sorry, we missed you.

MR. BULLIMORE: I just wanted to agree with Dr. Sugar.

DR. MANNIS: I agree.

DR. STULTING: Dr. Macsai?

DR. MACSAI: I agree.

MS. BANDEEN-ROCHE: I agree.

DR. PULIDO: I have nothing else but agreement.

DR. STULTING: Have we complied with the Agency's

--

DR. ROSENTHAL: Yes, you have, Mr. Chairman, as usual. Thank you very much.

DR. STULTING: Okay, as I see it, it is about 12:30. We will have a couple of announcements.

DR. THORNTON: Just in case there are those of you who are going to be leaving at this point -- those in the audience, I might add, not the Panel -- I did want to announce for you the 1998 Panel meeting dates that we have tentatively scheduled. Those are February 11, 12 and 13. April 23 and 24. July 23 and 24. And October 22 and 23.

Those dates are on the FDA Web Page. The address of the Web Page is www.FDA.gov. Changes or cancellations of those dates will appear as well as the draft agendas of planned meetings approximately two months prior to the meeting.

Information on planned meetings can also be obtained from the Panel hotline number, 1-800-741-8138. The Ophthalmic Panel code when prompted by the recording is 12396. Thank you.

DR. STULTING: Dr. Belin, you have a --

DR. BELIN: Where can we put these?

DR. THORNTON: I am sorry. I am sorry. For those Panel members, I would like to just ask you to leave your documents on the table so that they may be collected. If you do not want -- anything you want collected, please leave on the table. If you want to take your packets, put them on your chair or over here, they will not be collected. Yes, Eve, sorry.

DR. HIGGINBOTHAM: Quick question. Did I understand you to say that the February meeting is three days?

DR. THORNTON: Yes, you did.

DR. HIGGINBOTHAM: Not here, I hope. Another Holiday Inn.

DR. STULTING: Okay, we are adjourned for lunch, to reconvene at 1:30, please.

[Whereupon, at 12:30 p.m., a recess was taken until 1:30 p.m. the same afternoon.]

P R O C E E D I N G S

(1:52 p.m.)

DR. STULTING: I'd like to call the meeting to order once again. The topic for discussion this afternoon is the FDA Grid for intraocular lenses, and the PDP for intraocular lenses. I'll turn the floor over to Donna Lochner to begin the festivities.

Agenda Item: Proposed Revision of FDA Grid for Intraocular Lenses - Donna R. Lochner

MS. LOCHNER: Thank you.

We have provided to the panel members and the audience, copies of material that was prepared as background for today's discussion of an update to the FDA historical Grid of data. This information was prepared by Susanna Jones, and I would like to take this opportunity to thank Ms. Jones for her data analyses and excellent presentation of the data.

Unfortunately, she was not able to be here today, however, we are fortunate to have with us Drs. Eva Lydahl and Sverker Norrby. FDA invited Drs. Lydahl and Norrby because they both played pivotal roles in the development of international standards, organization standards for IOLs.

Dr. Lydahl provided clinical expertise in developing the ISO IOL clinical standard. She is with St.

Eric's Eye Hospital in Stockholm.

Dr. Norrby is the convener of the ISO working group under which the international ISO standards were developed. He is director of applied research at Pharmacy and Upjohn in the Netherlands.

We have invited Drs. Lydahl and Norrby to participate in the discussion so that they may answer questions you may have about the ISO standards.

By way of background, I would like to explain that FDA has undertaken several initiatives in order to harmonize our requirements with international requirements. Specifically, in the device approval area we are striving to move as an organization towards greater recognition of standards in our review processes. Within the Division of Ophthalmic Devices we have participated extensively in the development of the ISO IOL standards in meetings spanning over about seven years.

Because of the collaborative efforts of experts throughout the world, we believe the standards contain the state-of-the-art in IOL testing methodologies and criteria. In all areas of substance, we agree with the recommendations made in the IOL ISO standards.

I do not plan to go through in detail, the

background information that has been provided concerning the revision of the Grid, but would like to highlight some of the information provided. I would like to begin by going through some of the differences between the methodologies outlined in both the ISO standard, and in FDA's draft guidance document, and previous FDA guidance, because the clinical data collected under these studies will be compared to future Grid updates.

First is the reporting formats. As can be seen, ISO has tightened up the reporting time periods for the postoperative visits, including elimination of the previous Form 5 time period. I would like to point out one difference in this slide from the materials that were handed out to you, and that is in the Form 4 visit. There is a proposal that is being brought forward to ISO to revise the Form 4 from 90-180 days to 120-180 days. This again will tighten up the visit schedule, and may be a more appropriate time frame for assessment.

Some of you may remember that many years ago FDA agreed to allow sponsors to shorten their Tier B studies from one year to six months or Form 4 if the results at six months were acceptable. If a sponsor were to shorten their study, we ask that they manage their Form 4 visits so that

patients were seen at 120-180 days. In the years since we allowed that change there has been confusion regarding the actual time frame at Form 4. This proposal will move all studies to a Form 4 visit of 120-180 days. We would like to hear your comments about this proposed change.

Also in the ISO standard, at least 300 subjects are required to be seen at each visit, therefore, we believe studies conducted according to the ISO requirements will potentially report more instances of adverse events, and so data collected using these methods can be appropriately compared to the Grid.

Next we presented the effects of lowering the sample size from 500 to 300. This slide provides the lower detection limits for visual acuity for 500 and 300 sample size. These rates represent the maximum VA rates detectable as statistical less than the 1983 Grid rates.

Next is the upper detection limits for a sampling of adverse events representing the range of rates in the 1983 Grid, and the probability of observing at least one occurrence of an adverse event that occurs at the rates noted on the slide. Again, we believe that reduction of the sample size from 500 to 300 does not have a significant effect on the detection limits, and still results in a

reasonable assurance of safety and effectiveness.

I'm going to skip over the next two sections in the handout, namely the elimination of certain adverse events, and the definitions of adverse events, since these areas will be discussed in the questions to the panel.

Clinical data were collected from recent IOL experience for soft and PMMA posterior chamber IOLs and for anterior chamber IOLs. The posterior chamber data is presented separated by soft versus PMMA, and with the soft and PMMA data combined.

This slide shows the total number of subjects available for analysis. These slides provide the updated data without the detection limit information included. The data analyses provided in the handout include the detection limits for a 300 patient study, and a 100, or Level B study.

First, for posterior chamber IOLs, the expected improvement in overall and best case VA was seen in the PMMA data, and generally more so in the soft material data. Lower rates of adverse events were seen for the combined cumulative adverse event data, with the most marked improvement in the rate of surgical reintervention.

Persistent adverse events rates again, are lower for recent experience when compared to the 1983 Grid values,

particularly persistent iritis and persistent corneal edema.

The anterior chamber data is somewhat more problematic, as explained in the background material. First, the visual acuity data were not an improvement over the 1983 Grid values. Both the cumulative and persistent adverse events in the updated data were sometimes an improvement over 1983 values, and sometimes worse.

Note the increases in cumulative lens dislocations, persistent macular edema, and persistent secondary glaucoma. This later experience may represent more difficult cases using anterior chamber lenses, since routine use of anterior chamber lenses as a first lens of choice is not common today.

The next slides repeat the questions that we have asked the panel to address, which we can display as we step through the questions.

At this time, I would like to return the floor to Dr. Stulting for any comments before we go through the questions.

DR. STULTING: One comment that I had about this was the possible confounding effect of grouping lenses by type, when in fact these types are correlated with the surgical technique used to implant them. Do you understand

what I'm saying?

Let's suppose that it is true that one surgical type, let's suppose that just for the sake of discussion that clear cornea facial emulsification implantations are associated with lower complication rates and better visual acuity than extra capsular surgery. If you don't consider that in your stratification, and instead only consider lens type, then you may incorrectly conclude that foldable lenses have a better outcome than non-foldable, large, optic lenses just because they are associated with a surgical technique that provides a different outcome.

I think you need to address that when you look at the outcomes. In my opinion, it is much more likely that the outcomes would be related to the surgical technique than to the implant type, given modern techniques and modern implants.

MS. LOCHNER: Well, that's true. We are not able in the data that we have available to us, to separate out the surgical technique for posterior chamber lenses in terms of each of the outcome variables, visual acuity and all the adverse events. We don't have that data available to us.

DR. BULLIMORE: You raise an important issue. How would you propose that we would incorporate it into the

guidelines? Do you just want a line that raises the awareness of future panel members and reviewers, or do you think that really some sort of detailed breakdown and the development of a sort of three dimensional, rather than a two dimensional Grid would be in order, or do you just want to put it in as a caveat?

DR. STULTING: Well, the data are available in the world. The question is whether they can be gotten and put into this kind of document. I suppose one way of doing it is to request it from sponsors. I know for a fact that it was collected, because it is part of data that have been submitted for approval of exempt plans.

So the easiest way I would think, would be for the agency to simply request that sponsors who have submitted PMAs over the last ten years or so, and ask them if they would provide the data. It is to their benefit. The purpose here is to create guidance documents for the approval of implants in the future.

Any other comments?

DR. MACSAI: I think it would also be for our future product development protocols, which I know we are jumping ahead, but that information be provided to the panel, and perhaps data be stratified based on that, because

what you say is probably true. There are going to be less hyphemas for example in a clear cornea surgery than an extra cat.

DR. STULTING: We're looking at updating a Grid that is over ten years old. I do not believe that the outcomes of cataract surgery today are the same as they were over ten years ago. If the data don't show that, then I think there is something wrong with the way it is being collected and analyzed.

MS. LOCHNER: Yes, I think what you are saying makes perfect sense. The question you are getting to is our question number four, which I think we want to hear expanded upon when we get to that, but this issue of for posterior chamber data, what would appropriate stratification be? I think if the data is available, what you are saying makes sense as the way to present it. If the data are available, I think we would want to hear any alternate proposal.

DR. MACSAI: It's not if they are not available. They should be available. The technique used to implant the implant should be available from the sponsors to the panel, because the surgeons have to report the technique.

MS. LOCHNER: In some instances you are looking at studies that have been completed for a while. Now the

efforts it will take the sponsor to go back into their databases and stratify it out in that way, it is probably doable, but it is, you know --

DR. MACSAI: I'm sorry, I was referring to future studies.

MS. LOCHNER: Oh, okay. Maybe this can be discussed when we get to number four also.

DR. STARK: Are we discussing the time issue also? The time of follow-up?

DR. STULTING: We probably ought to get some organization into how we are going to proceed here. Would you like to -- are you finished with your presentation? Would you like for us to go ahead and discuss, or would you like for us to discuss one item at a time as you go through it, or what?

MS. LOCHNER: Well, we have a list of questions we do want you to address. The question that Dr. Stark is bringing up is in the first section, where we have outlined the basic differences between what we have required in the past in the ISO. So if you wanted to step through the background, at least step through Section I, and then from there on out, we've got our questions outlined. I mean, it's a suggestion.

If there are any questions with Section I, which are the differences between what we have done in the past and what ISO is recommending, at least we can have that discussion now, and I think Drs. Lydahl and Norrby would be able to answer any questions there. Then perhaps step through the questions, or you could just have open discussion, and then go through the questions.

DR. STULTING: It has not been clear to me what you are proposing, at least from the document that you have gone through before. Are you proposing changes in the reporting intervals to match ISO's?

MS. LOCHNER: Yes.

DR. MACSAI: It is not clear to me from 120-180 that is on this slide, that wasn't in the handout --

MS. LOCHNER: Right.

DR. MACSAI: Which one are you asking us to approve?

MS. LOCHNER: Our current proposal for both ISO and FDA is 120-180. It is not reflected in the materials you have. This proposal came after it was mailed to you.

DR. STARK: Can I just say one word? In looking at those numbers, it is now becoming more consistent with what the time follow-up is of a patient. You follow them

for two to two and a half months, and then you see them maybe at six months, and then at a year. Why, since you have your final follow-up at really 10-14 months, based on those numbers, why not have the six month follow-up five to seven months to give a little range there?

What you want is six months data I would imagine. It's not a big issue, but if they miss six months to the day, then you don't get a data point there.

MS. LOCHNER: I think more than anything that 120-180 days is coming from previous experience with IOLs, where when we shortened Tier B studies, which are the smaller clinical studies done on just smaller changes to the device, when we shortened those studies, we wanted them to be seen later in what was typically the Form 4 visit. So I think the 120-180 proposal is just coming from familiarity with that time frame that was used for Tier B studies. The Tier B studies, if the last time they were going to be seen was at Form 4, we wanted it to not go so early.

DR. STARK: And I agree with that, so my proposal would be to have it five to seven months, which would be 150-210 days. I agree, 120 may be a little short for a six month follow-up. I don't know which standards you are proposing, how they are written in stone, but it seemed to

me like the five to seven months would capture the six month better.

DR. VAN METER: I agree with Dr. Stark, Mr. Chairman, because I think the current practice guidelines -- and these are actually in the American Academy of Ophthalmology literature -- that six months after your initial one month follow-up visit, and so seven months would be an appropriate extension. I think most people say, see you back in six months, and this usually comes after the four to five week visit.

DR. STULTING: I am confused a little bit procedurally. The Grid is a collection of data that have been historically as a guideline for discussion when this panel looks at intraocular lens implant applications. Are we not confusing the Grid, which is a compilation of data, with recommendations and guidance for submitting PMAs?

MS. LOCHNER: These are somewhat separate issues. The reason we chose to go through them in this discussion is when you created the new Grid, we wanted the panel to be aware of differences in reporting time frame so that people were comfortable comparing new studies that might be conducted according to the new criteria, to this Grid that was collected perhaps using different criteria.

Now we have gone through these and assured in our mind that they would be still reporting worst case -- if they met the Grid, that would still be worst case, and the lens would be performing well. The time periods themselves have changed in such a way that we'll probably capture more adverse events, and so it would be appropriate to compare it to this historical data which was collected a different way.

So while this doesn't relate exactly to how you would update the Grid, we felt it would be good to go through it, because of how that future Grid will be used.

If I can just bring up one other point that Dr. Lydahl just pointed out. When ISO developed their time frames, they tried to stay within the previous FDA guidelines. They tightened up the range, but kept it within the previous, so that you could say you were comparing to the Grid; you were comparing apples and apples. By changing the format, it is not as a pure a comparison, but it may be appropriate on its own merits. I think that is what needs to be considered.

So the current ISO, which is FDA's current proposal, keeps within our previous requirements. It is still all within the previous Grid requirements, and any updated Grid -- of course those studies would have been

conducted using the previous FDA requirements, so future studies that were compared to it would be equivalent, we believe.

DR. STARK: Donna, it is very rare that you go back and compare Form 4 data with one lens, and base approval for another one. Really what you have done is --

MS. LOCHNER: It's cumulative adverse events.

DR. STARK: Pardon?

MS. LOCHNER: It's only in the sense of capturing the cumulative adverse events.

DR. STARK: What you have done is combined 4 and 5 really to cut out one visit. I think it is really important to collect six month data, because companies may want to come in at six months and begin their process of negotiation. I think that the longer out you have that six month, the better. So you are combining 4 and 5. Straddle it at five to seven months, and then you are collecting six month data. If you need to go back and look at some former application to compare, then you could combine your 4 and 5 follow-ups, but I don't think that is necessary.

MS. LOCHNER: Yes, I think that is a point well taken.

DR. BULLIMORE: Donna, what is the overall

motivation here? Is conformity between FDA and ISO, so that the FDA might be able to consider more international data in their approval process? Or is it just we want to be more like the Europeans?

