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(202) 546-6666

PARTICIPANTS

Voting Members:

James P. McCulley, M.D., Chair

Mark A. Bullimore, MCOptom, Ph.D.
Eve J. Higginbotham, M.D.
Marian S. Macsai, M.D.

Consultants:

Jose S. Pulido, M.D.
Joel Sugar, M.D.
Janice M. Jurkus, O.D.
Frederick Ferris, M.D.
Michael G. Harris, O.D., J.D.
Clifford A. Scott, O.D.
P. Sarita Soni, O.D.

Discussants:

Lynn Morris, Consumer Representative
Marcia S. Yaross, Ph.D., Industry Representative

Guest Speakers:

H. Dwight Cavanagh, M.D., Ph.D.
Oliver D. Schein, M.D., M.P.H.
Brien A. Holden, Ph.D., D.Sc.
Roger L. Tabb, O.D.
Harue J. Marsden, O.D., M.S.

Food and Drug Administration Participants:

Sara M. Thornton, Executive Secretary
A. Ralph Rosenthal, M.D.
Nancy C. Brogdon
Donna R. Lochner
Morris Waxler, Ph.D.
James F. Saviola, O.D.
Malvina B. Eydelman, M.D.
Bernard P. Lepri, O.D., M.S., M.Ed.
Jan C. Callaway

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Daryl L. Kaufman
Karen F. Warburton, M.H.S.

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PROCEEDINGS

DR. McCULLEY: I'd like to call the meeting to order, please, and can everyone hear me in the back? Brien, can you hear me? Good.

I'd like to turn the meeting to Sally Thornton for some introductory remarks.

MS. THORNTON: Good morning and welcome to all attendees. Before we proceed with today's agenda, I have a few short announcements to make.

During the break this morning, you may purchase coffee, tea, et cetera in the cafeteria. Water fountains are available in the corridors adjoining the conference room area, and I notice that we have, thanks to Dr. James Saviola, water on our tables, candy on our tables. God is good.

[Laughter.]

MS. THORNTON: And Jim is good.

And we certainly do appreciate that. Messages for the panel members and FDA participants, information or special needs should be directed through Ms. Ann Marie Williams, who is over here at the head door behind the table and Ms. Gloria Williams, who is at the back registration table.

Will all meeting participants today please speak into the microphones so that the transcriber will have an accurate recording of your comments? Now, I'd like to take time to extend a special welcome and introduce to the public, the panel and the FDA staff three panel participants who have recently joined the Ophthalmic Devices Advisory

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Committee and are panel participants for the first time. To my right, Dr. Janice Jurkus, panel consultant, is associate professor of optometry at the Illinois College of Optometry in Chicago. She has lectured and published extensively on contact lens materials and design, clinical complications, patient education and informed consent and is internationally recognized for her expertise.

Across from me, Ms. Lynn Morris, the consumer representative, is the communications coordinator and magazine editor for alumni relations at the University of California in San Francisco. She has previously served the Food and Drug Administration advisory committees on the Dental Devices panel, the ENT Devices panel and the Ophthalmic Devices panel.

Sitting next to her, Dr. Marcia Yaross, who is our industry representative, is a full-time employee of Allergan in Irvine, California. In her position as director of worldwide regulatory affairs and medical compliance, she has responsibility for the products reviewed by the Ophthalmic Devices Advisory Panel.

To continue, will the remaining panel members please introduce themselves, beginning on my right? Dr. Pulido?

DR. PULIDO: Jose Pulido; I'm professor at the Medical College of Wisconsin in Milwaukee.

DR. BULLIMORE: Mark Bullimore; assistant professor, the Ohio State University College of Optometry.

DR. McCULLEY: Jim McCulley, professor and chairman of the

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Department of Ophthalmology, U.T. Southwestern Medical School.

DR. SCOTT: I'm Clifford Scott. I'm a professor of optometry at the New England College of Optometry and at the VA Medical Center in West Roxbury, Massachusetts.

DR. MACSAI: Marian Macsai, professor of ophthalmology, West Virginia University.

DR. HARRIS: Michael Harris, associate dean and clinical professor of optometry at the University of California School of Optometry, Berkeley.

DR. SUGAR: Joel Sugar, professor of ophthalmology, University of Illinois at Chicago.

DR. HIGGINBOTHAM: Eve Higginbotham, professor and chair, University of Maryland in Baltimore.

DR. SONI: Sarita Soni, professor of optometry and visual sciences and associate dean for research at Indiana University.

DR. ROSENTHAL: Ralph Rosenthal, director, Division of Ophthalmic Devices, Office of Device Evaluation.

DR. KAUFMAN: FDA.

Notes on the agenda: the open portion of the meeting will adjourn at approximately 3:30 p.m. to allow for a closed session for presentation of data to the panel. The allotted hour for the open public hearing presentation has been split today into two 30-minute periods, to be held at the beginning of the morning and afternoon sessions. The

speaker time allocation given in the printed agenda is in error. The speakers are being given 5 minutes for their presentations.

Next, I would like to proceed with the conflict of interest statement for today's open session. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their 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 interests of the Government.

A waiver has been granted to Dr. Janice Jurkus for her involvement with a firm at issue that could potentially be affected by the committee's deliberations. The waiver allows her to participate fully in today's discussions. A copy of this waiver may be obtained from the agency's Freedom of Information Office, Room 12A-25 of the Parklawn Building. We would like to note for the record that the agency took into consideration certain matters regarding Doctors Michael Harris and Eve Higginbotham. Doctors Harris and Higginbotham reported recent or current involvements in the form of contracts, grants and speaking engagements with firms at issue.

Because these involvements are not related to the general matters before the panel, the agency has determined that they may participate in today's discussions. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse himself or herself from the involvement, and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon. The agency would also like to note for the record that Doctors H. Dwight Cavanagh, Brien Holden, Harue A. Marsden and Oliver Schein, who are guest speakers here today, have acknowledged professional relationships with firms that manufacture contact lenses. These professional relationships are in the form of grants and/or contracts for research, consulting and speaking arrangements.

Thank you.

[Pause.]

DR. McCULLEY: We'd like to open the open public hearings at this point. I'd like to remind the speakers, please, to identify yourself and any conflicts that you may have that should be disclosed. And Sally has remembered one more thing to do.

MS. THORNTON: The speakers who will be making presentations before the committee are doing so in response to the panel meeting announcement in the Federal Register. They are not invited to speak by FDA, nor are their comments, data or products

endorsed by the agency. Scheduled speakers are given a 5-minute limit. After they have spoken, the chair may ask them to remain if the committee wishes to question them further.

Only the chair and members of the panel may question speakers during the open public hearing. I'd like to note for the speakers that if you do not complete the presentation of your text due to time constraints, the remaining portion will be entered into the docket of records for this meeting. Dr. McCulley will recognize unscheduled speakers as time allows.

In the interest of time, I would like to ask any of the scheduled speakers who are not already sitting in the designated section or on the front row or close to the front to move there now so that you can be ready as soon as the person in front of you has finished. Presentations will be made in the order in which the reservation for speaking was made.

Dr. Peter Bergenske will now begin his presentation.

DR. BERGENSKE: Good morning. My name is Peter Bergenske. I'm an optometrist. I'm the current chair of the section on cornea and contact lenses for the American Academy of Optometry, and I would like to read for the record a letter from the president of the American Academy of Optometry. This letter is submitted on behalf of the American Academy of Optometry in response to the invitation for data, information or views pertinent to the Ophthalmic Devices Advisory Panel of the Medical Devices Advisory Committee discussion of clinical testing guidance for extended wear contact

lenses.

By way of background, the American Academy of Optometry was founded in 1922 and represents nearly 5,000 optometrists, vision scientists and optometric students. The objective of the American Academy of Optometry is to promote and enhance excellence in vision care by fostering research and disseminating knowledge in vision science. Given the well-documented increased risks associated with overnight wear of currently-available extended wear lenses compared to daily wear, removal of contact lenses prior to sleeping is advisable for the vast majority of contact lens wearers.

Safer extended wear is probably an achievable goal for the contact lens industry, and its quest should be encouraged. Patients want convenient, comfortable and safe contact lenses. If safety and comfort were assured, the convenience of not needing to remove and clean lenses on a daily basis would have significant appeal and benefit. Patient safety, however, must remain the overriding concern, and it must not be forgotten in the effort and zeal put forth to develop new lens products.

Human nature dictates that strict adherence to stringent practices is unlikely. So, systems and products must have safety profiles that allow for deviation from perfect practice by both clinician and wearer. The American Academy of Optometry extends its encouragement and support to this panel as it develops clinical testing guidelines for extended wear of contact lenses. The academy and, in particular, its section on cornea and contact lenses, has a keen interest in this subject and in this project.

Please do not hesitate to contact me should you desire further clarification

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or input. Thank you for your opportunity to comment on this important issue. It's signed sincerely, Gerald D. Lauther, president, American Academy of Optometry. Thank you.

DR. McCULLEY: Do any of the panel members have questions?

[No response.]

DR. McCULLEY: We'll go on, then, to the next speaker, Bruce Ishimoto, president, OcuMetrics, Incorporated.

DR. ISHIMOTO: My name is Bruce Ishimoto. I am the president of OcuMetrics, Inc. in Mountain View, California, and I'm here today representing OcuMetrics.

Fluorophotometry has been used in contact lens research almost from the beginning. A number of useful fluorophotometric techniques have been developed which may be used to evaluate the condition of the eye following contact lens wear. Today, I will concentrate on three of these applications that we feel are of particular interest in evaluating the safety of extended wear contact lens designs.

The applications that I will discuss are corneal pH, tear flow, tear turnover under contact lens and corneal epithelial permeability. We are indebted to Doctors Kenneth Polse, Joseph Bonano and Nancy McNamara of the University of California for their participation in this work. This group has written a review article outlining these techniques. This article has been accepted for publication in Optometry and Vision Science. The authors and Dr. Mark Bullimore, the general editor, have graciously given me the permission to distribute pre-publication copies of this manuscript.

In 1987, Bonano and Polse first described the use of a non-invasive fluorophotometric technique for measuring human in vivo stromal pH. Basically, the theory of the measurement is based on the principle that the fluorescein molecule contains pH-sensitive charged groups. Two different fluorescence intensity values are obtained when fluorescein is excited with wavelengths of blue light at 490 and 450 nanometers, and the ratio of these intensities is pH-sensitive.