MS. LOCHNER: Well, that is probably admirable, but the FDA is moving their program towards recognition of standards. Also, I think you need to be aware that we have participated for many, many years now with the ISO delegation in coming to these conclusions, and really reviewing the past studies, and what makes more sense. We have participated in that way, so we do endorse the ISO. We have participated quite a bit in the discussions, but we don't want to bring studies before you that you are totally unfamiliar with this new methodology of doing the studies.

DR. STULTING: Other comments?

DR. GORDON: From an industry perspective, I think the goal would be ultimately to have clinical trials that are conducted that meet as many of the worldwide regulatory requirements, so that you are not doing something different, because then again even for one product you have trouble comparing. There are not enough research dollars in the world to do a different study for every country and every registration. So I think it is a very admirable goal, and

moving toward standardization is really useful.

DR. ROSENTHAL: May I also comment that in the new FDA modernization legislation one of the items is asking us to harmonize as much as possible with international standards. So I think that it is an idea that is going to be very high on our priority.

DR. BANDEEN-ROCHE: I had a question about another aspect of these changed requirements which is requiring every single one of the forms to be included to include a patient in the sample. Is there any concern that that will lead to an extremely selected group of individuals? Bringing it to the current discussion, I would imagine it will tend to be conservative if the people who come in for every form are the ones who are having problems, are especially eager to be seen, but I don't know.

DR. LYDAHL: That is actually a misunderstanding of the ISO document. We have said in ISO that we want at least 300 forms from each reporting period. We want an intention to treat analysis, which means that we want all data reported. So we have gone away from the cohort definition, and said that all data are to be reported, but to make sure that we have enough data, we want to see at least 300 patients at each time period. It doesn't

necessarily have to be the same 300.

DR. BANDEEN-ROCHE: Yes, thank you.

DR. MACSAI: So then why do you have a sample size, Dr. Lydahl? I'm not sure I understand that, because if the goal is to have 300 data points at each form, then 300 sample size would be too small.

DR. LYDAHL: We want 300 evaluable patients. There is also a recommendation in the ISO document on how many additional patients that you should include to make sure that you have 300 at the end of the one year period.

DR. MACSAI: Okay, thank you.

DR. STULTING: Is it a given that we will have a revision of the Grid with updated numbers of some sort for inclusion in the guidance document?

MS. LOCHNER: That's what we would like to do, however, we'll go forward with the guidance if we are not prepared to go out with the revision to the Grid. We can add that in when we are ready. We were hoping after today's meeting we would be prepared to revise the Grid with updated data. I guess we don't have to. We would still have our guidance and still recommend the 1983 Grid.

DR. LYDAHL: It is something we have asked for ISO. We are aware that the data we are using now is very

old, and to have something more up-to-date is something that we need. So we are really welcoming this effort that the FDA has done to collect more recent data.

DR. STULTING: Proceed with what you would like for us to comment on.

MS. LOCHNER: Within Section I, which again, outlines basically the differences between ISO and what we have required in the past, were there other questions about the difference between ISO? I don't think we have fully come to resolution of the question of changing Form 4.

DR. STARK: Is ISO written in stone? Is it finalized and we're supposed to accept it, or we have a chance to recommend?

DR. NORRBY: That is one of the difficulties in international standardization. We are not always in sync. The ISO document now is up for voting at a certain level called DIS. That is the first appearance as a printed, published document.

It can be amended in the next round to follow depending on the voting results. In that voting, every country is casting one vote. Our feeling was that this change on Form 4 from 90-180 to be 120-180 would rather easily pass that voting procedure. If we, as you propose,

increase it from six to seven months, I'm not so convinced that it will go through. The chances that it will become approved in the ISO procedure, and then we will have a difference which is -- well, I don't like it, but that might be the outcome.

DR. STULTING: Would you like for us to go through this document? You are asking for questions, but would you like for us to go through and provide you with an opinion about whether these things are or are not appropriate?

MS. LOCHNER: Yes.

DR. STULTING: Let's define the questions you would like to address. So I'm not sure that these questions are inclusive of all the information that is in the preceding pages. So I think it needs to be agreed that anything that is not discussed, is not necessarily approved.

MS. LOCHNER: Our last question asks for any other comments.

DR. STULTING: I guess the reason I'm having problems with this is it seems rather disorganized for me to go down these questions, rather than simply going through the document front to back in an organized fashion. Does anyone else share those concerns with me?

DR. MC CULLEY: Maybe I'm getting confused now, or

maybe I'm confused and didn't know I was confused. Why can't we go down the questions?

DR. STULTING: Okay. Are we going to then discuss the draft guidance document separately? Is that what you want? Then the PDP is going to be a totally separate thing, correct?

MS. LOCHNER: The draft guidance document was presented as background material for the PDP. So really for updating the Grid, we need the answers to the questions on the Grid. The methodology we use to update the Grid really I guess if you think of it totally separate from how future studies are conducted --

DR. STULTING: Well, see, that's what I hear you saying, but the first thing you brought up was an issue of future studies, which is the reporting time frame. There is no way you can change the reporting time frame retroactively for the Grid.

MS. LOCHNER: Right. So regardless of what is done with the reporting time frames, we want to know the methodology to update the Grid. The primary reasons we have given you this background about the methodologies in this portion of the meeting is so that we could use Dr. Lydahl and Dr. Norrby to answer some questions. We weren't able to

use them during the reference PDP discussion.

So to the extent that we can talk about what the questions we believe need to be answered so that we can update the Grid, we would like to get those answers from you. Then to the extent that if there are any questions about the ISO requirements, and you can ask these questions of Dr. Lydahl and Dr. Norrby, we would like to allow that opportunity also.

If you focus on updating the Grid, and the questions we need answered in order to update the Grid, we might be able to make some progress.

DR. STULTING: Okay, but page 2, page 3, and page 4 for example, have nothing to do with updating the Grid, because they are referring to sample size for future submissions.

MS. LOCHNER: That is correct.

DR. STULTING: Okay, I think I'm getting a little bit clearer on this now. Let's do the questions on V. We are going to return to the things about data collection points and sample sizes later. That is not the Grid.

MS. LOCHNER: That's correct.

DR. STULTING: So let's go down the questions listed on page 10 then, "Please discuss any concerns with

the adverse events proposed for elimination from the Grid. (See Section II above.)" and then that is page 5.

DR. PULIDO: I have no problems dealing with the elimination of those, since they are encompassed in other data that is being collected.

DR. MC CULLEY: Is hyphema somewhere else? We could argue whether hyphema needs to be somewhere else. I looked carefully to see if it was anywhere, and if it is, I missed it.

MS. LOCHNER: We are proposing that the persistent rate of hyphema only be reported, instead of the cumulative rate. By persistent, we have somewhat redefined it for this one particular event, which is that we would like all reports of hyphema at basically the last two visits.

DR. MC CULLEY: So your feeling is that the cumulative data would be more related to surgical technique in patient selection? I guess you have given it a lot of thought. That doesn't just immediately necessarily jump out and set right. Stated more directly, clearly, I would wonder about retaining cumulative hyphema.

DR. STULTING: Other comments?

DR. STARK: Well, persistent hyphema will be extremely rare, but an eye can fill with blood and be a lost

eye from blood stain, but without a persistent hyphema. I think if it's not too much trouble, it would be good to include it. The issue was even asked this morning about hyphema. I think it is probably worthwhile including it.

DR. LYDAHL: It is the problem with the very early hyphema that is definitely related to the surgery.

DR. STARK: Not necessarily. Say if you have a lens that explodes into the eye, or a different insertion technique, one can tear the root of the iris and cause a hyphema. So there are surgical techniques and implantation of the intraocular lens, it can cause a hyphema. So your statement is not entirely true.

DR. MACSAI: It would seem that if in the future when we revise the next step, the PDP, then if data is stratified by method of implantation, it may eliminate that inherent bias or logical hyphema that might result after scleral tunnel incision, as opposed to a clear cornea incision.

DR. LYDAHL: The data is collected anyway. In ISO we are not proposing not collecting data on hyphema at every reporting form. So it is just a matter of how you analyze the data. If you analyzed it by cumulative and persistent, or just one, the data is there.

MS. LOCHNER: Both cumulative and persistent.

DR. RUIZ: Is there the sense that there should be no change from the treatment of hyphema from the way it is now, or from other events?

DR. MACSAI: Right.

MS. LOCHNER: Except to also do a breakdown with the persistent rate, which we didn't previously have in the Grid.

DR. MACSAI: Yes.

DR. BELIN: If we are going to try to eliminate let's say an insertional technique-induced hyphema, and we're looking only at cumulative and persistent, we are still not going to be able to do that unless we go back and look at the first reporting form, correct?

You can have a lens that for some reason induces a late hyphema, and it will show up both on persistent, and if it is persistent and cumulative, you will not be able to look at that data and determine whether it was surgically induced or not. You have to look at the Form 1.

DR. MACSAI: Well, it depends on if you stratify the data by surgical technique.

DR. BELIN: But if a lens is surgical technique-specific, you are still not going to be able to tell whether

that was a technique-induced, or was it something inherent with the material of the lens or anything else.

DR. MC CULLEY: Well, having the data, to me it gives us a red flag if we need to look more carefully. If don't have the opportunity to look for that flag, then we could overlook and not even question whether it was technique or lens or whatever.

DR. RUIZ: Well, the line gets very blurred between technique and lens too. When you put it in the sulcus, and you've got a late erosion, is that technique or is that the lens? The only lens-induced hyphema -- I think true lens induced hyphema were the original anterior chamber lenses, the ugh(?) syndrome. Other than that, I don't think the lens ever causes a hyphema.

DR. STARK: The point about that is you will not see that in six months or a year, the ugh syndrome usually, or lens-induced hyphema is going to be laid out. What you really want to capture is, is there something about the surgical insertion of this lens that is causing damage? That would be the thing I would be most interested in, and the thing you might pick up. So listing hyphema cumulative, if it is a high rate, one could go back and look, are they all at the first form? Is it one investigator that had a

problem, or is everybody getting a high rate of hyphema? It just might be to look at it as a little concern, so leave it.

MS. LOCHNER: So what I'm hearing is collect the cumulative.

DR. STARK: Well, persistent is going to be so low.

DR. LYDAHL: It is not a problem.

DR. RUIZ: Most of these late onset sulcus erosion type things are really recurrent rather than persistent. So if you happen to see them on the seventh month and they are clear, then they may have it on the ninth month.

MS. LOCHNER: Were there any concerns with the other complications that were proposed to be eliminated? I see a lot of heads shaking no.

DR. STULTING: It looks as if there are no other concerns on that one.

The second question, "Please discuss any revisions or additions to the definitions outlined in Section III," and they are found on page 6 and page 7. Does anyone have any problem with any of those, or any comment?

DR. HIGGINBOTHAM: This is almost predictable, but secondary glaucoma is not elevation of intraocular pressure.

So I would suggest that that be recharacterized to secondary elevation of intraocular pressure.

DR. MC CULLEY: Would you set a limit?

DR. HIGGINBOTHAM: That is also a predictable question.

DR. MC CULLEY: Sorry to be predictable.

DR. HIGGINBOTHAM: I don't know how much. You could analyze this to death, but I would say that we could characterize it in terms of a percentage compared to baseline. I don't know what is feasible here, but say if it is more than a 20 percent increase compared to baseline, that would be significant. It all really depends. You can't pin me down, I'm sorry.

DR. ROSENTHAL: That's why we didn't pin ourselves down to secondary elevation of intraocular pressure.

DR. HIGGINBOTHAM: Another way to look at this, in many studies you look at thresholds of five millimeter increase versus greater than ten. That could be another way to do it. I am more concerned about this characterization of glaucoma as elevation of intraocular pressure, so that we can make sure we keep our definition straight.

DR. LYDAHL: Actually, in the ISO document I have used the term "raised IUP requiring treatment." This is an

interpretation of the old term secondary glaucoma that was in the original Grid.

DR. HIGGINBOTHAM: I guess I have a concern about requiring treatments, because that is up to the investigator. We want to know if there is any significant increase. Certainly anything less than five would be perhaps within the realms of variation, but something more than five may not be. It is hard to really characterize this globally. You have to really consider each individual patient, as well as the investigator's threshold for treatment.

DR. LYDAHL: The problem is that today too with the definition as it is now, it says secondary glaucoma, and what do we mean? The data that is collected and that we base this update of the Grid on, it is collected using the terminology secondary glaucoma and nothing else. We have the same problem of whether to treat or not in the data that we have today.

DR. HIGGINBOTHAM: Well, that's why we probably do have to put a number on it as Dr. McCulley just whispered in my ear, but at the very least we should say secondary elevation of intraocular pressure, and perhaps start with a threshold of five as a starting point, and see what comments

we might get from the community from that as a definition. Then another category might be ten or great; five to ten, and then ten or greater.

DR. RUIZ: Starts at 11 and goes to 16; that's an elevation of intraocular pressure?

DR. HIGGINBOTHAM: By this definition, yes, but by the same token, that is probably one that is only going to survive the first form, and won't be present later on, perhaps, but we will have that data there. For a patient that has 90 percent cupping and split fixation, that could be a significant increase, but for a patient that has a normal cup and no visual field defect, that is not a significant increase. So there you have it.

DR. VAN METER: I think it is fairly well written the way it is. All of these scenarios play out here, there are three key words here. One is secondary glaucoma, which means that due to the recent procedure and/or the implant. Two is persistent elevated pressure, which is really how you are going to test for it anyway. Thirdly is requiring treatment. If the patient has 90 percent cupping, then one would be inclined to treat it, rather than watch it.

I believe you could leave it to the surgeon's discretion, but I rather like the way it is written here. I

think that covers all we need to cover.

DR. STULTING: Any other comments?

DR. MACSAI: I think the point that was being made is that elevation of intraocular pressure is not glaucoma. You need to have some visual field changes or optic nerve changes to make that determination of glaucoma.

DR. VAN METER: That's when you would require treatment. It's not elevated pressure, it is elevated pressure requiring treatment.

MS. LOCHNER: The one proposal on the floor was simply to change the designation from secondary glaucoma to secondary elevation of intraocular pressure. So that is one thing on the floor. The second thing is the actual definition, either, and/or. There we go, everybody is happy.

DR. HIGGINBOTHAM: I doubt that within whatever this time frame is, say even six months, you are going to develop glaucoma if you have never had it before within a short period of time. So I would just leave it as secondary increase in intraocular pressure, and then we can decide later if we want to add some definitive numbers and ranges.

DR. STULTING: Is there a consensus on that statement?

[Several panel members answer in the affirmative.]

DR. STULTING: I think there is consensus on that last statement.

Any other concerns about the definition?

DR. MANNIS: This may be more semantic than substantive, but under hypopyon on the use of the word "pus" is frequently associated with infection. I wonder whether it might be best to put white blood cells, since an inflammatory response is probably more likely what you are referring to. It's an ugly word.

DR. STULTING: Do you gain any additional information or any different information from hypopyon than you do from endophthalmitis?

DR. LYDAHL: I think you do. You don't necessarily have a hypopyon when you have an endophthalmitis.

DR. STARK: It's the other way around.

DR. MANNIS: Vice versa.

DR. LYDAHL: Okay.

DR. STARK: It's the other way around, and the reason it was put in was because we were seeing sterile hypopyon with the new ethylene oxide sterilized lenses. So they usually go together.

DR. BANDEEN-ROCHE: Under endophthalmitis here it says confirmed intraocular infection or sterile. So it seems like it is covered right there.

DR. LYDAHL: So maybe we could do away with hypopyon then.

DR. STULTING: Is there consensus that we would recommend doing away with hypopyon? Does anybody object to that?

DR. STARK: I would leave it in, personally.

DR. STULTING: You would leave it in? What additional information do you gain from that?

DR. STARK: You know that you've got a marked inflammatory response. It would just insure that either that or endophthalmitis was reported, because it says an inflammation inside the eyeball. It could be sterile or infectious, and I would like to make sure -- you could put after endophthalmitis, any hypopyon must be reported.

DR. BELIN: I think the example you gave earlier was just the problem in the past with the sterilization technique.

DR. MACSAI: So then what about the tritus(?)?

DR. STARK: I said you could take off hypopyon here, but you should just put it in brackets under

endophthalmitis. If you have an hypopyon, it has to be reported as an endophthalmitis. It could be sterile; it could be infectious.

MS. LOCHNER: Do we determine this rate simply by adding the endophthalmitis and the hypopyon rates?

DR. STARK: You are treating the same people. They are the same case.

MS. LOCHNER: So we could do with the endophthalmitis previous rates as the new Grid rate?

DR. STARK: Yes, it can be confirmed infection or sterile. For emphases, hypopyon should be reported here, because that is a sterile endophthalmitis by definition.

DR. STULTING: I think the issue is just a procedural one, whether we have to look in two places for the same cases or not, or whether the same case gets reported twice. It seems to me that if you define endophthalmitis as you have defined it here, it should include every case of hypopyon.

DR. VAN METER: But in truth aren't you interested in two separate things? One is a sterile hypopyon, which could just be defined as such, and the other is hypopyon secondary to infection. You are really interested in two separate things, so why not ask for them both, rather than

put them in one category.

DR. STARK: Well, they are already in one category.

MS. LOCHNER: The reason they were written this way, the endophthalmitis definition was written this way was to delete the intraocular infection rate that was previously collected. There was concern that the intraocular infection and the endophthalmitis could be being confused with each other. Whether we have made it any better in terms of --

DR. STARK: The numbers are going to be small enough that if you get a higher number that is suspicious, those cases would be presented separately anyway. So you just want to capture it. What you don't want to do is put in endophthalmitis and have someone develop a hypopyon, and the doctors don't put it down. That is the only thing I would be concerned about by eliminating hypopyon.

DR. SUGAR: Just trying to look at what the data are --

MS. LOCHNER: The thing to bear in mind also is the case report forms themselves will say endophthalmitis, and hopefully the doctor will have read the clinical protocol to be reminded of what that includes, but six months into the study when he is just following patients,

whether it is helpful to have the hypopyon listed separately as a box to check is another issue.

DR. SUGAR: On the cumulative data, the incidence of hypopyon exceeds the incidence of endophthalmitis. So it is certainly warranted to interpret it the way we are talking about it.

DR. STARK: See, that was in the Grid. When we saw some of the sterile hypopyons.

DR. SUGAR: They weren't called endophthalmitis?

DR. STARK: Correct.

DR. STULTING: Yes, but endophthalmitis I think back then was defined differently. It was defined as an intraocular infection, and so people who wanted to enter that data had no choice but to put it under hypopyon, but if you redefined endophthalmitis, then it is now included.

DR. STARK: What Donna is saying, six months into the study if it is not an infection, it is endophthalmitis, it may not be reported if you eliminate hypopyon from the recording.

DR. MACSAI: So let's leave it the way it is.

DR. STULTING: I'm not sure I would call it a consensus. We need to arrive at one. What is it?

DR. MACSAI: I move we leave it the way it is.

DR. STULTING: Is there any concern over the definition of macular edema? If we leave it like it is, I think we are going to get all kinds of rates depending upon how they are measured, and whether they look and everything else. I'm not sure how you are going to compare one lens to another. Is there any other concern about that except mine? Evidently not.

DR. PULIDO: Iritis probably should have after the comma, possibly causing pain, et cetera, et cetera. You can have the iritis without any of the subsequent symptoms.

DR. HIGGINBOTHAM: I have been thinking about your question about macular edema for the last few seconds, but I was thinking about it from another perspective, and that is if there are other medications, might we want to ask the investigators to make a determination if they think it is IOL related? There could be some other factors that could cause macular edema such as medications, and we don't really want to attribute that to the lens necessarily. So one suggestion would be to add the phrase, thought to be related to the intraocular lens.

DR. MACSAI: I think that would be a difficult thing for the surgeon to discern, because in many patients postoperatively there is clinically significant and

clinically not significant macular edema after cataract extraction. So that we might not know if it is related to the IOL until there is cumulative data to determine that, to see if it is outside the realm of the normal time of normal macular edema post-cataract extraction.

DR. HIGGINBOTHAM: I guess I was thinking more along the lines of a patient who might be on chronic propine for instance. So it wouldn't be related to the IOL, but it would be related to the agonegic agonus(?).

DR. MACSAI: But wouldn't that medication be contraindicated in the pseudoaphakic patient?

DR. HIGGINBOTHAM: Not necessarily if there is an elevation in intraocular pressure.

DR. STARK: See these are the kind of things that if we are going to do a 300 cohort, if you had a higher rate than expected, you could go back and analyze those cases. In fact we did. In one lens implant 10 or 12 years ago, they had a much higher rate of macular edema. Then they said, well, wait, we think this was all fluorescein macular edema and not clinically significant. So they went back and reviewed all the records, and yes, if they dropped out those that were fluorescein positive, but not clinically significant.

So I guess what you mean is clinically significant macular edema that would imply reduced visual acuity, where an investigation is done to look for macular edema. I don't know that you can make it any better than it is, because it is going to be each investigator that is going to interpret that, and if you get a higher rate, you just have to look at those patients individually.

DR. STULTING: Just to clarify once more, are we still talking about the Grid, the reported data? Is it not correct that any of this discussion of definition is superfluous, because whatever definitions were used when they were reported is what we have to stick with? Is that correct?

MS. LOCHNER: Well, the point you are making, you have to bear that in mind, because if you narrow the definition now, and you compared it to the old rates, you could overlook lens-related problems because you have narrowed it to lens-related problems only, and it meets the Grid, when the old Grid rate had both.

So if you keep it broad and require the analysis that Dr. Stark is suggesting, if you exceed the Grid rate, you would better be able to manage this as an historical control. It is not really just coming up with the

definition for future, but then when we compare it to things in the past.

DR. RUIZ: There are many other confounding problems, like surgery in a diabetic, surgery in somebody with chronic iritis, surgery in somebody who is on propine. How do you know which one is causing it?

MS. LOCHNER: Well, if you get a rate that exceeds the Grid, the sponsor will typically do all those subanalyses to look at the data and see if they have an explanation for the pathology or whatever.

DR. PULIDO: What about adding "possibly" for iritis?

DR. STULTING: Well, once again, maybe I'm the only person that has this mindset, but if we are talking about the Grid, which is a compilation of existing data, then it would be difficult or impossible for us to redefine that data other than the way it was originally reported, correct?

MS. LOCHNER: Well, I don't think adding a "possibly" actually broadens it. It doesn't narrow it. Before there was no definition associated with the Grid rate. It was just what was understood to be iritis.

DR. STULTING: Well, then that is what has to be

reported in the Grid, because we can do nothing but accept what was reported in the past, unless I'm totally misunderstanding what the --

MS. LOCHNER: I think what Dr. Pulido was saying is adding the word "possibly" causing pain, it broadens it up to all that could have possibly been reported for iritis in the past.

DR. SUGAR: No, in the cases it would be reported in the future, it would be a more inclusive category so that you have to have a higher number. You could have a higher number than the Grid and still not have a difference in disease. If we are not changing the basic principle of the Grid, we can't change the basic definitions of the Grid if the principle is to compare history with each future case.

MS. LOCHNER: Okay, but these definitions aren't the 1983 definitions.

DR. SUGAR: That's what I didn't understand.

MS. LOCHNER: There were no 1983 definitions, so what we are trying to do now is simply provide some definitions for clarity, but we have to recognize that since there weren't definitions before, we don't want to write the definitions so narrow that it is not an appropriate comparison to what was reported in the past.

I think what Dr. Pulido is suggesting by adding the word "possibly" doesn't narrow it.

DR. SUGAR: I'm in favor of it with the understanding you just gave us. I thought that we were taking what was and --

MS. LOCHNER: No.

DR. STARK: There were definitions, and they are clearly as you have written them here.

DR. STULTING: Should the definitions not reflect what is actually reported in the historical Grid that is going to be created?

MS. LOCHNER: Yes.

DR. STULTING: Then why do we not simply recommend that the Grid reflect what was actually reported, whatever that may be? It's not something that we should define here in the session. It should be what the data are.

DR. STARK: You are trying to give guidelines for the future.

DR. MACSAI: I think that if you broaden the definition, I think you are playing a dangerous game, because you will end up with a falsely elevated appearing incidence of a complication when you take future studies and compare them to the historical Grid that exists from all the

data submitted up to today. You will get every cell and every flare in every anterior chamber, and it will like every IOL that comes before the panel causes 90 percent iritis, and in the past they only caused 5 percent iritis. So what is the sponsor doing wrong?

So for that reason alone, you can't broaden the definition, because then --

MS. LOCHNER: I question whether we are actually broadening it, since this was not the definition that was out there in 1983. It was pretty much whatever the doctor thought it was. Now it makes our job more difficult today, because we have to come up with something that would probably be appropriate for the 1983 values given that it was whatever, but that would also provide guidance for the future, so we're at least making improvements towards getting towards a standard definition.

DR. BULLIMORE: I think that perhaps an artificially high reporting rate is not a bad thing, because we can deal with that on panel. What we want to avoid is underreporting. I think if we take a conservative, cautious approach, and have reasonable operational definitions of these terms, we just put the FDA and future panels in a better position. I think I agree with Dr. Pulido's

suggestion.

DR. MC CULLEY: The way it is written now, iritis would have to have all of these symptoms to be included. There weren't definitions before from what you said, so we are looking to try to come up with clarifying statements. I think that the way that this is written needs to be altered the way Dr. Pulido suggested to say "possibly."

DR. MACSAI: Well, then you might just want to call it postoperative inflammation.

DR. SUGAR: But this is persistent. This is at one year and at three years. All of them have acute iritis at Form 1. We're talking about Form 5, or whatever you now call one year.

DR. SONI: I think an additional thing that we need to keep remembering is that we are reducing the number from 500 to 300, and that is going to give us less incidence of adverse reactions. It is good to have a broader definition than to go back and to look at those subjects again, rather than narrowing it down and missing even those few that we may see.

DR. GORDON: Just one comment for the record. For the first sponsor that comes through with data using broader definitions, just a reminder that whoever is on that panel

and at that time, that is going to be given some real consideration and respect for the fact that a sponsor is attempting to capture more information, but not be bound to whatever the Grid was, because Doyle is right, the Grid is the Grid is the Grid.

Until there is another ten years going forward from new definitions on which to start establishing a new historical control, it is going to be a challenge for the first sponsor. So I think it is worth noting for the record that that needs to be a consideration. It doesn't mean we shouldn't do it, but we have to be thoughtful about that.

DR. BULLIMORE: I agree with you, but I just put the word "broader" in quote marks, because we are really putting down definitions where none previously existed.

DR. STULTING: So the discussion so far is with regard to future definitions of these adverse events. Any other comments on that?

DR. MC CULLEY: Some way or another I think we do need to keep in posterior capsular opacity. Do you not get rid of it completely?

MS. LOCHNER: The reason why we said not to include that in secondary surgical reintervention was because it was not included in previous values. It didn't

include those rates, primarily because the first Grid was written at a time when -- so the question you are asking really is to add a new entry, because we can't lump it in with secondary surgery, to add a new entry for PC rates.

We actually raised this question to the industry in August when we presented updating the Grid to them. The primary concern that they voiced was that it was really more of an academic item of interest, and that it wasn't needed for determining safety and effectiveness. When you consider the ranges of PCO that is reported, you're not going to be able to come up with a good number to compare it to.

The method of measurement would have to be very clearly stated up front in the protocol, and then compared to the same method.

DR. STULTING: You can make those same comments about every single item that has been brought up so far.

DR. MC CULLEY: Staying to that point, I do think that there should be a posterior capsular opacity -- and you can work on what the descriptors would be -- of clinical significance, because there potentially will be lenses in the future that stimulate. There may be a company wanting to come in with a lens that decreases the rate, and that would be their claim.

MS. LOCHNER: They would have the right to study that separate of the Grid. The question is if they want to study that separate and come in with a claim, versus I need this endpoint to determine safety and effectiveness. By all means, if they want to claim it, they have to set up the correct study.

DR. SUGAR: Will we still collect the data though? Will they still collect posterior capsule opacification data even if it is not on the Grid and presented to the FDA?

MS. LOCHNER: If we don't require it, they don't collect.

DR. SUGAR: I think we need to require it. Can we have things for future Grids where we have it, but the number is to be determined ten years from now?

MS. LOCHNER: If we did that, we would have to have a future discussion in terms of laying out how we would want to collect it, some standardized methods and what not.

DR. SUGAR: Again broadly, in the application we reviewed this morning there was data on posterior capsule opacification; no definition of how that was determined.

MS. LOCHNER: Really, I think the assessment of it is given a certain amount of -- since the rates that are reported out there are so broad, you view that data a little

bit which hand is raised higher, what the industry impressed upon us, because we proposed and why we sort of backed off was that was this really needed to determine the safety and efficacy of the lens?

DR. SUGAR: It may be.

MS. LOCHNER: Or if they want that claim, and then they study it and send it into us, of course we would review it.

DR. SUGAR: But what do we compare it with?

MS. LOCHNER: They would have to set their study up to a comparison, and then their claim would be whatever it was that the study was designed to show.

DR. MC CULLEY: I understand your position on that, but if on the other hand, the other side of it, the lens has associated with it an increased rate of opacification, then we need data for comparison. So I understand that they are going to make a claim. I understand what you are saying, the Grid would not be obliged to deal with that. But if it has an associated increased opacification rate, we need the data.

DR. BELIN: One of the reasons that we are trying to coordinate ISO and FDA I gather is that we can utilize worldwide studies, and not have to go through a ten year

period of where we really had no data other than ten year old data. I think we have to collect this information because now it will not require ten years to redo a Grid. It should be an ongoing thing, and every two to three years there should be significant numbers of data to then update the Grid.

Then if a company comes in and we know in three years from now that a posterior capsular opacity rate of 30 percent is expected, and someone comes in with a lens that has a 4 percent rate, that is appropriate information to look at.

MS. LOCHNER: But information is currently being captured whether or not a posterior capsulotomy was performed.

DR. BULLIMORE: I would caution us in terms of collecting PCO data, because we know from large scale, we know from studies which we reviewed recently there is a surgeon, a geographic dependence in YAG rates. It varies from single digits to close to 100 percent, depending on where you go in the country.

So basing any conclusion on the historical data relating to YAG capsulotomies is, I think, not prudent. If a company wants to show that their lens produces a lower

opacification rate, they need to do it in a randomized clinical trial. That is the only way we can demonstrate that, and I would encourage the FDA to go along that line, using historical controls for this type of adverse event, given its complexity and common place is really not wise at this stage.