For human in vivo measurements of corneal pH, the stroma is first loaded with 2 percent fluorescein by instilling drops every 5 minutes for 20 minutes. After the last drops, the eyes are closed for 30 minutes and then thoroughly rinsed with saline to remove residual dye. The subject is placed in front of a fluorophotometer and aligned. The instrument automatically focuses on the cornea and measures 100 fluorescence ratios, applying computer algorithms for blink and movement correction. Measurement time is approximately 15 seconds.

Fluorescein was loaded into the corneal stroma of 12 subjects. Two hours later, a thick, low water content contact lens was placed on the cornea, and the fluorescence intensity ratios were measured through the lens. Lines indicate lens on and off. Although this illustrates an extreme lens, this effect is also observed in even the most gas permeable experimental lenses during sleep.

Tear turnover can be determined by measuring the disappearance of a fluorescent dye from under a contact lens. Two microliters of 7 percent FITC-Dextran is placed into the contact lens concavity using a micropipette. The lens is inserted directly

under the cornea, and fluorescence readings are taken within 1 minute. Readings are then taken at approximately 3-minute intervals for 30 minutes while the blink rate is maintained at 15 blinks per minute.

Tear flow estimates under soft contact lenses are very low compared to rigid lenses. Ninety-five percent turnover is achieved in 29 minutes with soft contact lenses, compared to only 6 minutes for rigid lenses. This figure gives a comparison of tear flow under various soft overnight-wear contact lenses.

To determine epithelial permeability, a micropipette is used to deliver 2 microliters of 0.35 percent fluorescein onto the central superior bulbar conjunctiva of the subject's left or right eye, and the subject is instructed to close and roll his or her eyes in order to achieve--to evenly distribute fluorescein to the tear film. The same eye is scanned within 45 seconds after dye installation. Following this scan, the same procedure is repeated on the fellow eye, and the two eyes are then scanned alternately every 2 minutes for the next 20 minutes. To determine the amount of dye that penetrates the epithelium, both eyes are thoroughly rinsed three times with non-preserved sterile saline, and stromal fluorescence levels are measured five times over the next 10 minutes.

This figure displays the effect of one hour of eye closure with and without contact lens. Logged permeability measurements for each control and contact lens eye are shown. The mean difference corresponds to an average increase in permeability of 41 percent for eyes exposed to only one hour of contact lens-induced hypoxia, compared to the contralateral eye that was closed for 1 hour without contact lenses. Interestingly, this

mild corneal trauma typically did not produce a detectable difference between paired eyes in either slit lamp or corneal thickness measurements.

The OcuMetrics fluorophotometer is a tabletop clinical device controlled by its own computer. The tests are turnkey operations that can be performed by a technical or clinical assistant. In the case of clinical trials, our company can modify the control and analysis software to tailor the device precisely to each protocol.

In summary, fluorophotometric measurements can be made of corneal pH, tear turnover under contact lens and epithelial permeability. These test may give more sensitive measurement parameters and, thus, a better understanding about how contact lens designs behave in vivo.

The OcuMetrics fluorophotron master provides turnkey operation in performing these tests for clinical evaluation.

DR. McCULLEY: Thank you.

Do any of the panel members have questions for Dr. Ishimoto?

[No response.]

DR. McCULLEY: Seeing none, we will move forward.

Mr. Thomas Henteleff, general counsel, Contact Lens Institute.

MR. HENTELEFF: Good morning. I am Tom Henteleff, and I am here on behalf of the Contact Lens Institute, an association of research-oriented manufacturers of contact lenses and lens care products. Its members are: Alcon, Allergan, Bausch and Lomb, Biocompatibles, CIBAVision, CooperVision, Vistacon and Wesley Jessen.

The Contact Lens Institute and its member companies are dedicated to developing and marketing the safest, most effective and most convenient contact lenses and lens care products that evolving science allows. The existing database concerning extended wear contact lenses shows that, while not risk-free, today's extended wear lenses provide a safe, effective and convenient vision correction alternative.

These data include the seminal Oliver Schein et al. extended wear studies funded by the Contact Lens Institute and years of clinical experience with extended wear contact lenses. The research-oriented contact lens industry is always looking to develop new materials and products which will further enhance the safety and effectiveness of contact lens wearers, including safely increasing wear time for extended wear contact lenses.

The industry strongly believes that before new materials and new conditions of use are introduced into the marketplace that they should be shown by appropriate clinical studies to be safe and effective under the recommended conditions of use. Thus, we are looking forward to working with the FDA and this advisory panel to update the 1989 extended wear lens guidance document to provide guidelines for clinical testing which are based upon the latest scientific knowledge.

The goal of this effort should be to provide the statutory required assurance of safety and effectiveness without imposing unnecessary or unduly burdensome pre-approval testing requirements.

I thank you very much, and if there are any questions, I would be happy to

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respond.

DR. McCULLEY: Thank you.

Are there questions?

[No response.]

DR. McCULLEY: None; thank you.

MR. HENTELEFF: Thank you.

DR. McCULLEY: The next speaker is Cristina Schnider, representing Menicon.

MS. SCHNIDER: Good morning. My name is Dr. Cristina Schnider, and my position is director of professional relations and clinical affairs at Menicon USA. I'd like to thank the panel and the agency for allowing me this time to present my opinion on the extension of overnight wearing time beyond 7 days. I present my opinion based upon my experience as a clinician and a researcher in the field of contact lenses and especially rigid lens extended wear over the past 15 years.

While I defer to the experts invited by the agency in discussion of the current scientific data, I wish to make a few points regarding the consideration of rigid versus soft lens relating to performance, predictability and risk. The first issue is to consider simply the term extended wear. In most people's minds, both patients and practitioners, the term refers to overnight wear of contact lenses but more specifically to soft contact lenses, despite the fact that rigid lenses have been approved for up to 6 nights' extended wear for the past decade.

This is not surprising in light of the market penetration of soft lenses versus rigid, but it has obscured some basic differences between the two modalities. Key differences include oxygen transmissibility, corneal coverage, movement and tear exchange and the ability to predict complications before entering into an extended wear regimen. While oxygen transmissibilities of investigational soft contact lenses are finally nearing the century mark, those of some currently-marketed rigid lenses exceed those by half. In addition, rigid lenses typically cover less than 80 percent of the corneal surface, whereas, soft lenses cover the cornea completely, including the immunologically sensitive limbus and vascular conjunctiva.

Further, the minus-powered soft lens presents the thickest and least permeable part of the lens to the vascular limbus and peripheral cornea. This, combined with very limited movement, creates a possible stimulus for inflammatory reactions and, perhaps, for infective processes, as proposed by Dr. Suzanne Fleissig in her recent publication in CLAO.

Even though it has been well-established that both rigid and soft lenses are basically immobile during sleep, rigid lenses do provide for adequate tear flow and flushing of debris during open eye periods, thus limiting the potential for beginning overnight wear with a backlog of debris and/or bacteria under the lens.

The final clinical reality that strikes me is that most of the complications which would preclude success with an extended wear rigid lens regimen would be observed during a short daily wear period. Most serious ocular surface complications and

tear lens incompatibilities occur within a few days with rigid lenses, and inflammatory complications are exceedingly rare with these lenses, even on an overnight wear schedule. With soft lenses, however, there are few good daily wear indicators which would warn against an overnight schedule. Lens adherence has been suggested as a potential problem with rigid lens extended wear, but this can be easily detected by patient self-assessment and by the practitioner at a routine morning visit and/or during patient self-monitoring.

If the signs are observed, extended wear can be discontinued if the problem cannot be remedied by design changes or self-monitoring. Other changes commonly seen with rigid lenses, such as corneal sphericalization and minor topographical shape changes are hardly sight-threatening and occur with roughly equal frequency as with daily wear lenses.

The final point I would like to address is the issue of labelling, a duty I believe the agency and the panel take quite seriously. I believe it is incumbent upon all of us in the field to strive to give the most honest and accurate assessment of risks and benefits associated with any medical device or procedure. We know from experience, statistical models and common intuition that there is always a range of response to any procedure and that current clinical practice gives us precious few guarantees about where a given patient will fall on this continuum.

Therefore, I would propose that future studies for marketing approval are designed to attract the broadest possible audience, which would be more truly representative of the refractive correction-seeking public rather than studies designed to

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produce stellar results. Anyone interested in statistics, research or marketing knows of the quip "how to lie with statistics." We can all make our studies look pretty, but other than making our marketing departments happy, I fail to see what good such tidy results do us.

I would ask that the panel and the agency consider a more liberal approach to patient entry and success criteria, asking not what percentage fit the ideal category at the end of the study but more seriously evaluating what happened to them along the way and whether they are representative of the greater public. Labelling and advertising claims might then reflect a clearer reality; for example, that while 5 percent of patients successfully wore this lens for 30 days or more, 80 percent of them were at 7 days or less, as opposed to a new, 30-day extended wear lens. Those who wore their lenses for daily wear or 4 to 6 nights extended wear are not necessarily failures; simply points along the continuum we expect to see in biological systems.

I thank Ms. Thornton, Dr. Saviola, members of the panel and agency for the time to address this group. Thank you.

DR. McCULLEY: Are there questions?

[No response.]

DR. McCULLEY: Is there anyone in the audience who wishes to be recognized to come to the podium and make a statement?

[No response.]

DR. McCULLEY: Seeing none, this closes the open public hearing, and I would now like to begin the open committee discussion, and I believe we're beginning

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with division updates and Dr. Rosenthal.

DR. ROSENTHAL: Thank you, Mr. Chairman.

As you know, the FDA Modernization Act of 1997 was passed in the autumn of last year, and I wanted to advise the panel and the audience that the notice entitled FDA Modernization Act of 1997, Guidance for the Device Industry on Implementation of Highest-Priority Provisions, went on public display on February 5 in the Office of the Federal Register and was published in the Federal Register on February 6. This document can be obtained on the FDA Website, which is www.fda.gov and then go to FDA modernization information.

It contains all of the provisions of the new act; a timetable of the implementation and many of the issues which, I think, will be of interest to both the panel and to the members of the audience. Thank you, Mr. Chairman.

DR. McCULLEY: Thank you, and any questions for Dr. Rosenthal or comments from the panel?

[No response.]

DR. McCULLEY: It's the branch updates; Donna Lochner?

MS. LOCHNER: Thank you.

I'd like to just briefly update the panel on the status of premarket approval applications that have been previously brought before you. First, in July of 1997, you reviewed Mentor Corporation's PMA P-96-0036 for their memory lens posterior chamber IOL. I'm pleased to report that this lens was approved by the FDA on December 22,

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1997.

Second, in October of 1997, you reviewed Pharmacia and Upjohn's Heparin Surface Modified Posterior Chamber IOL, which was PMA P-96-0034. FDA is currently working with the company to resolve the remaining technical issues.

And last, in January of 1992, you reviewed Closure Medical Corporation's Nexacryl corneal adhesive, which is PMA P-91-0057. Again, we are working with the company to resolve the remaining technical issues.

Thank you.

DR. McCULLEY: James Saviola?

DR. SAVIOLA: Good morning.

I'd like to make a couple of brief comments to update the panel regarding contact lens care products, which are now regulated under Class 2 and also the two retinal tamponades which were approved back in September of 1997.

Since the reclassification of contact lens products became effective in July of 1997, the branch has received a total of 13 510(k)s for those devices, 10 of which have been for a lens solution type of product. There was a little bit of a lag in receiving those applications at first, but we have seen most of them recently. Many of those are still currently under review.

The total number of 510(k)s received in our branch since July 1 has been 33. That includes the care products and lenses as well. Of the 510(k)s we've cleared for marketing under Class 2, so far, one would have been a new PMA, for an RGP liquid

enzyme product. A second was for a change in chemical preservative system for an existing device which had already been approved under PMA, and that would have been a supplement; it would not have been a new PMA.

As for the retinal tamponades, the branch has received the final print labelling for the Richard James Silicone Oil 1000 Senistoke and also for the Vitrophage Vitrion product. Therefore, the final conditions prior to marketing those devices have been satisfied and, to our knowledge, are currently on the market.

Thank you.

DR. McCULLEY: Okay; any questions for Dr. Saviola?

[No response.]

DR. McCULLEY: I guess, then, Dr. Saviola, would you like to introduce the next topic, which is development of extended wear contact lens clinical testing guidance? And before you do that, let me try to state what I think the charge is to the panel, and that is to address effectively and to our best ability the list of questions that have been provided to us which were also provided to our three invited guest speakers.

And I would like to put my own little editorial comment in here. I think our job is to try to answer those questions to the best of our ability in the time allotted. We have a lot of expert opinions here and a lot of information that I think we could share that might not directly address the questions, so that those of you on the panel, I think, understand and those of you who are the invited participants understand our role is to try to answer the questions that have been put to us, and we need to try to spend our time and

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direct our efforts toward answering those questions.

There is a lot of information that we could share, but this is not necessarily the forum, unless the comments relate to the questions that have been posed to us. Is that a fair assessment of the charge to the panel?

DR. SAVIOLA: Yes, sir; I would agree with that.

As this is Dr. McCulley's first meeting as chair, I'm glad to see that he's starting out with some clear statements of leadership and direction to keep us focused on the discussion this morning.

DR. McCULLEY: Well, we've got a lot of expert opinion around here today.

[Laughter.]

DR. McCULLEY: And we can't share all of our expertise, or we'll be here until God knows when. So--and knowing many of the participants and the depth of their knowledge, this is--

[Laughter.]

DR. McCULLEY: This is self-protective. I want to come out looking like a nice guy at the end, not someone who's having to cut off the discussion.

Okay; with that, let me turn it back to you.

DR. SAVIOLA: Thank you very much.

As the panel members have received in their mail-outs, we did provide some background information as to the reason why and also, as Dr. McCulley stated, the

purpose for these discussions. For the benefit of those in attendance, we have been faced with the challenge of developing some guidance for the product development protocol or the PDP program within the Office of Device Evaluation, and in view of that, we have found it necessary to have this discussion in an open forum so that we may be better able to provide guidance to the industry in terms of developing PDP.

Along with that, we have also been faced with the interest in developing new products that go beyond 7 days or 6 nights of extended wear. We had had a discussion a few years back in which we had mailed out questions, received the answers back, and we had discussion at the panel meeting based on those questions. In this case, we are having the discussion in a sort of real time situation rather than having mailed out questions and have everybody answer the questions directly.

The invited speakers who have graciously agreed to attend have a great deal of information to share with the panel and also expertise to potentially contribute to the discussion as it progresses. I would like to introduce the first speaker and make note that in the interests of time, we did provide the panel with some background information on the first speaker's procedure so that he would not have to go over the whole methodology aspect of his study.

Dr. Dwight Cavanagh has been asked to present information on his technique for measuring the effect of hypoxia on bacterial cell binding to corneal epithelial cells and its application in evaluating the effects of contact lens wear. This methodology represents a novel approach to investigate the physiological response to contact lens wear.

Dr. Cavanagh?

DR. CAVANAGH: Thank you very much, Dr. Saviola. Is that left--there it goes; there it goes. Are they in backwards? I had them correct but--

Thank you. I provided to the panel over 80 slides, I think, and I'm not, certainly, going to try to even remotely show all of them. I'm going to hit the highlights of the highlights. You have copies of the slides; so, you won't need to take notes, and you have background material on the rest of the slides that will fill in the details for you.

I want to thank the chair, Sally Thornton, Dr. Rosenthal and members of the panel for the opportunity to be of help to you. Where are we in 1997 with this problem of continuous wear that ties into the safety and efficacy of daily wear? And I think I've tried to summarize succinctly the Conventional Wisdom that I think we would all accept in some form or another of where we are. I think as far as safety and efficacy are concerned, ulcerative infectious keratitis is the major gorilla, the big problem of contact lens wear.

Although we blame it all on overnight wear, if we got rid of overnight wear entirely, we would still have ulcers and infections; perhaps a quarter to a half of the cases that occur in daily wear. So, although the industry is successful, perhaps 80 million people worldwide and 30 million in the United States wear lenses in one form or another, and although we are willing to accept the small risks that exist, and these will be delineated in detail by Dr. Schein, the fact is that we could do better, and I think we should.

We all had the hope 10 years ago that the introduction of disposable lens

use would reduce these problems, and unfortunately, I don't want to get into that fight; I will leave it to Oliver. I think we would all agree, big-C, big-W, that it's become a convenient way to use lenses. The public loves it. It addresses cost issues, but it has not really solved the problem of ulcerative infectious keratitis.

Now, the problem, as we all know sitting here, is that we don't have an outcome measure that prospectively can be measured in a clinical trial with a few hundred patients or less over, perhaps, a year or two that will allow predictability of the rare event of ulcerative infectious keratitis, 4 per 10,000; 20 per 10,000 later on. And there's no way you can ask industry to do that from a cost point of view, and it's just not possible prospectively using slit lamp criteria and corneal thickness and all of the other things we've used to predict what happens when the new lenses, whatever they are, get out into 2 or 3 million people later.

So, obviously, backing up to the beginning of the problem, if you're interested in ulcerative keratitis and infection, then, you need to go back to the drawing board and come up with a new approach, a new paradigm. It may be an overused word these days, but it's certainly applicable.

Well, about 5 or 6 years ago, our group started looking at this, and it just seemed a no-brainer if you will that you couldn't have an infection without the bug sticking to the eye; in other words, no corneal binding, no potential infection layer. And, therefore, the question then was what does the lens do to the eye when you put it on, and what does the lens of differing oxygen permeability do to the eye when you put it on in

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terms of altering the normal binding that exists to bacteria? We all know that patients don't wake up in the morning with pseudomonas ulcers.

So, we zeroed in on the alteration of the bacterial surface binding, and we were not the first to do that. I want to give credit to Dr. Fleissig and Nate Ephron for the first paper that clearly showed differences between extended wearers and no wearers in terms of altering surface binding to pseudomonas. And the \$64 question for the panel and all of us is would a new generation of materials change this equation satisfactorily? I.e., if you made hypertransmissible oxygen lenses, would they influence this bacterial binding question favorably?

In a simple-minded fashion, we just wanted to know why is overnight lens wear the big problem? That's what came out of Oliver's seminal New England Journal of Medicine paper with his colleagues. Why is this? The hypothesis is that if you don't have enough oxygen, the epithelium doesn't like that; produces damage. The damaged cells start making binding sites that bind more bugs, and this is a--whether it's overly simple; whether it's right or wrong, most importantly, it's testable.

Well, we tested it in animals 3 years ago and published this data, and we used pseudomonas because it was half the infections; it's the worst infection; it's the bug that sticks the most readily, and we felt that if we could solve a problem with that, we would have a leg up on the others. We picked a standard test organism, which is the world's standard microbiology pseudomonas that's used for all of the antibiotic testing. It's been used for a dozen years to test infections in cornea by various groups, and most

importantly, it's genetically characterized. Every base pair is sequenced. And you can, growing single colonies over years, you can make sure that you're dealing with the same genetic test strain during testing conditions.

We then spent a year standardizing the testing conditions to get enough efficacy and sensitivity, and I won't belabor that, because it's published, and you have that in your other slides. If you go to the results, what you find in the rabbit model, placing the lens on the rabbit eye for 24 hours, no lens wearer versus lens wearer, you find very distinct and important differences in the alteration of bacterial binding with lenses of different oxygen permeability.

And it's worth going over this slide in a little bit of detail. We break them into rigid lenses, soft lenses, standard hydrogels and the new hybrid hypertransmissible oxygen lens categories. If you look at the rigid lenses, what you find are the old PMMA, and with lenses of less than ideal oxygen transmissibility, these all alter bacterial binding to the surface of the eye with wear. However, when you get into the hyper Dk area, over 100 to 150 range, even with a rigid lens on the rabbit eye, you can come in the next morning, and you can't tell the eye has seen the lens either by bacterial binding or scanning electron microscopy, which was published in that paper.

Most worrisome and, in a way, expected, because we all know that conventional soft lens materials do produce problems, we found that the low water materials, the mid-water disposable materials and the high water materials all produced marked increases in bacterial binding with overnight wear in the rabbit. And it wasn't until

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we went to materials that were not on the market, and these were obtained simply by scrounging: telephone calls to every company and do you have something I can test? And we were able to find soft hybrid materials at that time of two companies that did not alter bacterial binding, and these were in the roughly 100 Dk/L range.