DR. PULIDO: I would recommend leaving it in the Grid, and likewise for retinal detachment repair, and I'll mention why. In the Nature Medicine from September there was an article I believe from England where they were trying to modify the -- the researchers there were modifying IOLs to decrease the incidence of posterior capsular opacification. So I think we are going to start seeing those studies in the future, and I think we will still need historical controls.

Likewise for retinal detachment repair, I can envision a situation in the future where the lens designs may be so different that they could be impinging on the pars plana and causing retinal detachment, so I would like to leave that as well.

DR. GORDON: Just a comment on the issue of PCH and the YAG capsulotomy. I second Mark's comments, because we have had our own experience with an intraocular lens that

we studied in the U.S. and in Europe and found very differing rates of PCO that proved later to be, as we investigated, trying to understand why the patients who should have had best case outcomes did not, we investigated and found that geographically, especially as you go to international studies, meaning U.S., and the goal would be to do a study around the world, that the differences in when the timing of performing a YAG capsulotomy is subject to the timing of reimbursement, and when it is reimbursed, and how much.

So I agree that to obtain a claim, meaning if a manufacturer develops a product that they believe can decrease the rate of posterior capsular haze and secondary YAG capsulotomy, then one would need a randomized comparison where you would compare two groups, a standard lens and a new lens, because an historical control is not going to give you any information other than a broad range based on when the procedure can be performed under the reimbursement standards for that geographic area.

DR. BELIN: I agree with you. If someone wants an indication for this lens, reduces posterior capsular haze, they need to do a double blinded study, however, I will give you a scenario. Suppose the lens that they are using as a

control, something we did not know of, happens to be associated with a higher incidence of posterior capsular haze? They have lens A that they are studying as a control, which has an 80 percent rate; lens B has a 40 percent rate.

If we didn't know that the historical control was 40 percent, we would conclude that lens B reduces posterior capsular haze, when in essence the control is an inappropriate control. You still need an historical value. The historical value is there for strictly historical reasons, not to do a controlled study, but in order to validate the controlled arm of a double arm study.

DR. STULTING: We have to put this in perspective. The "Grid" has never been a performance standard. It is reference data, and has always been used that way. We are not talking now -- as I understand it, and that's why I have asked several times to clarify this -- we are not talking about what we are going to do in the future at this point in our discussion. We are talking only about compiling old data.

In my opinion, none of these definitions, or the vast majority of them are tight enough for collection from this point forward, but that is going to be the subject of a later discussion today, am I correct, where we talk about

the guidance document and what people are expected to do from here on.

So right now we are talking about compiling old data. There is a certain amount of inaccuracy that we are going to have to live with in old data. I agree with you as well, that when people want to make claims, simply beating the Grid, as we might call it, is not going to be sufficient. We have probably have already seen an example of that today.

MS. LOCHNER: Can I just make one other point to address something that Dr. Pulido said earlier? Retinal detachment repair was listed under secondary surgical by some sponsors. It was one of the reasons for secondary surgery that was delineated. We have eliminated it from that category. There is still a Grid item that is retinal detachment, and so that is just to prevent confusion with where do I report my retinal detachment? Do I report it under retinal detachment or secondary surgery?

DR. STARK: So Donna, just one thing for clarification. If you eliminate it from an adverse reaction, the information on posterior capsulotomy will still be collected?

MS. LOCHNER: The current case report forms

collect the information, and ISO recommends as a question, is the posterior capsule intact? If intact, the posterior capsule fibrosis -- these are yes or nos.

DR. STARK: This is at final visit?

MS. LOCHNER: At each form. If not intact, has capsule been opened since last reported visit? So this basic information is being collected. These are just yes/nos.

DR. STARK: So you would be able to determine an historical record?

MS. LOCHNER: Some basic way, yes.

DR. STARK: That's the only thing you can get from this information. I think it is important to include in the data collection, retinal detachment and capsulotomy, because if you see an unusual high rate of capsulotomy it may be surgeon, it may be IOL, but it may also influence the other complication rates too of retinal detachment and macular edema. So I think that information should be captured.

MS. LOCHNER: The retinal detachment repair as an entry under secondary surgery is being removed because there is an entry in the Grid that is retinal detachment. Then usually if any rate is high, the company goes through the complete case history of every case and what was done to

correct the problem.

So it was to prevent potential confusion with where do I report my retinal detachment. It is not that retinal detachments themselves won't be reported.

DR. MC CULLEY: But the capsular data could be lost, just as the data collected on that surgery is done, what surgical technique was done or used, yet you don't have ready access to that.

MS. LOCHNER: We could begin in our review process, to ask for the answers to these questions. I think we are hearing that message loud and clear. Whether we develop in the future, more refined ways of collecting the data may well be, but to include a Grid rate, well, we can't do that at this point in time.

DR. MC CULLEY: I know, but I'm just saying that if you lose the reporting of the PCO and YAG rate, then if you would go back to where your surgery is now that you now want to upgrade.

MS. LOCHNER: Yes, we hear that. We're not going to lose that.

DR. STULTING: Any other comments on that?

DR. HIGGINBOTHAM: I don't have a comment about that. I have another question. This may be a typo. On

page 7, this is more along the lines of revision, you ask for ciliary block glaucoma, not pupillary block. Did you mean ciliary block? Okay, thank you.

MS. LOCHNER: That was just a carry over from the previous slide.

DR. STULTING: Could you phrase question 3 for us, please?

MS. LOCHNER: In question number 3 we are trying to speak more towards the method we use to update the Grid, both the posterior chamber and the anterior chamber. Do you want a certain number of patients to be used so that we have a certain amount of experience, higher denominator data, or do you want only recent experience to be used, in which case we would have less number of patients, but perhaps more recent experience?

We sort of arbitrarily went back through so much information and pulled that data for you. It was arbitrary. So we are sort of asking about our methods used. Would you rather see only a certain time period forward used, or do you want a high sample size in the pool of data?

DR. MACSAI: It would seem to me that some years you might have completion of one PMMA and some years you might have completion of PMMAs. Is it unreasonable to say

every two years you include the data from the completed approved PMA?

MS. LOCHNER: How far back?

DR. MACSAI: So is the question how often we update it, or how far back, or both?

MS. LOCHNER: Well, right now since this is the first update since 1983, we need to know how far to go back.

DR. STARK: Well, I don't think you ought to go further back than ten years, because it is too rapidly changing.

DR. MACSAI: I was just going to say if you have the data in a standardized computer format, it would seem reasonable every two years to update it.

MS. LOCHNER: Add the two new ones in and drop the two oldest off, is that what you are saying? Or just keep adding to the total?

DR. MACSAI: You just go in 1995, you go back to 1985, including everything new from 1993 to 1995. In 1997, you go back to 1987.

MS. LOCHNER: So a proposal is on the table to go back ten years. Since we are in 1997 now, to only take studies that began in 1987 or later, is that correct?

DR. MACSAI: I was assuming you would go by the

date they were completed, as opposed to the date the began, but you can change it if you want.

MS. LOCHNER: That is fine with me.

DR. STULTING: Dr. Rosenthal, could you clarify for the panel where the data are going to come from, and what is going to be made available? I think there may be some assumptions here that are not necessarily accurate.

DR. ROSENTHAL: I was going to make a statement about this tomorrow, Mr. Chairman, but if you like, I will make it now. The data from PMAs is the company's proprietary data. The agency cannot use that data in making determinations about reclassification, guidance documents, other PMAs.

DR. MACSAI: Excuse me, Dr. Rosenthal, once it is public record, could former chairman use it?

DR. ROSENTHAL: Today former chairmen of this panel use it. If he or she made it in conjunction with a large amount of other experiential data, yes, but if they made it exclusively from PMA data, the answer would be no. It is a very complex issue.

DR. MACSAI: Then why are we having this discussion, Dr. Rosenthal? Where else is the data going to come from?

DR. ROSENTHAL: Well, there is literature.

DR. MACSAI: Well, but the literature is not necessarily in a standardized format.

DR. ROSENTHAL: There is another way we can do it, Dr. Macsai, and that is if we get the companies to give us a waiver on the use of their data.

DR. MACSAI: Okay.

DR. BULLIMORE: How about we use our Europeans friends who are sitting over here? Is that another option?

DR. ROSENTHAL: We can use any data that is in the public sphere. I didn't understand it either Dr. Macsai, but even though the SSE is publicly there, it is still the company's proprietary data. Now apparently in the new FDA modernization legislation, if and when it is passed, there will be a provision which will allow the agency to use data that is six years old or greater in its determination. This is law. I'm sorry, it is law.

DR. MACSAI: Let me go on the public record and say they are asking us to compare today's techniques to six year old data, and in ophthalmology that is not necessarily an appropriate comparison.

DR. ROSENTHAL: I would suggest you write the Congress who are considering this modernization bill and

make that point, but that's what the issue is. The company is being protected by the law, and it is their proprietary data. We can make decisions based on a lot of other information, and if we get the company to agree, we can use their data, which is what we are going to attempt to do in finalizing the Grid, is to the companies' approval to incorporate their data for use in developing the Grid.

DR. MACSAI: For my historical curiosity, perhaps Dr. Stark can address this. Was the company's approval obtained prior to the 1983 Grid creation?

DR. STARK: I'm sure it was.

DR. BULLIMORE: Since we have an industry representative on the panel, Judy what is your sense of what might go on here?

DR. GORDON: I think protection of the proprietary nature of data in a PMA is very important relative to its use in assessing other PMAs, et cetera, but I would support a broad industry waiver of recent PMA data in establishing a standard that applies to all lenses, particularly given that the outcomes have improved over time, and there is no reason not to do that.

I think limiting use of data in PMAs to those specific purposes has value for manufacturers who make

really substantial investments in generating these data.

DR. BELIN: How long was the end value for the original Grid?

DR. STARK: It was around 7,000. It was around 5,000-7,000 for different classes of lenses. Then we had an adjunct safety group where there was no formal reporting. It was supposedly adverse reaction reporting of 200,000, but we didn't get, I don't think, valid information from that group.

DR. BELIN: The original question was how far back should we go, assuming we do get cooperation from the sponsors. I think you need to come up with a number, which a statistician hopefully can do and back track. The goal would be to reach the number with the most recent possible data.

MS. LOCHNER: Reach the number that was in the 1983 Grid?

DR. BELIN: No, whatever number becomes -- you now have an historical basis to try to statistically determine what number you should look for, and determine how far back you have to go so that you can reach that number with the most recent data.

The problem with coming up with an arbitrary date,

if you look at let's say the anterior chamber submissions, is that you have had no recent anterior chamber submissions. So for anterior chamber lenses you may have data from 1985 upwards. For posterior chamber lenses you may be able to reach that data 1990 and forward, but there is a number that you have to have which someone should be able to work out based on known complication rate.

DR. BANDEEN-ROCHE: Certainly it is a bias variance trade off in terms of total error, right? So if you go too far back, we are biasing towards the overly historical data. We don't get enough numbers. We have an imprecise estimate that isn't very useful. So that's a complicated problem in terms of optimizing. I would nonetheless, encourage you to try.

The thing that I think is very, very important is to calculate meaningful precision estimates on the values in the Grid. That is not necessarily a straightforward problem, because it not only includes the overall sample size, but the amount of clustering, the degree to which different studies differ for whatever reason, the degree to which various physicians are more effective than each other.

So in summary, the amount of between study variation, even getting more technical perhaps between

physician variation, but FDA statisticians should be able to provide those values.

DR. STULTING: Is everybody clear on those issues?

DR. BULLIMORE: I think it is important though -- I can say this, because I have no expertise in the area -- I think that the panel should attempt to sort of draw a line in the sand in terms of the way technology and the practice of ophthalmology and medicine has changed, and say 1992, 1987, because that still has to factor into any statistical analysis that comes out of this I think.

DR. BANDEEN-ROCHE: I would say I agree with that. I agree that, and then just develop the estimates of precision carefully.

DR. BULLIMORE: To give another example, when somebody comes to Karen and asks how many subjects do I need, her first question is, well, what do you regard as significant? What is clinically meaningful? So I throw that question back to my colleagues on the panel.

MS. LOCHNER: Let's pose the question as is there a particular time period we should go back to? How far back can we go?

DR. PULIDO: I like Dr. Belin's idea, because it will depend upon the kind of implants. He is right, AC

IOLs, you just won't find good data anymore. So instead of putting a date, I think using his approach would be the best; just keep going back until you meet the data.

MS. LOCHNER: Okay, we can work with that.

DR. STULTING: Any other comments on that one? Should we move to number 4, "How should differences in materials for posterior chamber IOLs be handled? Should the differences in materials be taken into consideration in the review process, or should the Grid update include an analysis that accounts for the two material types (i.e., separate Grid values for soft vs. PMMA)? Note that Tables 2 and 3 contain data separated by material type and combined."

The floor is open for discussion. That was a how should, not a yes/no.

DR. MACSAI: Donna, why did you combine silicone and soft acrylic?

MS. LOCHNER: Silicone and soft acrylic? Because basically we separated them by whether they could be folded or not.

DR. MACSAI: That is just arbitrary, right?

MS. LOCHNER: Right, and we're asking for your opinion on how we should do it. We made an arbitrary cut of soft versus hard. The question right now is asking we

should --

DR. MACSAI: Maybe you should separate it by material.

MS. LOCHNER: First of all, it's not feasible to have a Grid for every material IOL that there is, because there are some under development that don't fit any of those three categories. Secondly, we are setting more or less a control that should be able to be used to make reasonable assurance of safety and effectiveness.

It might not be reasonable to have one Grid value, given the discussion earlier, somebody sort of reposed this question as should it be broken up by surgical technical? So the question is, do we need a Grid that breaks the posterior chamber data down by either by material or by surgical technical or what? Or should we just have one posterior chamber Grid value that is equally applicable to all materials?

DR. SUGAR: I think there should be one Grid value regardless of material. That is, if something is safe and something is effective, it is safe and it is effective. Effective isn't less important if you can fold it and put it through a smaller hole, and do it in 10 minutes versus 20 minutes. So I think that the standard should be across the

board for a lens style.

The reason for having differences in lens style is that anterior chamber lenses are used under different circumstances. Ideally, there should be a single standard for all lenses. That is, a cataract operation should be safe and effective, period.

DR. RUIZ: But if you have brand new material and it folds, you can't just lump it under fold.

DR. GORDON: Why not? Isn't the purpose of a Grid just to establish a threshold for this is how safe all lenses should be?

DR. RUIZ: I think a fundamental question though is, is the material safe.

MS. LOCHNER: You have to also consider the endpoints that are the Grid -- visual acuity. If it's a new material, does it have to have a different standard, or is visual acuity the same no matter what material you are talking about?

DR. SUGAR: It can't be a lesser standard.

MS. LOCHNER: This gets back to what Dr. Sugar was saying. If you are saying a certain historical control number is the threshold for comparison, what Dr. Sugar has basically put on the table is that that could be one number,

no matter what the material of the IOL is.

DR. STULTING: Remember, there are two separate issues here. One is the Grid, which is an historical compilation of data to be used during evaluation of lenses. The other is a performance standard, which is what we think a lens ought to be doing. I think we are confusing those two issues. They are two separate issues, and right now we are talking about Grid, that is, compilation of historical data, am I correct?

MS. LOCHNER: Right.

DR. PULIDO: We need a gold standard, and regardless of what kind of material, we need to look at it compared to a gold standard.

DR. STULTING: That is a different thing. Now we are talking about performance standards for the guidance documents and the PDP.

DR. PULIDO: No, I'm using the Grid as our standard.