Well, the question was is oxygen the whole story? Well, oxygen is not the whole story, because you can go to a pure silicone lens, a silsoft lens. No one knows what the Dk of that is. I've been unable to find a good value, and I'm looking for one, and I would appreciate a reference if someone has one. Probably 300. Well, placing that lens on the eye produces among the worst type of increased binding. So, the lens not only has to be oxygen transmissible under this testing system; it also has to be user friendly and has to be hydrophilic, and this is another equally important need to be satisfied.

Well, these results were very encouraging, but rabbits aren't humans. So, we moved along rapidly towards a prospective, blinded, randomized single institution study, and we needed a surrogate measure in the human, because you can't put live bugs on the human eye. So, we adapted an irrigation collection exfoliation technique that was pioneered by Graham Wilson, where we collect only corneal epithelial cells from the rabbit shown on the top, the human shown on the bottom and no lens wear on the left and lens wear on the right, and under standard testing conditions, even in daily wear, even in daily wear over 6 hours, rigid and soft, we can detect differences in binding, reproducibly done in a blinded fashion.

So, with this technique standardized, and this is again published, we had to

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answer two important questions before moving on to do the clinical trial in humans, and that is can you relate exfoliated binding to total surface binding, which is what you want to measure? And if you can't, then, you don't have a study, and many people said, well, you're just irrigating off dead cells, and the binding doesn't reflect what's going on on the cornea, and that's a very legitimate question.

The thing is, though, we did that experiment. We related very nicely with a P value of 10^{-3} , the binding to exfoliated cells correlating with total surface bindings. So, that allowed us with confidence to move on to the human clinical trial. A subset question came out of that study, and that was that we observed binding to both sides of the exfoliated cells, and there were those who, perhaps, thought that was not physiological. I'm delighted to see in this month's CLAO journal that Dr. Suzanna Fleissig acknowledges now that in an organ model, that you get binding to both sides of the cells with pseudomonas. And so, I think that controversy has been put to rest.

Now, our clinical trial was sponsored by a variety of people. I will acknowledge it and including the National Eye Institute. And we finished it just a few weeks ago: 115 patients; 3-year prospective randomized single-center masked clinical trial using 10 test lenses, stratified from rigid to soft varieties of various decay that are shown, as you can see.

We used normal eyes, stringently observed. We went -1 to -5. We didn't want much cylinder, because people had to see during the study, and we had a 2-week transition from daily wear into extended wear, and we did our measurements based on

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controls at 24 hours, 1 month, 3 months of wear, and we had a concurrent control group totally matched that never wore lenses to look for seasonal variations in bacterial binding, and I will tell you now that that didn't show anything.

We calculated EOP by Benjamin's equation.

Well, here's what we found. It's not very good, I'm afraid, but it's reality.

Most of the lenses in the world are either low water hema or mid-water disposable and not picking on any of the companies--they're all the same--what you find is, in the human, from baseline, no lens wear, going from daily to extended wear over 3 months that you have an excellent correlation showing a very definite alteration of surface binding in the human eye over time with the low water lenses, a suggestion of some attempt to recovery with the mid-water lenses, which also is shown by the higher-water lenses, which I'm not going to show for reasons of time.

But this establishes definitively in the human that extended wear over time with the conventionally available lenses alters the bacterial binding behavior, and whether or not there are other mechanisms such as stagnation of bugs bound to the lens, it certainly goes a long way toward explaining for me why those lenses might show up with small but definite infection and ulceration rates.

The good news is that--and I show the rigid lens on the left and the hybrid soft-high Dk lens on the right for those of you in the back; I think the important thing is that these lines are flat. These high ultra-transmissible oxygen lenses don't do this. They just don't. And they do not alter in the same way the bacterial binding behavior to this

pseudomonas organism over time that the conventional lenses do.

Now, graphs are fine; numbers are better. And what I've done here is 3 months' wear for you, because at 24 hours going into extended wear, the eye can be a little red. We get correlations at 24 hours, 1 month and 3 months, but I'm going to show you 3 months' data in the interests of time.

When we first analyzed this data and showed it at the AAO meeting in San Francisco and the other AAO meeting in San Antonio, I had used a -3 standard median power because we were having trouble getting, from the companies, the exact thickness for every power, for every lens worn on every individual eye for 150 people plus the controls. I finally got those numbers, and that data is shown on the right, and I've shown it deliberately both ways. You can look at the spread, and you can look at the graphs. And this has important implications for how we do controls in the future. It turns out that the only valid control is the individual patient themselves, going from no lens wear to wearing a particular lens and the behavior of that eye over time.

You can compare different lens-wearing groups to different lens-wearing groups, but what you really don't want to do is a contralateral eye control, and you don't want to try to establish a separate control. But what you find here is at 3 months, you get an excellent correlation between EOP, a Dk/over L and log Dk. In fact, the log Dk of the material had the best predictive value in terms of not altering bacterial binding.

If you then do all of the data, that is, the individual thicknesses for every lens and every patient, you get an even better P value. For EOP, for example, it goes from

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0.008 to 0.002 or 0.004. So, I think this establishes, in my mind, the fact that certainly, with a hydrophilic lens, you're getting--a lens that's wettable, you're getting better oxygen transmission, and you're also getting less bacterial binding.

You can also look at this data, the Dk/L for the individual patients, and again, here, you see a distinct important PO₁/PO₂ value for the individual lenses.

Now, another finding came out of this which you do have to at least be aware of, and that is that all test lenses reduce the ability of cells to get off the surface of the eye, and this is counterintuitive, and counterintuitive observations are usually important in biology. When you put the lens on and take it off, you think that the cells would just be aching; that if you flush the surface, you would get more debris and more cells off, and exactly the opposite--the reverse.

The cells stay on, and not only do they stay on, but whether you measure the individual gamma cells, the large cells that are going to exfoliate or the other ones that are in the process of getting large enough to exfoliate, they increase in size.

Concomitantly, the thickness of the cornea decreases, too. So, the question was, and we'll answer in a minute, is this bad? One more aside, and that is what does pure oxygen, hypoxia alone do? We did an experiment where we put medical students for 6 hours under pure nitrogen and nitrogen, 95 percent nitrogen with CO₂.

As we expected, we got a lot of corneal swelling. But we got no significant increase in pseudomonas binding, but we did get a significant decrease of surface cell shedding, shedding off surface apoptosis of the cornea. So, pure hypoxia alone

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won't do it. It's the lens plus hypoxia.

Now, let's go to the conclusions that we found from our study. These are not changing. The numbers are just getting better as we get more information, and our data analysis gets better, and I expect this will be published within the next 3 months. All of the conventional lenses that we are all now prescribing that the FDA has approved under current wearing conditions produce increased bacterial binding. And, by the way, we have followed the FDA guidelines here in this study, six nights on, one night off times three months. We didn't have them wear the lenses continuously for 3 months; we followed the guidelines.

And they are known to be associated with a small but measurable level of trouble, and you can see that diagrammed here with a negative r value and a P 0.004 value correlating PA binding with surface oxygen.

Hypoxia alone in the test subjects produced no increased bacterial binding in the presence of a lens, and the lens producing hypoxia appear to be required. The lens oxygen properties drive this bacterial binding. The new ultra-high Dk lenses don't do it. Whether they're made out of a rigid material or a soft material appears to make no difference, and you see--again, I'm going to repeat that diagram for any of you who want to copy it down.

Strikingly, all lenswear shuts down normal surface shedding, and the ultra lenses shut it down the most. There is a very definite, again, minus r correlation, P 0.01, between oxygen and surface descromation. That's a most interesting relationship. But the

punch line is that the aging cells gradually increasing in size do not bind more bacteria unless hypoxically challenged. So, I think, as far as the bacterial binding situation and the potential for future infection is concerned, this is an interesting finding but not a fatal one.

This data would predict if this--if this technique or approach is adopted as a surrogate outcome measure that could reasonably be expected to predict future ulceration infection problems. It would make a flat prediction that the new ultra lenses will show a decrease prevalence incidence rate of ulceration infection, and the risk factors might go down as well. It cannot relate or predict numbers at this point. I would hope maybe 1 in 25,000 instead of 4 or 20 per 10,000 would be better. But if we adopt this, when the new lenses get out into the population, an adequate epidemiology study, such as what Dr. Schein has done before, needs to be done.

This will then confirm and be the final proof that would be required that this methodology is really a good way to go. If that turns out, there is a wonderful spinoff, if it works, and an experiment needs to be done. And I'm not saying it will or it won't; I'm pleading to do the experiment at this point for you. But if that works, then, you can see from the Ns I'm using--N equals 20; N equals 10; N equals 30--these are small group numbers. Within 3 to 6 months, you could test these new plastics very easily and cost-effectively. And this would open up a potential explosion for some of these very gifted polymer chemists to come up with some new lens designs to correct bifocal lenses for presbyopia and a whole bunch of other things.

The industry has been held back, and we have all been held back, by cost in

an inadequate way to assess future safety.

DR. McCULLEY: Nineteen minutes, Dwight.

DR. CAVANAGH: And these are my last two slides.

So, I hope to convince you that this isn't a sure thing yet, but I think it certainly looks like something we all ought to pursue.

I want to acknowledge the supporters who--you can read for yourself, but I really want to acknowledge my colleagues: Hongwei Ren, who has led this project and will be first author on the manuscript; Matt Petroll; Jamie Jester; Jennie Fan; Bill Mathers; Bob Kennedy; Joe Bonano; Lore' Ann McNichol and Graham Wilson, who is a consultant, all of who are probably far more responsible for this than I am.

Thank you very much.

DR. McCULLEY: Thank you. That was 20 minutes right on the button. What we've asked is that the speakers limit, if possible, to 15 minutes and no more than 20, and we've allotted 30 minutes for each of the experts. So, we now have 10 minutes at this time to query Dr. Cavanagh, and keep in mind that we will come back to the individual questions at the end, and each of the experts will be asked to participate in those discussions as well.

So, at this point, I guess what we would want to do is ask if any of the panel members or FDA have specific questions for Dr. Cavanagh.

Dr. Harris?

DR. HARRIS: Thank you; Michael Harris.

Dwight, very interesting work and certainly something that we need to be mindful of as we review the safety and efficacy of extended wear contact lenses. We all recognize the fact that increased oxygen is going to be a significant benefit to the health of the cornea, but, as you indicated, it's not the entire answer to the problem of infection and the other potential adverse effects of contact lenses worn on an overnight or continuous wear basis.

As you're aware, I'm sure, Suzy Fleissig, in a series of very elegant studies, has found that the stagnation of the cytotoxic bacteria onto the corneal surface is likely to be a contributing factor to the pathogenesis of infections associated with soft contact lens wear. How do these new ultra materials that you've been reviewing differ in the rate of tear replenishment or in their effectiveness in preventing stagnation in addition to their increased oxygen?

DR. CAVANAGH: Our group has not looked at that, and you certainly are in a good position to comment, because I understand that from recent presentations, the group at Berkeley has been looking at tear turnover under some of these new materials. But let me comment on Suzy's paper, because I have the utmost respect for Dr. Fleissig.

If you look at this paper, what Suzanne has done recently--it's in this month's CLAO--she's taken--gone from growing epithelial cells in a monolayer on a dish and putting the pseudomonas on for hours and showing penetration, even intracellular penetration, to an organ culture, where she takes the eye out and also bathes the corneal

surface in different bugs of different toxicity.

Now, there aren't lenses involved in this, and what she found recently is that if you have a super bug strain that makes a lot of toxin, if you incubate for 2 hours, it takes 2 hours. The toxin, then, can produce toxic effects in the epithelium which can show up by a variety of ways, and I would predict that those would show increased binding, but the lens hasn't been introduced into that model. And I made the plea 2 years ago out in Colorado at the contact lens meeting to do that experiment with a lens.

Now, it may be that there are super bugs out there. We know there are in other infections. And if there is a super bug that if five of them get on a lens and get under it, and they make toxins, and this trashes the surface even with enough oxygen that the bug can then go on and cause an infection, the new ultra lenses are not going to solve that problem, and maybe even flow under the lens won't solve that problem.

And that's a separate problem, and there are ways, now, to make surfaces that will not trap and bind bugs, and there are even ways to make surfaces that will kill the bugs if they do get bound. That isn't an easy problem either, but that is a different problem for another day.

The question is how many of the infections we see on a scale of 100 are due to trapping, and how many are due to just producing a lot of hypoxic damage so that if any average bug wanders by and gets on the eye, it can produce infection? My feeling would be that the vast majority of them probably result from us having damaged the surface with transient colonization, either of the eye or of the lens, and probably only a

few of them are due to super bugs. But that's another area of research that I can't help you with beyond pointing out the problem.

DR. McCULLEY: Dr. Macsai?

DR. MACSAI: Dwight, thank you for your presentation.

I have a question for you about the methodology that's--

DR. CAVANAGH: Yes.

DR. MACSAI: --described in your paper from January.

When you incubate the cells with the pseudomonas, what's the oxygenation of that system? And does the oxygenation of the microenvironment alter the binding properties of pseudomonas or the toxin-producing properties of the pseudomonas such that if you're incubating cells in a higher oxygen system than really exists on the surface of the eye, perhaps you're getting less binding than might actually be taking place in a lower oxygen environment.

DR. CAVANAGH: That's a good question. What Dr. Macsai is asking is when you get the cells off the eye, should you standardize the oxygen conditions? And frankly, no one that I know of has done that, and that would be an interesting experiment. When we were pursuing this, Marian, we tried to find a system that would discriminate. The two problems we had were if you washed the bacteria, as many authors were doing, you didn't get enough binding to measure.

If you didn't wash it and used too high a concentration, then, you got too much binding, and the noise swamped out the differences. By using non-washed bacteria

of a standardized strain grown under standardized conditions the same way every time and by fixing the cells at the conclusion of the binding experiment, which halted binding exactly at a fixed point, and then, it also clumped the excess bacteria and allowed us to get rid of it, we were able to discriminate in 6 hours between daily wear of a rigid lens or soft lens and show meaningful binding differences.

My feeling was that I was anxious to get on with the clinical trial rather than to spend 2 more years refining the measurement. I thought now, if we did it the same way every time, if we were only asking and answering a question about lens A versus lens B or control no lens versus lens wear for some period that we would get data like this that would show us differences.

What you're really asking is what are the real binding numbers, and what are the real differences on the eye? And I don't know the answer to that yet. That's another question I'd love to know.

Even if I did know it, even if we measured two and it's 10, the absolute difference between lens A and lens B should be, you know, in looking at differences. When you look at differences, and you do it the same way, you get rid of a lot of problems. And the--even if we knew it was 10, how do we translate 10 extra binding sites into infection? You see, you can't measure infection. You can measure binding. And your brain tells you that's a good surrogate measure.

But what we really need is Oliver to come back later and say uh-huh, you know, a difference of so many, so much binding translated into a reduction in risk rate or

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prevalence rate of whatever. That's why his--the backup epidemiology study here will do more to help us quantitate what those differences mean. It's just intuitive to me that if you can put a foreign body on the eye and not alter the ability of the cornea to bind bugs that you should see less problems.

We're seeing now 4 per 10,000 in daily wear and 20 per 10,000 in extended wear. Those numbers ought to go down. And at least right now, I think it's a reasonable experiment to compare six nights on and one night off with letting people sleep for 30 days in the lens, and if that doesn't show a difference, then, I think with the new materials, you've shown equivalence to what already is approved.

Then, when that gets approved, if it does, you can do the epidemiology study that will then really let us refine this methodology towards predicting infections rather than just looking at bindings.

DR. McCULLEY: Okay; we've had two questions and two five-minute answers. We have 30 seconds left in the allotted time; so, one question, Dr. Pulido?

DR. PULIDO: Could different types of lenses change the cell adhesion models on the surface of epithelial cells? And maybe what you're seeing is just an up-regulation of certain cell adhesion molecules for pseudomonas with one type, and maybe other bacteria would bind other cell adhesion molecules with different kinds of lens materials.

DR. CAVANAGH: The short answer is yes.

DR. McCULLEY: Thirty second answer.

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DR. CAVANAGH: The short answer, yes; we haven't looked at that yet.

DR. McCULLEY: Okay; I think we need to move on. We will come back to questions, and we will want the input from each of you again.

The next speaker is Dr. Brien Holden.

DR. SAVIOLA: We invited Dr. Holden to attend due to his extensive experience in clinical research of contact lens extended wear materials. He, as we all know, comes from Australia, and he is going to touch on a subject that is very important. Even though we all speak the same language, our definitions can sometimes mean different things, and the presentation will touch on some different ways people consider adverse reactions to be defined.

He's assured me that he has timed out his presentation to be 20 minutes. The thing we may not all realize sometimes is that in Australia, minutes are 70 seconds long instead of 60 seconds long.

[Laughter.]

DR. HOLDEN: The letter said 30 minutes but--

DR. SAVIOLA: Thank you very much.

DR. HOLDEN: --I'll do my best.

It's a great pleasure to be here in Washington. I apologize for the language, the accent, I should say, rather than the language. There is a language problem. I went to the hairdresser yesterday and asked for a number four razor, and it turns out to be a number 0.4 razor.

[Laughter.]

DR. HOLDEN: This study is all about inflammation, and it's a joint effort. If I flash the thing, could you just move forward?

And this is a very large project. The project directors in the clinical area noted here and biological sciences noted here; there is a fairly large team of optometrists working in India and in Australia and a group of research ophthalmologists working with on these projects. And those who are the biological scientists flash before your very eyes.

Our commercial circumstances: this research is supported by the Australian Government; those organizations: the Optometric Vision Research Foundation and the three companies. The next one, please.

It is a condition of grants from the Australian Government under our research scheme that if we do something that's useful, it can be patented, and we'll make money out of it. We accept money from anybody under four conditions: one, that anything done on a confidential product remains confidential to the company; two, once the product is released for commercial use, we are allowed to publish stuff relevant to safety and efficacy of the product; three, we earn the scientific copyright; and four, our material cannot be used for promotion of a company or a product. And though we have arguments with lawyers from time to time, generally, the companies stick to those rules. Next.

I also would like to acknowledge the input of the ISCOR adverse response panel, which are the people noted here who have discussed this work. Let me briefly tell

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you about the studies that we've conducted--next one--which are prospective controlled clinical trials. There's only one clinical trial here that's randomized, a properly-randomized clinical trial, and that was spectacles versus daily disposables, but these controlled trials are prospective and to do with spectacles, daily and extended wear, 6 and 30 nights of disposable hydrogels in both Australia for the last 10 years and India.

I point out the difference because the differences are very significant in our results. There are 51 patients followed for 383 eye-years, because very often, we use one eye to test something and one eye to test something else; for an average period of 5 years or for a mean weighted period of 5 years; extended wear, 270 subjects; 926 years. So, in Australia, in Sydney, we've had 321 subjects with an average weighted mean of 1.9 years.

In India, the studies have been much more controlled in terms of time scale, around about 1 year on average, and we've had 147 patients in specs; 146 in daily wear and 444 in extended wear, giving us an average of 1,228 eye-years.

So, this leads to a pooling of these results, which is inappropriate statistically but just gives you an idea of the size of the study.

Definitions: this has been a serious problem for us, dealing with both the industry and the industry's relationship with the FDA and with other organizations and groups. We have tried to stick to the English language, and we have tried to stick to dictionaries to define the terms that we use, and Spilker, who was recommended to us by the NEI, was our Bible for defining severe adverse reactions, adverse reactions and adverse events, the difference being reactions being the result of the therapy; serious

meaning life-threatening or, in our case, blinding; adverse reactions, unwanted resulting from treatment; and adverse events, something that is just detected in the population.

This is all summarized in the handout which was prepared by the people at the CCLU and LVPEI, which you have in front of you.

Ulcer has been another contentious issue. Ulcer is an interruption of the continuity of the epithelial surface with an inflamed base, such as a stomach ulcer. Of course, in corneal ulcers, we're talking mainly about necrosis and erosion and other definitions including infectious ulcerative keratitis. Next slide.

Infiltrate is another one that's caused a little bit of discussion, and we are, traditionally, in our discussions between ophthalmologists and optometrists in particular, an infiltrate to an ophthalmologist is a big white thing in the cornea with pus leaking down the cheek. In the contact lens world, an infiltrate could be fluid, dissolved matter or cells in the tissue.