DR. STULTING: Yes, but that's incorrect. That's the point I am trying to make. Now correct me, Ralph, if I am misstating the FDA's position in what we should be talking about. The Grid is historical data that are to be made available during the evaluation of implants. It is not

the standard against which they are supposed to be compared. It is not a performance standard. A performance standard is something we are going to talk about later when we talk about the PDP. Am I correct?

DR. ROSENTHAL: Yes. The two could merge into one.

DR. STULTING: They can be the same, but they are not necessarily, and that's why I keep coming back to this so that everybody understands what we are talking about. We are now talking about Grid values, that is, compilation of historical data which may or may not represent something that we should consider a performance standard in the future.

MS. LOCHNER: How these data are used is that most companies identify the historical control, the Grid values as their control in their study. Some companies are studying other aspects of their lens, and do not identify the Grid as their control. They enroll a prospective randomized control, but in most of the basic just determining safety and effectiveness kind of studies that go before the panel, in the past most of the companies have used the historical Grid, the historical control as their control in their population. So that's how it would be

used.

DR. STULTING: If a company happens to exceed a Grid value, that doesn't necessarily mean the lens will not be approved. Similarly, if they meet the Grid, it does not necessarily mean that the lens would be approved.

MS. LOCHNER: That is correct.

DR. ROSENTHAL: May I add Mr. Chairman, that when you consider the PDP, you have to consider what standards you expect these companies to meet. You may use the Grid as your standards, because if they do not meet those standards, they may be in jeopardy of not passing the PDP.

DR. STULTING: That is the Catch-22 that we face as we sit here today, because we do not know how the Grid will be arrived at, because we have no way of knowing what data we are going to get, or where it is going to come from. So we can't -- at least I can't from my perspective, say that this is the gold standard, because I don't know whether it is going to represent 1983 data or 1996 data, nor how many lenses will be in it, or anything else.

I do know for sure that we need to separate the discussion very clearly into those two segments. This is Grid discussion.

Any other questions about what we are talking

about?

DR. HIGGINBOTHAM: I guess I was going to speak in favor of considering soft versus PMMA. As I recall, one of the things I had to review was a quad polymer. As a further refinement, you might consider separating out -- are you going to tell me this is not an appropriate comment?

DR. STULTING: Go ahead. I haven't heard it yet.

DR. HIGGINBOTHAM: I just had that look.

One consideration might be to further define the group as those that have more than 50 percent PMMA in their material versus less. So I think some of the newer lenses have less PMMA. As a function of time we might see less PMMA of lenses, but a lot of the historical controls have PMMA, so it is good to have that as one group as a predominant component.

DR. BELIN: My opinion would be that if we separate the posterior chamber lenses, we do it along insertion techniques not materials, because materials are constantly changing. An example would be the memory lens that got a recent conditional approval. It is soft lens when it is warm, but it is a completely rigid lens at body temperature. So is that a soft lens, or is that a rigid lens? But it should behave in a surgical technique as a

folded lens.

The surgery itself is likely to contribute to some of the reported rates. We are more likely to see corneal edema on day one with clear cornea than if we do a sclera incision, high firma from scleral incision. So I think it is more valuable to separate it along insertion techniques than materials.

DR. VAN METER: I second that motion, because the foldable lenses came about not because they necessarily performed better, but because it enabled a different surgical technique. I think the general consensus is that the technology of cataract surgery now is probably ahead of the technology of lenses, and lenses will probably try to catch up and permit insertion through a smaller and smaller incision of functional lenses.

So as an historical guide, I think the Grid does not necessarily need to separate out the PMMA from acrylic or silicone lenses, but if you want to sort these out in the future according to implantation technique, that is probably more appropriate. I'm not even sure that that is necessary, because if the Grid is indeed an historical guide for control purposes, then it doesn't matter how you put the lens in, it's how the patient performs afterwards.

DR. BULLIMORE: If Dr. Van Meter was indeed speaking in favor of a single reference Grid, then I support it. I think being a simple soul, having one set of numbers to refer to, and not regard as a threshold or a performance standard is where we should be going.

I get a little nervous with the periodic updating of a reference standard though. There is a danger that the bar will creep up, not because of advances in technology, but just due to the fact that the studies that are going to be included down the road are going to be the successful ones, i.e., the ones that exceeded the reference standard.

I think there is also a danger that we make, but encouraging periodic update of a reference standard, that we don't make sort of busy work for the agency, when really looking at this when they feel it is necessary is just a better way to approach the issue.

DR. STULTING: Any other comments? Perhaps we should move as fast as we can through this now that the purpose perhaps has been clarified a little bit.

Question 5, "Anterior Chamber IOLs: The revised grid will have separate values for posterior and anterior chamber IOLs. Our data analysis shows that the data from the most recent PMA approvals for anterior chamber IOLs are

generally not an improvement over the 1983 Grid."

"a. In the past, FDA has required anterior chamber IOL data to be stratified by indication (primary ICCE, primary ECCE, back-up use ECCE, secondary implantation). Should the updated Grid include an analysis that accounts for the two materials? Note: This may not result in an improvement over the 1983 Grid values, but may be a more appropriate comparison."

"b. As an alternative, we would retain the 1983 Grid values for anterior chamber lenses."

DR. BULLIMORE: Indications.

DR. STULTING: That's what I think it should say, don't you think?

MS. LOCHNER: We corrected that. It is supposed to say indications.

DR. STULTING: Does anyone disagree with that, that it should continue to be stratified by indication? That makes sense to me. Everybody agrees with that.

As an alternative, we could retain the 1983 Grid values for anterior chamber lenses. In other words, not update anterior chamber lenses.

DR. MC CULLEY: I think we would have to see some data to be able to make some judgment, wouldn't we?

DR. STULTING: I could agree with that proposal. Does anybody else have a comment on that? You would like to see the data before answering that?

DR. MC CULLEY: We saw data on these other things. To be able to respond to that, we would need to see the data.

DR. BULLIMORE: Is it true to say that the data just don't actually exist for these lenses?

MS. LOCHNER: The breakdown by ICCE versus ECCE, that breakdown?

DR. MC CULLEY: And secondary, the indications?

MS. LOCHNER: Yes. The breakdown by the indications, we should be able to pull that together. Since in the past we have had an anterior chamber analysis that was overall indications, the tables you have today are just the overall updated data for anterior chamber. When we looked at that overall data, we saw that it was not an improvement, and so that is what caused the question. We could either sort of table this until we can show you the breakdown by indications.

DR. STARK: I personally think that if you look at any more anterior chamber lenses, they should be compared to the posterior chamber, because the Grid really reflected a

worst case analysis. When the studies were originally set up, you were not supposed to implant a lens if you lost vitreous. Somehow vitreous loss wasn't even recorded on the form back on 1978 and 1979. So we could not determine on anterior chamber lenses when they were used as a primary intent or a lens of secondary intent.

So the results were actually worse than one would expect with a good anterior chamber lens. That is a problem in comparing any future anterior chamber lenses to the Grid. I think it ought to be compared to a posterior chamber lens, and if they don't meet posterior chamber lenses' use as a lens of primary intent, then there should be a warning on that.

DR. MC CULLEY: But who is going to put in an AC IOL as primary intent?

DR. STARK: I don't know. I don't know that she will get any more.

DR. MC CULLEY: You wouldn't, but there might be a better AC IOL to put in for secondary intent that would be an improvement. If we require that they perform as well as the PC that is a primary intent, we are never going to have another AS IOL.

DR. STARK: If you are talking about just

secondary intent lens.

DR. MC CULLEY: So we need to see the data based on the surgical indication.

DR. BULLIMORE: I agree with Dr. Stark. I think if we are going to have a primary lens as an anterior chamber lens, it should conform to the posterior chamber Grid, or if you like, the current state-of-the-art. If we have got a secondary lens, if we don't give the manufacturers the ability to develop an anterior chamber lens for heroic or secondary or whatever circumstances, we are going to be implanting 1985 lenses well into the next century. So we have to leave an opening, pardon the pun, for that kind of situation to arise.

DR. SUGAR: But then you can't compare it against posterior chamber lenses.

DR. BULLIMORE: Exactly.

DR. SUGAR: The lenses are put in, in situations where you know you are going to have a higher incidence of corneal edema or you are going to have a higher incidence of CME, maybe hyphema, maybe secondary glaucoma, and you buy that trade-off in putting that lens in. You know that. I don't know what standard you compare it with, because now all of the lenses are going to be secondarily intended, and

I don't know that you have the data in 1983 of enough data of secondarily intended lenses.

DR. MC CULLEY: Somewhere in that report we had secondary lens implantation, because I remember the figure was a little over 5 percent loss of 20/40 or better visual acuity. The numbers were small, but those are again, 1980 data with secondary lens implants used then. I don't think you are going to get the data from the literature or from the past studies.

DR. STULTING: Any other comments?

The final question is requesting any other comments on the Grid.

MS. LOCHNER: I'm sorry, I didn't catch the answer on the previous question. Did we leave it as -- we didn't present this because it's going to be a substantial effort to go through and find this data, but is that what we are hearing we'd like to hear? Okay.

DR. STULTING: The consensus I heard was that there were no data available, and it was difficult to answer the question in the absence of data.

MS. LOCHNER: Or should we just update the Grid with worst values?

DR. MC CULLEY: Can't we see data?

MS. LOCHNER: Okay.

DR. ROSENTHAL: I thought the consensus was, Mr. Chairman, that you want the anterior chamber lens implants to be evaluated by indication?

DR. STULTING: There were two parts to the question. That was the first one, and that one was settled.

DR. ROSENTHAL: We don't have that data for you, because we haven't done it.

DR. STULTING: The second was to whether or not the 1983 values should be carried forward, or whether they should be updated with new information. It was my understanding that Dr. McCulley's comment was with regard to that question, which was on the floor at the time. Am I incorrect?

DR. MC CULLEY: Yes, I think we want to continue to see things stratified. We said yes to that. To answer the second part of the question, it is difficult to answer without seeing data, the stratified data. We would like to see the stratified data.

DR. STULTING: Did anyone else understand it in a different way?

DR. ROSENTHAL: All right, that's understandable.

DR. STULTING: So the last question was, other

comments about the Grid?

MS. LOCHNER: About the methods we are going to use to compile the data; any further questions you may have about the ISO study format, which was included in Section I of the handout; any other comments?

DR. BELIN: A quick question. You are looking under definitions at cumulative adverse event and persistent adverse event. I can think of -- and I want other people's opinion -- some validity to looking another grouping which in essence looks at let's say Form 2 and later.

An example would be that we have run into a few times recently where because the cumulative adverse event reflects really an operative I don't to even call it complication, but an operative event, that the cumulative adverse event is abnormally high when we go back and compare.

Though it won't be picked up in persistent, because it doesn't persist, I think maybe a better indicator of safety of the lens versus the operative procedure is to look at cumulative adverse events from Form 2 and after, or Form 3, whatever is about a one week or a two week period, to get out of the immediate operative period. So I'm throwing out the thought of perhaps adding a third grouping,

or maybe getting rid of cumulative, which I think doesn't tell you a whole lot.

DR. STULTING: Any other comments?

DR. STARK: Doyle, did we give our sense of opinion to our European colleagues about Form 4 follow-up? I heard what I thought was more of a consensus that what we wanted would be six month data at Form 4, so why not straddle it at five to seven months? Twelve month data is straddled 10-14 months, so that you get your 12 month data. I would say if you want six month data, you go from five to seven months, rather than up to exactly six months and stop. It would be more consistent with our practice patterns also.

As I understood it, that is subject to vote. If it is a consensus that most of us would prefer it that way, maybe our opinions could be delivered.

DR. LYDAHL: The reason was that we are still comparing with data collected during the other time frame. So we don't have the data collected at five to seven months. So that is the only reason. We wanted to keep the time frame within the time frames of the data that are collected, and that we are comparing with. So we don't have a Grid.

MS. LOCHNER: Because of modified models, that we only require a 100 patient study, the companies only have to

follow those out to six months if the data look okay at six months. So when you do the Grid comparison, which we don't bring these studies before the panel, but let's say they want a new haptic material or something like that, we require 100 patients, and the company does 100 patients to six months and compares it to the Grid.

So in the past whenever --

DR. STARK: If they could get it at 91 days, that would be considered six months?

MS. LOCHNER: No, in the past it was 120-180 was when they were supposed to do that visit. So that is why that is the current proposal.

DR. STARK: Four months to six?

MS. LOCHNER: Four to six. Is this something other people feel strongly about? We can put a recommendation forward to ISO to consider 150-210, or we can keep the consistent definition of 120-180, consistent with these smaller studies that firms have done in the past.

DR. RUIZ: But that is not consistent with ISO, is it?

MS. LOCHNER: Yes.

DR. RUIZ: They are 90-180.

MS. LOCHNER: They have a proposal that is just

recently -- since that handout went out, they had a proposal to go to 120-180.

DR. RUIZ: I don't see anything magic about six months, Walt. If that's the way it's going, it's fine.

DR. HIGGINBOTHAM: Your other time points don't straddle, so I would keep it 120-180, or otherwise have all your time points straddle; not just straddle one time point.

DR. MC CULLEY: The current ISO standard is 120-180, or is that the proposed one?

DR. LYDAHL: The proposed one.

MS. LOCHNER: The standard is not yet finalized. It has not been voted for final approval.

DR. RUIZ: I think it is valuable to all do the same thing, and I don't think there is anything magic about six months. I think we ought to try and get in synch.

DR. BULLIMORE: Does that mean we're going to be adopting the metric system too?

DR. STARK: So in effect, if a company is smart, it will be four month data, is all I'm saying. So if you want four month data, then you leave it at 120-180.

Agenda Item: Reference Product Development

Protocol for Intraocular Lenses - Donna R. Lochner

DR. STULTING: Should we move on to the discussion

of the product development protocol, which is here? I at least have two separate copies of the IOL guidance document, one that is entitled, "Draft IOL Guidance Document," and the other one that says, "IOL Guidance Document," draft document that is attached. Now are these totally the same?

MS. LOCHNER: For the PDP discussion, what you should have in front of you is a document that is entitled, "Reference PDP," an attachment that is entitled, "Attachment A," which is the FDA guidance document dated 9/5/97. The third attachment, "Attachment B," is the ISO draft standard. For the purposes of the discussion of the PDP, this is what we want you to have in front of you.

DR. STULTING: Does everybody have those, so we are all talking about the same documents?

Do you have a presentation that you would like to go through to guide discussion on this?

MS. LOCHNER: Yes, I have some brief comments to make. We're asking the panel to review a reference product development protocol, or PDP, to determine if the PDP contains the methodologies, endpoints, and success/failure criteria that you believe are appropriate for the evaluation of an intraocular lens.

General background into the PDP process has been

provided in the handout. Perhaps the most important factor in the PDP process is the fact that panel review occurs prior to initiation of clinical studies so that the studies can be designed up front to contain the information need to assess safety and effectiveness.

The reference PDP is essentially the framework that can be used by a sponsor to create their protocol for their IOL. As described in the background information provided to you, if a sponsor were to propose a clinical study that was substantially similar to the criteria outlined in the reference PDP, and if the data met the criteria outlined, FDA could approve the IOL for marketing.

If, however, the sponsor proposed a different protocol, or if unusual results that could impact upon safety and effectiveness were seen, FDA would bring this information to the panel for their review.