And corneal infiltrate has been defined by Josephson and Caffrey as a collection of inflammatory cells, and there is another couple of other definitions. Move along, please: infiltrates from Stedmans; migration of cells to a well-defined foci or, in Tomlinson or Liebowitz, aggregation of neutrophils, focal granular opacities, generally meaning PMNs. Next one, please.

So, in this brochure, what we have tried to do is to use those definitions to bring about a classification for a common language between ourselves and sponsors of studies and hopefully, in the future, research groups around the world. We have very

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active input from people from the major international research contact lens centers, such as Waterloo, Michelle Guillon's shop in London, ourselves and people in the United States.

Definitions lead us to our classification. We can roll this forward a little bit. And what we've classified as serious, at least in our circumstance, is anything that warrants permanent discontinuation or has the potential to produce significant vision impairment. As significant an adverse reaction that warrants temporarily discontinuing from contact lens wear, and these are usually symptomatic, both of these; and non-significant, which has been the toughest one, which is usually asymptomatic, discontinuation is not normally carried out.

Next one, please. So, what we've said is that the only slight threatening condition that we have is microbial keratitis, and that leads to permanent or temporary discontinuation. We have called contact lens acute red eye; contact lens peripheral ulcer and infiltrative keratitis significant. In the non-significant basket, asymptomatic infiltrative keratitis and asymptomatic infiltrates, and there are other things I won't even discuss that we see in corneas.

We also rate the severity of each response, which we think is important, because when we see something like a peripheral ulcer, we may define it as definite if we see it actually happening; probable if it happened a few days ago, and the signs are there; or possible, if this patient had not reported in to anybody, came in for a routine visit and was seen with a little circumscribed scar in the cornea which wasn't there before and, when

questioned, said yes, I had a red eye 2 weeks ago. So, it's very important for us not to confuse the condition with the severity rating as seen in the clinical study.

We rate them from very slight, because many of the things that we see in contact lens research are, indeed, very slight, very slight, slight, moderate, severe.

And this is the range of responses that we see. In microbial keratitis, we very rarely see anything that's in the four as defined by the ophthalmologists and optometrists who developed this scaling system. These conditions here: contact lens, CLARE, infiltrative keratitis and viral conjunctivitis, can range from very slight to moderate, because you see them in various stages, and the asymptomatic ones are fairly innocuous.

Let's just move forward now into the conditions. Microbial keratitis--let's not linger on that. In the three cases that we have seen out of the 2,500 patient eye-years, they have been rated, generally speaking, around a three or a moderate on our severity scale. We have taken these bugs and put them in corneas; in this particular case, in the mouse model, and we can produce ulcerative keratitis and show a massive erosion and infection of the cornea. We are very much in cooperation with Suzy Fleissig. Our chief microbiologist, Mark Wilcox, is swapping strains with her all of the time and looking at the responses of the animal models to these various bugs that we get our hands on.

And there are some preliminary suggestions from the mouse model work that we don't see a real role for adhesion mechanisms, and protease production does not seem to be important in producing microbial keratitis.

The biggest discussion point, I guess, on contact lens-induced keratitis is the incidence, and the most recent study that I've put faith in is Nilsson's study in Sweden, which is fairly modern contact lens practice. I think his study started back there in 1986 or thereabouts. And those are the numbers that come out of his practice, out of his study of 440,000, whereas, about four per 10,000 for current extended wear lenses.

We have had one microbial keratitis in Australia. We've had two in India, and together with these type of hydrogel disposable extended wear lenses, we see about 18 in 10,000. This is not a valid statistical number to give us an incidence rate just reporting what we find.

However, if we look at the business of two lines of visual acuity or more lost, it is a bit difficult, more difficult, to pull the data out. We have never ever, actually--let me rephrase that. In 1973, we had a very devastating microbial pseudomonas infection. I was sued; the company was sued; the university was sued, and that patient had a very severe infection. In the recent studies over the last 10 years, we have had no serious microbial keratitis episode leading to a loss of vision, but, of course, that's not an incidence figure.

Sven Erik and Pierre Montagne, in their study, had three patients with two lines or more loss of visual acuity out of 61,500 eyes or a rate of 0.5 per 10,000. I was interested to compare this with LASIK and PRK, where the estimate is something like 3,000 or 3 percent, I should say, 300 is closer to the--Mark, I got a bit carried away there with the multiplication. 300 would be expected to lose three lines of acuity or more, and

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this is what we call contact lens peripheral ulcer, and this has been through a number of different names.

This is definitely an ulcer, because there's a full thickness loss of epithelium. It ends up in a scar, and we don't call it CLPU unless the scar is seen 6 months later. Next one, please.

And this is an inflammatory reaction to the cornea, characterized at its active stage by the focal excavation of the epithelium and the inflammation underlying. That's just about perfect, actually, if Scotty would move his water bottle. Thank you very much.

And the average rating here is somewhere between slight and moderate, as seen by the ophthalmologist in the clinic. That's their rating of such an event. The differential diagnosis of contact lens peripheral ulcers versus microbial keratitis is very important, and I'll summarize the key issues here and in the bracia. The most important thing is that CLPU heals up rapidly in an uncomplicated fashion.

We have done four biopsies. We have done about 20 scrapings of these very small lesions and four biopsies of patients who are consenting adults, and what we see with these biopsies is, in fact, a massive PMN inflammation of the cornea. We see a typically extended wear sick epithelium associated with a hypoxia, and we see an intact Bowman's Layer, and in all of the CLPU patients with biopsies so far, which is four, the Bowman's layer is important in the rapid resolution of these cases, we believe.

We have seen absolutely no evidence of microorganisms in any of the

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scrapings, any of the swabs and any of the sections from the cornea. Although we are going to investigate this more aggressively with sophisticated techniques and ophthalmologists and pathologists who are experts at recovering difficult bacteria, we see no evidence at all of any infection of the cornea. We believe this condition is caused by an infection of the lens.

These peripheral ulcers have been reported with daily wear and even with daily disposables. In Australia, we have seen in daily wear zero; in extended wear 0.6 percent or 6 per 1,000. In India, however, we see a very significant increase in the number of contact lens peripheral ulcers, both in daily wear they're seen and in extended wear.

Next, please. And the location of these ulcers above the upper and near the lower lid indicates that maybe tear thinning has something to do with it and the proximity of the lens to the cornea in those circumstances. We have seen one three days ago when I was in India in a spectacle wearer who came in with one of these contact lens-related peripheral ulcers. This is not called a contact lens peripheral ulcer; it's called a corneal peripheral ulcer, but it had exactly the same circumstances and course as the ones we've seen. So, maybe, out of the 3,000 spectacle patients I've seen in India in the last year and a half, we've seen one of these in a contact lens wearer.

The association here is with gram positive bacteria, and we do this; we have expected or collected about 30,000 lenses in these studies and looked at the microbial contamination of most of them, and we call a person a carrier of gram positives

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or bacteria on their lenses if bugs are isolated on one or more occasions over 12 months or two or more occasions in more than 12 months. And here, you can see a statistically significant association between those who have gram positives on their lenses and those who do not.

And staph Aureus seems to be the most important source of these peripheral ulcers, and that's staph Aureus carriage on the lid. So, we believe that toxins released by staph Aureus colonizing the surface cause this condition, and the risk factors are extended wear and the lens material interaction with the cornea, and that does vary with the materials, and we're following this up with an animal model.

The next one is contact lens acute red eye, which is generally a painful condition caused by small focal infiltrates, no significant staining, which is important. The patient is usually woken during sleep. We've seen 67 of these and studied them, and the severity rating is again around two, which is somewhere between slight and moderate.

Next one.

We see about 1.4 percent in Sydney in these extended wear hydrogel patients and, again, six times as many in the India studies, and what we see here is lens carriage status with clear is not with gram positives but with gram negatives. Next one. We see haemophilus influenza and other haemophilus species, and when we see someone at the time of an event, and here are the results of taking the lenses and growing the bacteria, it's various forms of gram negatives.

Next one, please. Let's move on. The bacteria isolated from CLARE,

however, are not capable of infecting eyes, and in the mouse model, we have been able to show that they do not infect the cornea; just roll along through the introductory slides here. This is the CLARE pseudomonas mouse, and when it's actually--the cornea is cut, and it's put into the cornea, we see inflammation but no colonization or infection of the cornea by the bacteria, and Mark has confirmed this predilection for certain subtypes to cause different conditions in a number of different bacteria.

We're moving on with the CLARE model to try to get a more realistic animal model, and in the guinea pig, we see that we can produce a CLARE-like response with a properly-fitted contact lens and dead bacteria. We believe that langerhans cells may be involved in recruiting the cells in CLARE, and this is a work from Pedmaja Sankaradug (phonetic) who has shown the recruitment of langerhans both in a diffuse manner and a focal manner in response to extended wear of soft contact lenses.

The most important thing about contact lens acute red eye is that there is no staining and no epithelial problem.

Let's move rapidly through infiltrative keratitis, which is a grab bag for inflammatory conditions; severity, generally speaking, slight. We see these ratios in Australia and in India, again, more infiltrative keratitis and a more similar occurrence of infiltrative keratitis, no real associations with bacteria in general; bacillus may be involved somewhat, and we isolate at some times streptococcus from these infiltrative keratitis events.

These are important because they can scar and be confused with contact

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lens peripheral ulcers, and obviously, they are not multifactorial. And all of this tends to get confused by us from time to time or clinicians with viral keratoconjunctivitis, which is very different, of course, because of the multiple nummular type infiltrative events. Next, please.

If we move on to the asymptomatic ones, asymptomatic infiltrative keratitis without patient symptoms; next one, generally speaking, very small focal infiltrates, and these little infiltrates here can be observed in a significant number of patients, but they are considered to be of relative unimportance in the lens-wearing episode. Next one, please. And bacterial carriage is not very relevant to that circumstance; maybe streptococcus, again, is involved.

In Australia, we see asymptomatic infiltrative keratitis in those rates in daily wear and extended wear, and we see them in spectacle wearers which, of course, says to us that this is not necessarily a contact lens related event, especially in India.

Next one, please. And lastly, asymptomatic infiltrates, infiltrates from the cornea without patient signs or symptoms, and these are small focal infiltrates up to 0.2 millimeters in diameter, and they are definitely collections of cells, or at least, they look like that under higher magnification. We have looked at 153 of these, and they are considered to be 0.3 of SFA in terms of clinical significance.

These are probably normal occurrence in corneas with and without contact lenses and are a response to a toxic environment in general. So, if we look forward, keep going down the track a little bit, infiltrates from the cornea, asymptomatic infiltrates, very

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similar, in fact, in Australia and India, and the rates are similar in the spectacle wearers, daily wearers and extended wearers. Thank you.

Contact lens papillary conjunctivitis, I'll just briefly mention this. Next. Because we give it a rating of 1.3. We don't see GPC, because we turn the lids back on a regular basis, and our rates are, in India, 0.5 on daily disposables; 0.2 in Australia and around 3.3 on extended wear.

So, let's just briefly review these clinical events and say that these are what we would suggest and we are hoping to work with our colleagues on in terms of description. The consequences: if we look at the severity ratings of these events, what we find in general is that the asymptomatic events, we still collect information but are relatively unimportant. We are concentrating on using these as an indicator of improvement in the lot of the extended wear contact lens wearers.

So, in commenting on the suitability of endpoints in lieu of ulcerative keratitis and firstly looking at can we do anything about quantifying loss of two lines of best corrected visual acuity, the answer is not very likely, because the two lines of loss of visual acuity does not occur in our studies at the present time.

So, we add this to the grab bag of things that are impossible to measure, and we turn to the incidence of adverse reactions and corneal infiltrates as the best indicator for us that these lenses are presenting a challenge to contact lenses, to the contact lens wearer.

And so, in terms of 30-night extended wear, what we are considering

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ourselves is if these products are giving a substantial improvement in an important aspect of extended wear performance; that is, eliminating hypoxia, and what we should see is at least equivalence or improvement from high-Dk soft in the occurrence of adverse reactions and significant corneal infiltrates. We do see that these lenses eliminate hypoxia when worn, as indicated by the work that Dwight has presented in this series of studies, after 12 months, 140 patients; the microcyst response, which, in our hands, is the best indicator of chronic hypoxia is virtually no different from no lens wear.

So, we add together the significant adverse responses, and they are 1 percent rate and 3.9 percent rate for extended wear in Australia. In India, it's 21 percent, which means that if we're looking for an improvement in the circumstances of the extended wearer, and we set as an absolute reduction of 15 percent on the rates seen with six-night conventional extended wear, we need 100 patients per group to complete a study in India to give us that level of confidence that we've made a significant progress compared with other alternatives.

Next. And the non-significant events do not help us at all--next one; next one--in discriminating. So, we would suggest, if we're looking for clinical endpoints to monitor if we are improving or if we are comparative to current products, we would look for CLPU clear and infiltrative keratitis added together as our response variable.

Thank you very much for your attention. I apologize for hurrying through this information, but I'm trying to get to 20 minutes. How did I do?

DR. McCULLEY: You did good; 25. That was very good, though; thank

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you, Brien.

That leaves us 5 minutes for now. This will not be the last opportunity that we will have to pick your brain, but in this portion of the deliberations, we have 5 minutes for panel or FDA questions for Dr. Holden.

Dr. Macsai?

DR. MACSAI: Dr. Holden, thank you for a very nice presentation. I was wondering, in the patients with the contact lens peripheral ulcers that were sterile, how many of those patients had concomitant lid disease?

DR. HOLDEN: Lid disease, probably none. We've looked at the blepharitis ratings and the scaling and all of the other indices. We developed about five indices to look at lids. We saw no obvious signs of staph infection of lids. Now, whether they have subtle higher levels of contamination, that would be indicated by the fact that we swabbed, going into the study, every patient's lids and conjunctiva, and there is a statistical association between the lid carriage of staph Aureus and the appearance of CLPUs. It's definitely a risk factor, but it's not obvious when you look at the slit lamp.

DR. MACSAI: So, on clinical exam, the patients don't appear to have blepharitis as we clinically define it, but they are culture-positive for staph Aureus.

DR. HOLDEN: Yes; only in the statistical context, because if you look at the 21 percent had some significant staph on the culture plate, and for us, significant staph Aureus is 1 CFU or more.

DR. MACSAI: Right.

DR. HOLDEN: Compared with, say, 12 percent in those that did not develop a peripheral ulcer. So, it's difficult to use that as a discriminating factor before the patient goes into contact lens wear.

DR. MACSAI: Okay; thank you.

DR. McCULLEY: Dr. Higginbotham?

DR. HIGGINBOTHAM: Very nice presentation. I was curious about the difference in the adverse reactions between the India group compared to the Australian group, and I wondered if, for instance, if there were novice contact lens wearers, perhaps? Could you expand on that?

DR. HOLDEN: Yes; I should say that all of the incidence data was developed from neophyte contact lens wearers. We used--now, I should correct that--the vast majority of it was neophytes. In other studies, we have used half neophytes and half experienced wearers, but they are not experienced extended wearers; they are extended daily wearers.

There is another problem with comparing India and Australia, apart from the food and the excellence of their cricket teams.

[Laughter.]

DR. HOLDEN: And that is that our studies have been going for a longer period of time, so that we're working with patients who have been screened out, and I believe this is the case in America. You are working with a population who have been screened for extended wear, and those who are in it have corneas like bricks, if I can sort

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of use a scientific analogy.

[Laughter.]

DR. McCULLEY: So, you think it's patient experience that's the difference.

DR. HOLDEN: No, there is definitely--

DR. McCULLEY: Not the water quality or--

DR. HOLDEN: There is definitely an environmental factor associated with dust and staph Aureus in India, because we have at least an eight times higher CLPU rate in novice wearers going into the same lens over a 12-month period of time. The discrimination on the basis of gram negatives is a little less clear, and, in fact, in our 10-year-old studies in Sydney, we tracked the pseudomonas in the water supply in Sydney versus time and showed a very strong association between when it goes up in the tap water and when we got it on the surface of contact lenses and got contact lens acute red eyes.

But, I must say, over the last 10 years, the Sydney water has improved to the point where they bottle it and sell it.

DR. McCULLEY: Maybe they bottle it and sell it because it was so bad out of the tap.

DR. HOLDEN: Yes.

[Laughter.]

DR. McCULLEY: Cliff?

DR. SCOTT: When you were talking about the staphylococcus-induced infiltrative keratitis, you mentioned several factors that had to do with it, one being tear thickness. You glossed over one point that is very germane to what we are looking at here, and that is the lens material cornea interaction. Can you elaborate on that a little bit?

DR. HOLDEN: Yes; there is no doubt in the studies that we've done that different materials have different proclivity for causing what we think is a removal of the mucous coating and maybe even the lining of the epithelium and setting up a better condition for the staph toxins to do an ulcerative job, and in comparative studies, one eye versus the other, we can see differences, very clear differences between materials. It's probably not appropriate to mention which materials are the bad ones until the papers are submitted for a peer-reviewed publication.

DR. SCOTT: But it sounds like a very important issue to what we're discussing.

DR. HOLDEN: It is, and we believe that if we were--in our own studies, when someone says to us we have a new lens; we think it's great, we will head straight for India, after doing some pilot studies in Sydney to make sure that things are, you know, sort of comparable in terms of lens movement and all that sort of stuff; we will head straight for India and look at the adverse response rate, because that's the best way of screening for the challenge to the eye.

Now, you know, you might say, well, isn't that a little bit harsh on the Indians? The fact is that there are 3 billion people in Asia, and extended wear is rife in

Asia. Probably 50 percent of lenses fitted in Indonesia and in--Malaysia's getting better--but are extended wear soft contact lenses, and the problems are out of control.

There is another reason for going to India, obviously, and that is the cost. The cost of an optometrist's salary is a tenth of what it is in Sydney. So, we can do much larger studies.

DR. McCULLEY: You're clearly overpaid.

[Laughter.]

DR. HOLDEN: It's still a tenth of what you get, Jim.

[Laughter.]

DR. McCULLEY: Touche'.

DR. HOLDEN: Even my salary is a tenth of what you get.

DR. McCULLEY: I doubt that.

DR. MACSAI: You might want to move to West Virginia.

[Laughter.]

DR. McCULLEY: We're going to have to end here.

DR. MACSAI: I just have one more question.

In India, did you look at the lid cultures? Were there significantly higher levels of patients with staph Aureus positive cultures? And did you look at the water supply?

DR. HOLDEN: Yes; we've done both of those, and there are higher levels of staph Aureus in the environment in general, not necessarily in the water supply, because

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we find that those reflect more the gram negative bacteria that are used to that sort of environment. And in lids, we do see a higher level of staph Aureus in India than we do in Sydney, but it's not that high.

DR. McCULLEY: Dr. Holden, thank you very much. We'll have the opportunity to get more input from you as we move forward.

I'd like to poll the panel at this point.

DR. HARRIS: Potty break.

DR. McCULLEY: Now or following Dr. Schein? Before? Now?

DR. MACSAI: Now.

DR. McCULLEY: Marian is squirming in her seat.

Okay; we will take a 10-minute break.

[Recess.]

DR. McCULLEY: Would you like to introduce our next speaker, Dr. Schein? Dr. Rosenthal, if you'll take your seat?

DR. SAVIOLA: Thank you, Dr. McCulley.

Dr. Oliver Schein has conducted a number of studies concerning epidemiology of extended wear contact lenses. He has been asked to present information on the limitations of analysis for studies of relatively low sample size and small event rates and to address the concept of large-scale contact lens studies as a mechanism to gather data post-approval for lens materials, attempting to demonstrate among safety in extended wear.

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Dr. Schein?

DR. SCHEIN: Thank you, Jim.

I'd like to thank Jim and the FDA staff for inviting me here today and for providing the most complete summary of the available publications on the risks of extended wear that I've seen, and I know the panel has that, and I won't be spending any time today discussing the actual historical studies.

By way of background, I'm very glad to be here. This is a topic that has interested me for almost 10 years now. The challenge is how does one assess safety where the major safety concern occurs at a relatively low rate, but the potential application of the new technology is to a very large population and where there are alternatives, whether they be spectacles or contact lenses? And related to this topic, it's appropriate to indicate that I've acted as a consultant to FDA, to Summit Vision, the laser company, and to Bausch and Lomb.