Before you review the clinical protocols, I would like to draw your attention to the following points. Some of these have been captured in the information provided, and some are recent updates to our proposed clinical requirements. First, as we discussed earlier, we would like to revise the Form 4 visit from the current ISO requirement of 90-180 days to 120-180 days.

Second, I would like to point out that the reference PDP that was provided to you contains a requirement for all posterior chamber IOLs to be studied for one year. In the past, when sponsors proposed a new material lens, for example the first soft material lenses, we required a post-approval three year study. We have not found the three year time period to provide additional knowledge beyond what was learned at one year, and so we are proposing removal of this three year requirement.

Last, to follow-up from a meeting several years ago, the panel recommended that the effective lens position or ELP be placed on IOL labels. The effective lens position is defined as the expected separation the secondary principal plane of the cornea and the position of the equivalent thin lens. The ELP was chosen because it is independent of power calculation formula.

Proposed guidance for determination of ELP has been incorporated into FDA's draft guidance document, and a copy of this guidance has been provided to you in your packets this morning. While this will not require sponsors to collect new or different clinical data, it will require additional data analyses to determine the ELP.

As requested by the panel, data should be

collected so that the standard error of the mean ELP is less than or equal to 0.05 millimeters. One aspect of our proposal that is different from that recommended by the panel several years ago is that we are requiring that all ELPs be determined from clinical data. The panel had suggested that the parent lens ELP be determined from clinical data, and that subsequent modifications to the parent lens be determined from engineering analyses.

We have come to believe that it will be difficult and probably very inaccurate to predict the effective lens position from these engineering analyses, and so we are recommending that all ELPs be determined from clinical data.

Finally, the information that we provided for your review contains clinical protocol information only. The protocols to be used for preclinical testing, including optical, mechanical, biocompatibility, microbiology, and physical and chemical testing are substantially similar to the ISO IOL standards for IOLs.

These protocols, including endpoints and pass/fail criteria have been extensively reviewed and discussed with experts throughout the world at the ISO meetings. We believe that these protocols have received extensive review and so they are not presented today.

After discussion, we ask that you answer the questions provided to you, and repeated on the slides. We will leave the first question up until you are ready to get to the questions, and I'll turn the floor back over to Dr. Stulting, who hopefully, can lead you through the discussion.

DR. STULTING: Now we are talking about proposed methods of collecting data, and proposed standards for comparison. Just to reiterate what Ms. Lochner said, a PDP is a method of analysis and proposed standards for comparison that would permit the acceptance of a product without lengthy panel discussion if it met the standards. So now we are talking about real standards and things that we would like future devices to measure up to.

So with that brief preamble, let me open up the floor to questions or concerns about the PDP document that you have in front of you.

DR. ROSENTHAL: Mr. Chairman, may I just clarify one issue, which probably will be brought up by one of the panel members. That is, if we do approve a PDP, and the company comes in with their PDP, it has to come back to panel for their approval. The generic approval PDP is just to give us the broad outline basis on which the PDP will be

developed, but the individual ones, as I understand it now, the agency has ruled will have to be evaluated by panel. It may not be in full panel session. It may just be in homework assignments, but each one will have to be evaluated to insure that it is correct.

DR. STULTING: Okay, does everyone understand that? Any questions for Dr. Rosenthal?

DR. BANDEEN-ROCHE: I have to admit that I'm not entirely comfortable with the 300 sample size for a couple of reasons. First, if you think of the width of a confidence interval on something like 10 percent visual acuity not met, that interval would have a width of 0.08-0.1 with that sample size, and I don't know if that is adequate or not.

Second, given what we saw this morning, if you require 300, then including cohort, you may not even get 300, so it could even be worse.

Then finally, there seems to be so much within provider clustering sometimes, that those best case estimates of precision are probably optimistic. So with that summary, could you just explain what motivated the 300 sample size?

MS. LOCHNER: Well, let me speak to your second

comment, because that is just the simplest. The 300 sample size is how many they must end up with at each form. They are allowed to enroll additional subjects to reach that 300. We have kept the criteria on the number of additional subjects exactly consistent with the 500-700 studies of old, and the lost to follow-up rates we have kept the same. So the only thing we have changed is just the number, just to clarify that point.

Now I don't know that my statistical knowledge can necessarily answer all your questions, but basically as was sort of laid out in the update of the Grid information, what we did was we actually did confidence intervals around a 100, 200, 300, 400, and 500 patient sample size. We did this when we were working with the ISO on their standard.

The break in where you see the confidence interval expand, the range around the value, there was a clear break at 300, where we felt when looking at the 300 numbers, the interval wasn't that much wider than the 500; that it was still a reasonable assurance clinically, safety and effectiveness, versus when you just saw a clear break less than 300.

So we basically agreed that lowering the sample size shouldn't have a large effect clinically, because what

you were able to detect wasn't expanded by that much.

DR. BANDEEN-ROCHE: Right, I certainly saw that appropriately in the document. I think just as an approach I would prefer to have some guarantee of being able to estimate the key parameters of safety and effectiveness with the precision that everybody is comfortable with, rather than just kind of saying let's make it 300.

MS. LOCHNER: So to more or less determine what that is, and maybe send it out to you or something? I tend to think that you would be the one, if you were comfortable, everybody else would be comfortable.

DR. BANDEEN-ROCHE: Right, although I would certainly appeal to everybody else, what is a reasonable precision to estimate say achieved visual acuity rates with? Is it assurance of accurate values within 0.02 or 0.04 or what have you? That is not something that I can decide.

DR. ROSENTHAL: Could you explain what you mean? I'm at a loss to understand it. I'm sorry.

DR. BANDEEN-ROCHE: Given the way that people come in and compare and say, look, my rate is higher than the Grid, but in fact an estimate this morning could plausibly have ranged within about 0.03 below and 0.03 above given the amount of data that went into the estimate, even under the

best case, which I don't even think the best case was satisfied. So that is all I mean, is let's keep the precision of the estimate in mind.

DR. STARK: I think that's addressed in the document we were just reviewing. The first few pages of that goes as you lower the end from 500 to 300, what the range is going to be of complication rates that you may or may not miss.

MS. LOCHNER: I think though Dr. Bandeen-Roche's point is we have not laid out what the assumption of precision is.

DR. BANDEEN-ROCHE: Although I think you are right, that certainly does bear on it. So one question would be, looking at those, is everybody satisfied with it? The second is that to my knowledge, you certainly don't account for clustering within providers in actually making that standard error calculation.

Now it might, but I became alerted to it looking at the proposal from this morning where there really did seem to be substantial differences between providers. Two of them accounted for more than a quarter of all the patients.

MS. LOCHNER: And this would not be captured in

just the combinability analysis?

DR. BANDEEN-ROCHE: Not in my opinion.

DR. STULTING: Any other comments?

DR. HIGGINBOTHAM: The same issues from the previous document I hope will carry over to page 6, because the same issues exist. Just to clarify, the 30 percent follow-up at three years, you are still going to have 300 as a minimum. So 30 percent would mean they probably have 500 patients, but at least they have 30 percent of those -- or 70 percent of those; at least they will have 300, is that right?

DR. BANDEEN-ROCHE: Well, it is allowing a greater number of patients to be lost to follow-up, as in they couldn't find that patient at all. It is requiring 300 to be found.

DR. HIGGINBOTHAM: That's the main thing.

DR. BANDEEN-ROCHE: Yes, it is still requiring the 300, but it is allowing less to be accounted for. In the one year studies, we require a 10 percent loss to follow-up, as in 10 percent that you know nothing long-term about, but we are allowing more to be lost in terms of you know nothing about, as long as you have the 300 at three years.

DR. MC CULLEY: I read this reasonably carefully

front to back, and I only have very few comments. One is on page 6 as well, and there again under cumulative adverse events, I still want to see hyphema. Somewhere I would want to see the posterior capsular opacity again. I guess you have the iritis dealt with.

The only other comment would be on page 8, should there be additional data analysis for 20/20? I agree that there needs to be the 20/20 as well as the 20/40. That is page 8.

Then there were just two other minor points that I didn't quite understand. Back on page 5, if the sample size, case report Form 7 for a three year study is less than 300, a sponsor may make up the missing subjects from any modified core study population. I just don't understand that. It may not be important that I do, but I don't understand that.

One other minor point, on page 3 of Appendix A, I assume that in A you have intended replacement of the anterior segment in the eye, that that is implied to include anterior and posterior chamber lenses when you say anterior segment of the eye?

MS. LOCHNER: Yes.

The statement about modified core is just that in

certain instances even given the lessened requirement for loss to follow-up at three years, sponsors simply were not able to get 300 patients at three years. So in those instances in the past, we have allowed them to go into their modified core population to get sufficient experience at three years.

What the modified core population is, is it is an additional number of implants a sponsor is allowed to do during their study. Once they have completed the initial enrollment and they are awaiting for the PMA to be approved to allow the investigators to continue to have experience with the lens. They are giving some additional implants while FDA and the panel is reviewing the PMA.

So in the past when they couldn't reach the 500 number for three year, we have allowed them to go into a modified core. From the standpoint of once they have exhausted their efforts in the core, it is more important to us to get a sufficient sample of experience at three years, to see how the three year data looks. So it is sort of like plan B if they can't get them all in the core.

DR. MC CULLEY: My comments that were on page 6 we have already discussed. I hope that they would carry forward and hold.

MS. LOCHNER: I should have said that in my comments. All of the comments earlier this morning will carry forward.

DR. MC CULLEY: So I don't want to beat that dog anymore.

DR. PULIDO: Not that I put these in, but when I recalled there were cases of silicone IOLs that may have discolored, turned yellow in the past, does this new PDP capture that kind of event, where the implant discolors?

MS. LOCHNER: The case report forms -- a sponsor would be required on the case report forms, the investigator would have to write anything unusual that is happening. So in the sense that there is like an "other" on the case report form, it would be captured.

The issue with discoloration of lenses has primarily been addressed through preclinical testing. All the experience that was gained when that was happening, led us to believe that this was an issue that needs to be captured in the preclinical testing.

So FDA has changed some of its requirements; required further testing, validation that any of the possible reasons why the lenses discolored, and they were all basically somewhat different reasons, we have required

that to be captured in the preclinical testing, which is not to say that if it occurs clinically we don't want to know about it, but we think it is a much rarer occurrence now, and probably doesn't need a force choice item on the form, although we would like your opinion on that.

DR. HIGGINBOTHAM: Page 8, the various analyses that you listed, and one of those is gender bias analysis. I would think that a race analysis would probably be more important than gender. We saw this morning the data regarding Asians versus non-Asians, and their various differences between African Americans and Caucasian Americans regarding the prevalence of systemic diseases that could influence inflammation can be a difference. So I would suggest that there could be some other analyses that aren't listed here, specifically raised.

MS. LOCHNER: Yes, actually we have required that. Unfortunately, the catch-all phrase "gender bias analysis," has been carried forward throughout the office somewhat, but we actually intend race, age; basically the demographic information analyses. In our updated guidance -- this guidance is literally being updated week by week -- we have given examples of what we mean by that. It does include all the items you just listed, so we would make this clearer in

any reference PDP. We probably should change the name to make it even more clear.

DR. HIGGINBOTHAM: Just as a reminder, drugs also have a big difference in terms of their efficacy in terms of iris color, so that may carry over in terms of how we deal with some of the adverse events, and how they might report out, et cetera.

MS. LOCHNER: Well, now that's one thing we have not done before for IOLs, is any analyses by iris color.

DR. HIGGINBOTHAM: Actually, I'm not sure what the term would be statistically, but often times iris color follows the race issue, so it could be a substitute. I mean the race could be a substitute for the iris color. I'm not suggesting yet another.

MS. LOCHNER: I do think that should be on the floor for discussion, because that is a new requirement.

DR. MACSAI: Many of my issues were addressed by previous panel members, but on page 3, number 3, we talk about the number of investigators, the minimum number of subjects to the study population, and no more than 25 percent. Is this enough?

What about surgical technique? I think that somewhere that needs to be specified in this PDP, because if

a lens is only being inserted in trials using a clear cornea incision for example, then it should be labeled as such, and touted as such. Surgical technique, as we have stated earlier, may affect outcome.

MS. LOCHNER: The issue of sample is amongst the investigators, these numbers were basically arrived at through help with the statisticians in terms of what would be a reasonable distribution. Of course if they don't exactly meet this, they may be able to do some statistical tests to show that the variance is okay, but this is the ballpark of what a sponsor should be shooting for.

Regarding surgical technique, in the past we have never required surgical technique to be explicitly specified unless a particular technique was required to use the particular IOL. I mean we basically left it outside the parameters of the protocol. So if what you are saying now is the need to be more specific, how specific are you talking, like for an example?

DR. RUIZ: I just think that a lot of the things that we are measuring bear more on the surgical technique than they do on the implant, and we have to arrive at some way of breaking that down. I think it is important how long the wound is, and the location of the wound for example.

DR. SONI: I'm going to change the topic. I'm interested, Donna, in loss to follow-up patients. I understand that if you want to finish with 300 subjects at the end of a study, and you have a 10 percent loss on a year, that you probably need 310 or whatever, 330 to begin with, but how are those subjects that are lost to follow-up going to be dealt with, especially in cases where a subject had an adverse reaction at the last follow-up? What is the responsibility here?

MS. LOCHNER: We have always required a separate lost to follow-up analysis, but that was not explicitly stated in the protocol. We can state that additional analysis more explicitly in the protocol.

DR. MC CULLEY: You didn't have your 90 percent and only 10 percent in here? I thought you did.

MS. LOCHNER: No, we have the 10 percent, but I think Dr. Soni was asking for the 10 percent that were lost, what do we do with those 10 percent? Do we do an analysis? We do in fact -- we have always required a worst case analysis, what we call loss to follow-up we typically call the worst case analysis, but maybe the protocol should explicitly state that that is required.

DR. SONI: I think that is important, otherwise

they may not have that data, and then we will have the same sort of discussion that we have had in the past on the panel -- what happened to those patients? Where are they? How are we going to check on them?

I think at the moment, the way your document is, it is 10 percent loss for the first year. For a three year study, that would be a 30 percent loss. So if there is 30 percent loss over a three period, I think that needs to be documented.

DR. STULTING: Other comments?

MS. LOCHNER: I'm getting away from a couple of comments, I'm not sure how they were resolved. The surgical technique, are you mainly recommending that the wound size be specified?

DR. MACSAI: And placement.

MS. LOCHNER: As far as iris color, were we going to let that one drop?

DR. HIGGINBOTHAM: Well, you can analyze this to death. From my standpoint, I guess I'm more interested in the race issue just because you have the systemic diseases. Diabetes and hypertension are much more prevalent among African Americans compared to Caucasians, so it is important to know how perhaps, if not at all, those issues can

influence the behavior of this device in the eye, et cetera.

Certainly one could subsequently look at iris color. Is it possible to ask the investigators to note iris color at least at the time of the surgery so if we wanted to back, say if there was some huge difference in terms of the outcome of African Americans versus Caucasians, it could always be retrieved? Is that possible?

MS. LOCHNER: It sounds reasonable to me, but maybe Dr. Gordon may like to comment about how the industry may feel about that.

DR. GORDON: I guess my general comment is that what I think is a positive trend is that the product line that is well established, such as intraocular lenses, and well defined, to be introducing new criteria for assessment -- like surgical technique is a different issue, because that is in evolution and it does help, I think, the manufacturer separate out what's the lens and what's the technique.

But I haven't, in all the years of coming to panel meetings or looking at our own data, seen anything related to iris color. So adding information that hasn't proven to be useful or needed, I would challenge that. I also think that if there were a problem, one could go back to the

patients and find out. There have to be problems in specific patients, one would guess.

So again, it's just another field to enter and the time for the investigator to do it, the cost. It sounds small, but it is all incremental, and it is important to do that for data that is useful.

DR. VAN METER: Mr. Chairman, if I may go back to the idea of incision location, make it clear that this is not an astigmatic evaluation of whether it's a 12 or a 3 or a 10. It really is whether it's clear corneal or limbal or a scleral pocket. That can be broken down into a check A, B or C. It need not be too complicated.

DR. STULTING: The gist of this is that we want to make certain that it is an evaluation of lens performance, not of surgical technique performance. So that information needs to be recorded so it doesn't confound the analysis.

DR. HIGGINBOTHAM: It is my understanding that iris color hasn't been looked at, so how you can know if it is not an issue unless you actually look at that as an issue? We need to really understand whether or not this could influence how for instance these lens deposits may collect on the lenses. It could be related to iris color. If it is never noted, we'll never be able to catch the data.

So all I'm suggesting is that perhaps on the data forms we might capture that data. It could always be looked at if we need to later. Iris color is becoming more and more of an issue in ophthalmology for a number of reasons, so it may be a big issue as time goes on, particularly as we look at new polymers and combinations of polymers. Maybe perhaps different combinations of polymers respond differently with regards to different iris colors. There are so many unknown questions in the future, we just don't know.

DR. STULTING: We have to remember that our job here is to evaluate the safety and efficacy of a device, not to investigate whatever question that might come up.

Are there other comments about that?

DR. BULLIMORE: Well, Mr. Chairman, I think I would like to phrase and apply them to the U.S. population. If our guidelines, be them FDA panel or whatever, ignore substantial portions of the U.S. population, then we are not ultimately fulfilling our role here. So I have two questions in that regard.

One is for the drug folks sitting in the audience, is iris color something that is considered? The other is for the FDA. Is there a policy on inclusion of a diverse

population in these trials?

DR. STULTING: Would someone from the FDA like to comment?

DR. STARK: Race is already listed.

DR. BULLIMORE: The issue is not included as a check box. I mean the -- a simple no, Ralph, is fine.

DR. ROSENTHAL: I know gender is required by law. I do not know about iris color. I certainly agree that racial diversity should be taken into consideration. I would rather take into consideration racial diversity than iris color, because that addresses more the issues of racial issues, than iris color issues. I don't know what the law is to be honest.

MS. LOCHNER: I don't think we have an office policy that is quite as specific as what you are saying, however, we have office guidance that talks about designing clinical trials, and the need to analyze by certain factors, such as race, gender, et cetera.

In information we would send out to the industry in terms of how would you collect appropriate clinical trials, this kind of stuff is carried through in explaining to companies how to design a study correctly. Obviously, it has never gotten down to the iris color issue, but that is

an issue that I think what you have to speak to is whether it is a safety and efficacy perimeter you want evaluated, or if it is just for interest purposes.

I think some of what Dr. Gordon was saying about if you had a problem, you could certainly go back and get this information and see if that was a determinant. It is one way to look at it. So is this something that you need really to determine if the lenses are safe and effective, or is it more academic and interest?

DR. HIGGINBOTHAM: No, it's not academic.

DR. STULTING: It seems to me that we are obliged to take the data that we have and to determine the safety and efficacy. If we don't get data about a segment of the population about which we have questions regarding the safety and efficacy, then we can recommend that the product be labeled as such. But it is my understanding that we have no authority to require that a study specifically evaluate a certain subpopulation, although it is understood that there cannot be a study that is biased on entry into the study, that for example, excludes men or whatever from entry into the study.

MS. LOCHNER: Keep in mind that the purpose of this PDP is to have the sponsors collect what you feel is

needed. So right now your authority today is if you believe it is needed, that is what we will recommend be in the PDP, and we will probably carry that through into the PMAs. Yes, if you are recommending that to us today, we can put that on the forms, or require companies to put that on the forms.

DR. STULTING: For example, we don't require that drugs be evaluated in children. We don't require that devices be evaluated in children. We don't require that drugs be evaluated in pregnant women. They are still approved, but the products are labeled so that you don't have any data to use them in those situations.

MS. LOCHNER: No, it's a little bit different in that --

DR. BULLIMORE: It is very different. What we are talking about is generalizability. We are taking 300 people and generalizing the results on those 300 people to the entire population or the entire target population for the drug, device, whatever.

DR. STULTING: If you insist on having --

DR. BULLIMORE: I don't insist on anything.

DR. STULTING: If we insist as a requirement on evaluating efficacy and blue irises and males and people who have a various ethnic backgrounds --

DR. BULLIMORE: Mr. Chairman, that is not what I am insisting on.

DR. STULTING: Can I finish my statement, please?

DR. BULLIMORE: Oh, I do beg your pardon. I'm sorry. I apologize.

DR. STULTING: If we insist on doing those things, then we're going to have subpopulations that are so small, that we won't have statistical validity, and it will affect the sample size in such a way that we will have to have very large populations to evaluate the product in the first place.

If we go this route of requiring these very small subpopulations, then we have to consider what it is going to do to the availability of these products to the general public at some point down the road.

DR. BULLIMORE: I apologize for interrupting you, Mr. Chairman. That was rude and unnecessary.

I am not insisting on anything. I am not proposing subgroup analyses. I am [not?] suggesting stratification. All I'm suggesting is that there should be some verbiage in these guidelines that encourages investigators, sponsors to include a population that in some way reflects the target population for the device.

I agree with you; I do not want Judy's colleagues in industry to have to recruit 300 men and 300 women and 300 African Americans and 300 Hispanics. That is not what I'm insisting on or even suggesting. All I'm suggesting in our advisory role on this panel, that there should be some mention or some statement in the guidelines.

Dr. Higginbotham raised this to the sponsor at the last meeting, and was given I thought, a rude and unprofessional and inappropriate response. So I am just encouraging the FDA staff to consider drafting these guidelines in accordance with the suggestions made here.

DR. BELIN: I don't really disagree with anything that has been discussed. I do think we need to keep in mind that we are looking now at a PDP for a product that is generally considered safe and effective, with a long historical basis of an excellent safety record.

I think we need to design this so that the sponsors and the clinicians doing the studies can get the data out in a manner that is commensurate with them continuing their practice. You are not going to get people to do these studies now on IOLs if the paper work is cumbersome. This is not a new device. This is an established device that is looking at a new modification, a

slightly new material. I think we have to be careful that we're not making it so burdensome to the sponsor and the clinician as to defeat the purpose, which is to get the best material possible.

DR. MC CULLEY: This will be real quick. If my memory serves me correctly, we used to gather data on iris color in these patient populations. So my own assumption would be that it was gathered and it was found not to be terribly useful, so we stopped gathering it. My memory could be not serving me correctly, but I think in earlier studies we gathered it, and I assume it was dropped because it wasn't helpful.

DR. STULTING: Well, you would sort of think that with the vast experience of these things so far, we would have had at least one or two publications in the literature somewhere that would lead us to believe that this was an area for concern.

DR. MACSAI: Well, I had another question, but I would like to strongly endorse stating something about racial analysis within this PDP, because it is now the second time on the second device that it has come up, and clearly it is information that is lacking concerning the United States population, as opposed to the Swedish

population.

But my question is regarding the study phases. On some of the previous applications that we have reviewed, after the first 50 patients have reached Form 4, then they submit the data to the FDA. Then the second phase begins. What if there are modifications to the device? Because we have had this in the past where we are looking at something that was style one in phase one, style two in phase two, style three in phase three.

I find that very difficult to evaluate in terms of safety and efficacy. I would like to see if there is a way that we could make that not happen in the future through this guidance document.

MS. LOCHNER: We've never made really specific guidance to companies about modifications, because the timing of the modifications and the nature of the modifications determines what the company will have to do. For example, if they make a significant change early on in the study, after maybe five or six lenses have been implanted, we wouldn't require them to start over, but if they make a significant change after 200 lenses have been implanted, we may require 300 more lenses with the modification.

So there is really not a simple answer. It depends on when the change is proposed, and how significant it is. If it is a significant change, and we make the cut on its technical merits it could impact safety and effectiveness, we decide whether the company restarts back at zero and collects 300 more, or whether they proceed forward with that change.

Now if they proceed forward, let's say they have enrolled 50 or 100, and it was a relatively minor change, we felt little impact on safety and effectiveness, we would probably allow them to make that change and require them to analyze the data by pre-change and post-change.

So this guidance doesn't specifically address it, because it is very hard to come up with a specific statement.

DR. MACSAI: I guess if it is not going to be specifically addressed, I would ask that the agency be reminded of some of the problems in the past with modifications.

The other question I have is when we are talking about intraocular lenses here, we are not only talking about lenses that replace the crystalline lens are we? Aren't we also talking about potential intraocular lenses that might

be used for refractive --

DR. STULTING: No, if the labeling --

DR. MACSAI: Well, they are intraocular lenses.

Only for aphakia?

DR. STULTING: Labeling specifies that.

MS. LOCHNER: That is clear. We are only intending for aphakia.

Can I just follow-up to that modification statement? The concept of the PDP is that you agree up front what the device is and how you are going to test it, et cetera. So some of the PDP is meant to alleviate some of your concerns with modifications, however, the overall FDA working group working on changes that will just naturally occur during the course of the study, no matter how much up front work the companies may do, they will have changes that occur.

The overall FDA working group is coming up with a sort of policy document on changes, and to the extent where we have seen some of these general statements written about changes, we have tried to get in ophthalmic-specific guidance where appropriate.

In instance where they are not taking ophthalmic comments -- in an instance where the overriding office

policy is to allow a change to be made, but we do not agree with it specifically for ophthalmic purposes, we have been writing those changes into our guidance document. So we didn't actually hand that document out to you today, because again, it is extremely complicated. You can't talk about changes in a general sort of way, there are so many specifics.

We are trying to get in specific what we have learned in the past that these kind of changes cause problems with IOLs, we're writing that into our guidance document; this kind of a change, you need FDA's approval, which more or less means that we would assess where are they in the clinical study? Do they need to start the study over, et cetera?

So there is this other document being created about changes. I wanted you to be aware of that.

DR. STULTING: I would like to add two comments of my own before we run out of time. The first is that on page 25, which is actually in the guidance document, there is a section called "Data Analysis." I think this whole section is inadequate. Normally when you design a study -- and this is basic science kinds of things that I'm about to say -- you design a study and you say what the primary outcome

measure is going to be. You say what the secondary outcome measures are going to be, and you say what the criteria are for acceptance.

This section really doesn't do any of that stuff. It is sort of a procedural thing that says what is going to be reported, but it fails to indicate what the primary indicators are going to be for safety or efficacy. I think the whole thing really needs to be rewritten. When you do that, what you are going to find out is that when you start dealing with adverse events for example in setting parameters for outcome measures, you are going to then have to deal with these definitions that we brought up earlier today.

The fine tuning of those definitions is going to set the acceptance parameters. For example, if you define secondary elevation of intraocular pressure in one way, then the acceptance parameter is going to be at one level, and if you define it in another way, then it will be at another level. So those two things are tied to each other very closely. I think there is an enormous amount of work that really needs to go into this.

MS. LOCHNER: Dr. Stulting, the reference PDP does have the adverse event endpoints added and the definitions.

DR. STULTING: What is the primary outcome measure to be for safety analysis?

MS. LOCHNER: For IOLs we have never identified a primary. It has been all the items on the Grid.

DR. STULTING: That is my point, that we need to say this is what our safety analysis will consist of. This is our primary outcome variable; these are our secondary variables; and here is the acceptance level. This is basic science.

MS. LOCHNER: Well, from the standpoint that we have outlined all the items in the Grid. This reference PDP includes the most up-to-date guidance. This information where we have outlined all the endpoints from the Grid will be in the FDA guidance document. Unfortunately, it was a timing issue that you have an older version of the guidance. You have the September 5th edition.

It has already been revised to include the information that is in the reference PDP, which is a listing of all the adverse events we are collecting information on. It currently refers the reader to the 1983 Grid, because that is all that we have published.

DR. STULTING: I understand all that.

MS. LOCHNER: So you are saying you want to take

it one step further and specify one of them as the primary, and all the rest as secondary?

DR. STULTING: When you evaluate a drug to treat cancer, you say my primary outcome measure is death and life, and I will accept that it is effective if it reduces the death rate by 50 percent or something like that. We need an equivalent measure when we are evaluating devices. We need to define what we are going to accept for an endpoint, what needs to be measured, and what the criteria are. I don't know how to say it more clearly. Am I saying something that no one agrees with?

DR. MC CULLEY: I'm not sure I understand; I might or might not. We have multiple endpoints, and I'm not sure that I would necessarily want to pick one as being primary and relegate everything else to secondary and so on.

DR. STULTING: It also has statistical implications, because the evaluation of statistical significance depends upon what criteria you establish before the study is initiated.

MS. LOCHNER: We included the statistical analysis for the whole range of adverse events.

DR. GORDON: I think typically you were describing a drug study. In a drug study you would have a primary

efficacy outcome and define what the target is, and maybe also some secondary, but I don't think it's even appropriate to think of identifying a single adverse event or safety outcome as a threshold. You would look at the overall incidence of each event, the way the Grid does, and the Grid establishes a threshold of a sort for what is and what isn't acceptable.

DR. STULTING: The Grid, remember, does not establish that threshold. That's what we have been discussing.

DR. GORDON: But you also hear that this group could decide that the Grid does establish that threshold.

DR. STULTING: Yes, except we don't have anything except the 1983 Grid. We may not get any future Grid, and you can't use PMA data as a threshold.

DR. BULLIMORE: I'll step up and give a primary outcome measure. Primary efficacy outcome measure is visual acuity. Primary safety outcome measure is loss of visual acuity.

DR. STULTING: I agree. Those are the things that we should be discussing, and loss of visual acuity is different from total adverse event rates, although we ought to be talking about where they fit in too, because that is

important, et cetera, et cetera.

From my perspective, there is no fundamental difference in a drug study and an IOL study. This is just science. It is just plain science. You have to set up your study beforehand, identify your outcomes measures and set up criteria, and we ought to be going down those lines.

I have one real concrete complaint, and that is somewhere in here the optic diameter is given as 4.25. That would be on page 8 in the intraocular lens guidance draft document appendix under optical testing, B, clear optic diameter.

MS. LOCHNER: This refers to the clear optic diameter, the part that is refractive. We are saying positioning holes haptics can't infringe on the central 4.25. If they do, additional requirements may result.

DR. STULTING: Do you have a criteria for the overall diameters?

MS. LOCHNER: No.

DR. STULTING: If someone had a one piece implant with a 4.25 optic, it would fit into this definition with no positioning holes?

MS. LOCHNER: What this is saying is that the central 4.25s must be clear. It doesn't say that the optic

size itself has to be 4.25.

DR. STULTING: But if someone submitted a one piece, no positioning hole lens with a 4.25 optic, then it would be acceptable, is that correct?

MS. LOCHNER: We have only allowed down to 5, the optic body.

DR. STULTING: I didn't see that in here. Am I missing it?

MS. LOCHNER: The optic body diameter, which I believe specifies.

DR. STULTING: Well, without spending a lot of time looking for it, I think that number is too small, if I am interpreting correctly.

MS. LOCHNER: Yes, it's in the section that you didn't receive. The central 4.25 refers to the part that must not -- the positioning holes must not fringe upon. In another part we have a requirement that the overall optic size needs to be 5.5 or less. If they go less than 5.5, they may need to do additional testing to show that glare won't be an issue.

DR. STULTING: Okay. Any other comments?

DR. STARK: On page 8 it does say 4.25 millimeters for the optic diameter.

MS. LOCHNER: Clear body optic diameter, which refers only to the portion of the optic which contributes refractive power. We're saying you can't infringe upon that portion. When you get below 4.25 there would be additional requirements for testing. The overall diameter has to be 5.5 or greater.

DR. BANDEEN-ROCHE: Dr. Stulting and Dr. Bullimore's comments just raise a question in my mind. Just how automatic is this process ultimately supposed to be? In other words, I get a little bit of the sense we really want to streamline things, and that's all good. We'll set up something in advance, and if we check things off, then they are done. That is easier if we can identify a very limited set of endpoints, but if not, then statistically by chance we expect findings, at which point it seems that it becomes less automatic, and there is iteration needed about scientifically what's going on.

MS. LOCHNER: FDA will still review the information that comes in. If all the standard endpoints meet the criteria identified, that would be considered a success. If an unusual result occurred, and we felt that result could impact safety and effectiveness, we would bring that before the panel to determine whether there were

concerns with approval of the lens.

This is meant to set up a system which with most of the studies is just a matter of them meeting the criteria. We don't always see unusual results.

DR. STULTING: Any other comments?

DR. HIGGINBOTHAM: In the midst of that heated discussion earlier Mark had asked the question about iris color and the influence that that might have on drug efficacy, and there is definitely an impact, specifically with anti-glaucoma medications.

DR. BULLIMORE: I was aware of that, Eve. I just wanted to know how the drug folks approached that on their panels. Dr. Chambers has probably got an answer at his fingertips.

DR. CHAMBERS: Wylie(?) Chambers, FDA.

In all drug trials it is required that it be recorded. The basis for that is we know that it affects a number of different things, both drugs, as well as things like inflammation, as well as things like pupil dilation. Your pupil dilation will affect what some of your postoperative complications are.

So if you were to run a trial which had only light color irises, you can expect less postoperative adverse

events to occur in a couple of different categories, and you would never notice it. So it would not compare against what you are typically used to seeing. If you don't at least record what type of percentage of light colored irises versus dark colored irises you have, you will never know it.

DR. STULTING: How do you handle that? Do you require inclusion of a certain segment of diverse iris colors? Or do you just review it when it comes in?

DR. CHAMBERS: We review the data when it comes in. We would not accept a series of studies or a study that had less than -- the general guidance we have given is less than either 20 percent of either all light colored irises or all dark colored irises. The times when it has most significantly affected things have been the Scandinavian trials, where you have virtually all light color irises, and you see different results occur.

As long as you don't exceed the 20 percent on either side, we have not thrown studies out, but we do look at that.

DR. STULTING: We probably ought to go back and at least say something, try to come to a consensus on this, because it is a big data collection issue. Race has always been collected and always been shown, as far as I know, and

it has always been analyzed, so that is in there.

Is the sense of the panel that iris color should also be included and analyzed?

DR. HIGGINBOTHAM: My opinion would be that at least it should be checked off in terms of at least noting, so that one could go back and do an analysis if necessary, but not necessarily ask that the companies submit an analysis as part of their package.

I do think this is an important issue. I suppose others on the panel do not, but since I live a lot with this issue, iris color and now with a new anti-glaucoma medication that can change iris color, and not knowing what influence that might have in terms of any IOLs that might come on the market, we just have so many unknowns here, it might be important to at least include one more box, not a whole page of data.

DR. BELIN: This is a question. I have been told in the past from some sponsors that anything that they have to collect, they have to analyze. Is that correct?

MS. LOCHNER: My understanding is that after we collect a report -- about a product from whatever --

DR. BELIN: But you don't have to analyze it?

MS. LOCHNER: You have to do something with it.

DR. BELIN: I just want to get back to the point. Realize these little things we ask end up having to be analyzed. It means they have to be stratified. It means they have to go through statistics, et cetera. So it's a little thing to do up front for us to check off, and it may be valid in drug studies, it may be valid in some other studies, but we have a fairly big historical base on IOLs that it does not appear to be a point of major safety or efficacy.

DR. GORDON: Maybe I could add one comment in regard to an unanticipated outcome or deposits or something that we don't know, that we might not see in the future with a new material or something. I can assure everyone on this panel that when there is a lens that suddenly has deposits, or lenses that yellowed or discolored, many, many of the medical monitors, the company staff, everybody is looking at that patient. That patient comes in a lot, and understanding is gained of what has happened there.

So iris color would be readily identified in those situations. That doesn't speak to though, understanding the effect of iris color overall in a lens study, but I do think that when there is a problem with a patient, we can identify iris color, because we are going to see that patient on

repeated occasions. I don't know if that is adequate.

DR. STULTING: At this point we have about 15 minutes left to go. I want to try to do our job properly and provide input on this. I would like to move to closure on this one. I think everybody has said what they want to say, and we're getting repetitive comments now.

I would like to just have a vote on this, and then I would like Donna to give us some feedback about whether you think we have properly addressed your questions. We really haven't stopped and done votes or anything, but maybe if you could identify some specific issues that you would like to have cleared up for you, we could vote on those in the remaining time. Would that be acceptable?

MS. LOCHNER: I think so, yes.

DR. PULIDO: I would like to make a motion that we recommend that for PDP where there has been no change in the kinds of chemicals used, rather minor changes, that we not look into the iris color situation, but rather when it comes to a major change in the chemical composition of the IOLs, which would not be then a PDP, that we ask that iris color be involved and used.

DR. MACSAI: Dr. Pulido, do you mean not biologically equivalent?

DR. PULIDO: Correct.

DR. GORDON: Marian, I'm not sure everybody heard you. Could you please repeat that?

DR. MACSAI: I asked Dr. Pulido if he meant for an intraocular lens that is not biologically equivalent to those previously approved, should we then look at iris color, and he said yes.

DR. GORDON: Can you define what you mean by not biologically equivalent? Are you saying a new material? You would want to see iris color for new material?

DR. MACSAI: Substantially different, not substantially equivalent.

DR. GORDON: So I would propose then that perhaps for a new material where there would be a phase one, an evaluation of the first 50 patients, that iris color be documented and included. Then if there are no issues or differences that in further patients there is no need for additional documentation of iris color.

DR. MACSAI: I don't think I can agree with that, Dr. Gordon, because phase one is 50 patients. On a new material, I don't know that we can necessarily find a significant difference with an N of 50.

DR. GORDON: It seems like everybody wants iris

color. I'm not going to say anything more.

DR. STULTING: How many people are in favor of recording and analyzing iris color for all materials, even the old ones? I don't see any hands.

How many are in favor of analyzing iris color for new materials, that is not substantially equivalent to ones that are now in existence and approved? I see five hands.

How many are in favor of not doing iris color for anything, even old materials and new materials? That's five.

I can't remember for the life of me what the other counts were. Did they add up to the right number?

PARTICIPANT: No, you had 5 out of 12. There are 12 votes.

DR. STULTING: There were two abstentions.

There is a sheet in your packet that says "Reference Product Development Protocol for Intraocular Lenses, Clinical Questions for Panel Discussion," that we should provide an answer to. I think that is what we are supposed to do during the last part of the meeting.

The first one is, "Does the reference PDP outline the information needed for an acceptable protocol?" Those that believe that it does, please raise your hand.

[Whereupon 11 members raised their hand.]

Those that believe it does not please raise your hand.

[Whereupon 1 member raised their hand.]

DR. BANDEEN-ROCHE: If I could just clarify, I think the key for me is the word "outline." I think it probably does outline the information, but I'm not sure that given this document, I would be convinced that a given study using it was going to come back with any good information.

DR. STULTING: Second question, have the correct endpoints been identified? Those who believe that it has please raise your hand.

[Whereupon 12 hands were raised.]

Those that believe that they have not, please raise your hand.

[No hands were raised.]

There were no hands, so that is 100 percent yes.

The third question is, have the appropriate pass/fail criteria been identified? I didn't write the question. Maybe the FDA could explain that.

DR. ROSENTHAL: I don't think we have provided you with a pass/fail criteria, unless you use the Grid.

MS. LOCHNER: I think what we have provided in the

current reference PDP is the 1983 Grid, because that is all we have available at this point.

DR. STULTING: How many think that the answer to that is yes? That would be no hands. How many no? One thinks that the appropriate pass/fail criteria have been identified, that is two.

[Whereupon there were two votes in favor of the pass/fail criteria.]

How many believe that the appropriate pass/fail criteria have not been identified? That is eight.

[Whereupon there were eight votes against the pass/fail criteria.]

So the message is that we have made progress, but have not yet identified the pass/fail criteria.

Are there any other questions that you would like for us to address on this issue?

DR. SONI: I am making a statement that the appropriate pass/fail criteria hasn't been supplied to the panel. Maybe this is an opportunity for the sponsors to set up and give us the data that they have to be able to put a new Grid together.

DR. STULTING: So what you are saying is that you would like to see data on existing intraocular lens implants

in a form that we could use for reference when we do this in the future? Would that be correct?

DR. SONI: Yes.

DR. STULTING: Since this is probably the fifth or sixth time that we have said that, I think it should be fairly clear at this point what it is we want.

MS. LOCHNER: Can I ask this question another way? The criteria we have outlined are what we have available today. The understanding is that these data would be updated once we have updated the Grid. I asked have we outlined the appropriate criteria given what we know today, which is not to preclude it from being updated in the future.

I asked primarily because you reached a decision today on a PMA and were able to decide that the endpoints were appropriate. My question or concern is that these answers seem to be discrepant. Maybe the question wasn't asked explicit enough.

DR. STULTING: Well, let me just take some liberty and make a comment. It was our impression, including mine, that we would come here with a presentation of information that was a compilation of past studies. We didn't get that.

So you are now asking us to provide this

information from other sources. I think many members of the panel would be willing to go out and glean that information from data that are publicly available or published. We would be, I think, happy to do that, but we need to be given that assignment, rather than the belief that they are going to be presented to us.

I would recommend that we, as a group, come back later with this information, prepared to quote references and to provide it to the agency from our own experience, and from the literature.

MS. LOCHNER: I didn't want to take it quite that far. We have compiled the data that was included in the information. What we hope to be able to do is to get some type of waiver statement from the sponsors saying that they would allow for the purposes of compiling an updated Grid, allow this data to be used, not for the purposes of lowering any other sponsor's requirement, using their data to support approval of a new sponsor's PMA, but solely for the purposes of updating the Grid.

So I guess the framework we were working under is what we have available today is the 1983 Grid. What we presented to you earlier today was the updated Grid, which we acknowledge we need further information from the sponsors

to allow it to be released. We presented a proposal in terms of how the data would be compiled, and we presented a compilation of the data.

DR. STULTING: We need to address the problem very directly. Are we or are we not going to get compiled data from the FDA that represent past experiences with intraocular lens implants? That is, PMA summary safety and effectiveness data from the FDA?

MS. LOCHNER: If the sponsors allow it to be released, we will. We should know that maybe even by the end of the week.

DR. STULTING: I'm just saying that an alternative to this is for the panel to come to you with these numbers from elsewhere. Maybe we should discuss whether we should do this.

MS. LOCHNER: Or whether the 1983 data that we use today to assess a lens, is that sufficient?

DR. STULTING: I think that the panel has already gone on record on multiple occasions to say that the 1983 data are antiquated and not appropriate for today. Am I correct in stating this? Although we use them, that they are not appropriate.

DR. MC CULLEY: That's the best we have.

DR. STULTING: Because it's the best we have, but we would like better. Does the panel support what I'm saying?

DR. MC CULLEY: Yes, I fully support what you are saying. I would like to see the FDA come back to us with data. I understand that that means they have to get approval from industry. I would encourage industry to support the FDA's effort to do. If they do not, then I think we have to readdress the issue, and our alternatives would be to stay with the 1983 Grid, or to come in with data from the literature on our own, or with FDA's help.

DR. BELIN: I thought one of the original goals of the PDP was to come up with a set of performance criteria that if a sponsor met, the lens did not have to necessarily come to panel. To me there was nothing contradictory in what happened today. We took what we consider antiquated data. We listened to a lens being presented, and we used our clinical judgment to determine whether that lens met what we consider safety and efficacy data for approval.

What we're not comfortable in doing is using the 1983 data, and not have the company come to panel for both an example would be let's say if you looked at the rate of hyphema, which we talked about. It's higher now because of

the change in surgical technique. We understand that.

What we are saying is -- and it makes sense -- we understand what you have written here. We agree with it, but without the data that reflects more current reflection of both IOLs and surgical techniques, we are uncomfortable in not having a lens brought to panel for our discussion. If we are comfortable with the new data, then the answer would be yes, once we feel that those represent valid endpoints.

It goes back with what Dr. Stulting was saying earlier. We don't have these endpoints. We don't have what is our primary goal, what is our secondary goal, what is our safety, what is our efficacy. We really can't because we don't have the more recent data. So I don't see a contradiction to what we are saying in what we did.

DR. ROSENTHAL: I don't either, and I know you have been hamstrung, and I apologize that you have been hamstrung, but that is the law, and we have been told we have to obey the law, ergo, you had to be hamstrung, and you will be hamstrung tomorrow in the same way.

What we needed from you, I think we have received. We do understand that you are frustrated in not being able to have that data. We will do everything in our power to

get that data. We didn't really know we couldn't do this until early last week, and it was impossible to get even a legal opinion relating to the waivers as quickly as we wanted to.

Hence, we will try to do what the panel wishes us to do. We are delighted that you have given us the other option, which is if we cannot do what you would like us to do, that we come back to you and ask you do what we need to be done, and we are delighted that you have given us that option, so thank you very much.

DR. BELIN: Is it inappropriate or is it advisable for us to ask our professional organizations to contact industry and support this, asking them to basically release their data?

DR. ROSENTHAL: Well, I think we should first try to get these waivers and see. The industry helped us develop the Grid. I don't know what their response is going to be when we are asked to use the data from their PMAs to produce the final Grid. They were there when the new proposed Grid was established.

DR. STULTING: It isn't going to be quite as simple as it seems, because of the contemplated definition changes in some of these adverse reaction rates, and the

fact that we are grouping some together, these numbers are not going to just fall out of the past data. We are going to have to think about them when we establish them as acceptance criteria. I would recommend getting those out of whatever we can find early, and allow panel members to look at the literature and try to then get some good numbers for us to work with.

DR. ROSENTHAL: I agree.

DR. STULTING: I'm sorry, I didn't mean to cut you off.

DR. GORDON: I just wanted to add a comment that I agree with Dr. Rosenthal in terms of going to the professional organizations. Companies haven't yet been contacted provide these waivers, so before there is arm twisting, I suggest we be given the opportunity to do that.

Additionally, Donna mentioned that within a week there may be a response. There has been a group that has been meeting regularly, an industry group on this document. They are meeting for a whole day pre-Academy, and I'm guessing that this will be a subject of discussion. I'm also guessing that those of us from industry who are here will have a few days to think about it and make the decision. So it may be quicker than you think.

DR. MACSAI: I move we adjourn.

DR. STULTING: We don't have to vote on that, I don't think. If nobody objects, we are adjourned.

[Whereupon the meeting was recessed at 5:05 p.m., to reconvene the following day, Tuesday, October 21, 1997, at 8:30 a.m.]