I'm not getting any advance on the right side.

[Pause.]

DR. SCHEIN: Let's try that again.

[Pause.]

DR. SCHEIN: Is the bulb out?

DR. McCULLEY: I think--turn the tray over and see the under--there you go.

[Pause.]

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DR. SCHEIN: Okay; thank you.

One of the issues that's recurrent, as I was saying to someone this morning, in a way, this is deja vu all over again, because the perception of risk evolves with time, and if one steps back into the early 1980s, the original PMAs showed ulcer rates in the range of 0 to 2 per 500. It was perceived by the panel at that time to be adequately safe, except when applied to an increasingly large population, up to the 4 or 5 million range, there was a large absolute number of ulcers, which then led to a realization that the existing data was really quite poor; a very late form of post-market surveillance study which, in effect, what the CLI study was, except this was 5 years after the approval; the ulcer estimate was a stable estimate; in other words, more precise, but, in fact, it was not dissimilar from what the original PMA might have indicated and, as you are all aware, the production in approval and no knowledge as to what the effect on rate of that reduction actually initiated.

Now, one has to take into account not only the FDA and the practice perspective but how the public looks at alternative methods of correction. I think this is very important. This, on the right, was taken from New York Magazine. I was in New York about four or five months ago, and here, 98 percent of patients can drive without glasses safer than sleeping in your contacts; exceeds Government safety standards; call 1-800-LASER.

[Laughter.]

DR. SCHEIN: And, so, from the public perspective--Ralph, you writing

down that number?

DR. ROSENTHAL: Yes.

DR. SCHEIN: From the public perspective and from the way in which some of our colleagues in the profession present the alternatives, these issues are important to take into consideration from the patient perspective, where patients not only look at the absolute rates of adverse events, but they put those rates--hopefully, reliably estimated rates--into their own perceptions of risks and to their own issues relating to quality of life, function and their preferences for different outcomes.

And these kinds of comparisons with eximer laser, I think, are appropriate. A point I'm trying to make is that the comparison group is not just with conventional daily or with extended wear contact lenses but with the alternatives, and although this cannot be done for all outcomes, there are some that can be measured directly, such as loss of vision or predictability of scarring and outcomes which I think are equally important to measure relate to patient perception of dysfunction or important symptoms such as night driving difficulty. This can be done with the kind of questionnaire which I've developed with colleagues or other questionnaires that are currently available or in development.

Now, the reason that I was speaking today has to do with the limitations of standard premarket studies, and there are a variety of limitations which I have listed here, and I am going to run through them very quickly.

The first and perhaps the most important relates to size, so that if one is interested in a significant adverse event, in this case, an ulcerative keratitis, and if the true

rate is, let's say, one in 500, you would need approximately a sample size of 1,500 to be 95 percent sure that you would see at least one case; or, to put this another way, if you had premarket studies as were done in the 1980s of 300 to 500, and you saw zero ulcers, you would not be very, very sure that, in fact, the ulcer rate was not 1 in 300.

So, size is a major issue, and it's because of the relative rarity of the most significant event that you cannot plan, you cannot size a premarket study on the basis of ulcerative keratitis.

Populations that go into PMA studies are not representative of the population at large, whether they're by age, astigmatism; usually, there are study exclusions. Studies, in general, are 6 to 12 months or, perhaps, a year, and we make a tacit assumption that exposure is the same for one person for a year or two people for six months when, in fact, that may be true for some important side effects but not for others.

Patients are clearly different; the ones that come into these new technologies, and the practitioners are different in ways that one can speculate about but never really know. There is usually more expertise; there is always more motivation, and these are potential biases which may affect the results of these studies in unpredictable ways.

The environment is also unusual. You look at Brien's detailed observations; this is analogous to what I call the observation effect, which is that if you're looking very, very closely and frequently at patients, you're likely to pick up small and less clinically-significant events, such as these asymptomatic infiltrates. On the other hand, you

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have what I will call a threshold effect, which is you're seeing corneal findings which may be on the pathway to more severe events, and you change the practice, or you intervene in some way, you may actually be preventing the outcome of biggest interest.

These problems cannot be adequately resolved by simply increasing the sample size, by going from 500 to 1,000 or 1,000 to 2,000. The larger sample size will help, usually, in narrowing the confidence intervals around estimates of efficacy, but for rare events, usually, you get very little incremental value.

So, what are the issues here? And they are identical for eximer lasers as they are for new generations of contact lenses; the public health needs are identical, and the inadequacies, the limitations of the PMA studies, are also identical.

So, what are the public health goals of the surveillance approach postmarket? They are to detect and to estimate in a stable fashion the rate of these visually significant, potentially blinding events; to educate the public and profession and to deal with cartoons in New York Magazine or elsewhere. By post-market surveillance, I mean something very specific in that there are systematic or rigid approaches. They are not the currently existing form of post-market surveillance, which is voluntary reporting. You might imagine, given my own interest in this field and the fact that I spent half of my time as a corneal specialist that I would be someone who would voluntarily report these things, and I've never reported one.

We have no idea why some people report them and others don't, and you have no way to compare rates either by lens type or certainly across company. So, there is

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no risk assessment in that mechanism.

Medical literature is the traditional way, but it's, besides being inexpensive, I think that's the only pro. They are always late. You never get rates from these case series, and again, there are all kinds of reasons why people study things and publish things.

Another mechanism which I liked is what Scott McRae and some others in this room did in 1991, they collated all of the PMA data and, quite remarkably, for an extended wear soft, they collated, pooled PMA data, gave essentially the same risk as we generated in the larger surveillance study at about the same time. But these studies were conducted in 1979 through about 1984 or 1985. So, there is a long lag time. And, as I understand, there are currently legal, regulatory issues regarding access to these PMA data at any rate.

So, what is the strategy? These are not simply large, randomized trials. Purposely, one wants these to be observational. The concept is to get a large population that is representative both of the patients and the practitioners who provide the new technology and to choose simple, important outcomes. So, for example, an outcome might be the need for antibiotic treatment for an acute corneal inflammation within a given year, or the outcome might be visual loss. The outcome might be something where there is really no doubt that something significant happened.

We'll come back to this ascertainment methodology in just a moment.

There are substantial advantages to everyone to unify the approaches across industry.

I'll raise some issues related to the cohort size in a moment, but it comes

down to reasonable assumptions about what levels of risk are thought to be tolerable and the differences between those rates and currently acceptable rates. That is not a right or a wrong answer. That's something that has to be developed by all of the players by consensus.

An ideal system would be one in which patients receiving the new technology, whether it's the new eximer laser treatment or a new extended wear contact lens, that there was a mechanism of registering all patients during a given time period so that the total denominator would be known from which a statistical sample could be drawn that would be representative of the entire population, and if there were indications from premarket studies that geography or age or myopia or other issues were of importance, then, the sample could even be stratified based on those kinds of variables.

Now, I'm not here to suggest a particular design or to recommend a particular sample size, but I just wanted to give an illustration of the effect of various assumptions on the size of these kinds of studies. Let's assume, for a moment, that we're looking at a severe complication rate in the range of 1 in 1,000, and we wanted to do a study that would be sufficiently powerful or would have enough precision so that you would know that your new technology with either 95 or 90 percent alpha was no greater than twice the existing risk. So, a rate ratio of 2 to 1.

You would need on the order of 4,000 to 6,000 patients. But you might say two times the risk? We're talking about blindness here; we're talking about something very important. We don't have a tolerance for twofold excess risk, even though the

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absolute rates are low. I only have a tolerance for a 20 percent difference. I want to know whether the rate's not bigger than 1 in 800 as opposed to 2 per 1,000. The effect on the sample sizes are tremendous. Now, we're up into the 50,000 range in order to be equally precise in that estimate of difference.

So, again, this is meant for illustration only, and the important decisions, and they're one which need to be made by all of the involved players, is what is the estimated risk? What is the most likely risk? And what level of difference do we think is reasonable to entertain for a new device that presumably has some kind of benefit?

During a surveillance period, there are a variety of ways to overcome the difficulty of studying contact lens patients, those difficulties having to do with their age and mobility. One is to obligate to providers for information and the other is to provide certain incentives for patient response. I essentially imagine a situation in which one can draw a statistical sample that is, in some way, representative of the application of the new technology; it's aimed at elucidating only the major events, and this methodology will be fed back to the FDA, to industry and to practitioners in a timely fashion.

I'm not so naive as to think that there are not challenges to organizing an industry-wide approach to this; so, there are issues of trust; competitive interest; different timings for bringing new products to the market. There is not an exact overlap. But I believe that these kinds of things can be overcome, and the advantages outweigh the disadvantages, even for industry; that there are advantages to having a level playing field; to having a credible source of data. As Dwight has indicated, perhaps even sharing the

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cost of these kinds of surveillance systems, and the advantage over the longer term for industry is that this kind of data in hand over a relatively reasonable period of time, if it were favorable, provides a very powerful argument for accelerated conditional approval of future products.

Particularly, one can imagine a situation where an existing lens has been conditionally approved. There is very strong data on a 30-day lens. There is--and that data is even stronger than, perhaps, expected. There is then the logic for even extending 30 days beyond. Conversely, there is already a logic, if the data is not as good as hoped, to provide a warning strategy, an early mechanism for withdrawal that will not take the 10--8 years that it took last time. So, there is an opportunity not just for the FDA with its regulatory abilities but for industry to accelerate approval and to have, potentially, a marketing device that it has currently no access to.

For practitioners, this kind of approach would also be valuable that allows a very informed methods for patient education, for benchmarking new versus old products and, of course, most importantly, the public will benefit from a credible source through which it can assess new technologies and receive new technologies, potentially in an accelerated fashion.

Jim, I can stop here. I brought additional material related to issues that I think are important related to design issues in PMA studies. I don't know whether you want to address these now or later.

DR. McCULLEY: Well, we're about 20 minutes into your presentation.

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DR. SCHEIN: Okay.

DR. McCULLEY: I'm not sure how much longer it would take for you to address the issues you have formal presentation for.

DR. SCHEIN: If you're planning a few minutes later today on issues related to PMA studies and how to randomize and so forth--

DR. McCULLEY: You've seen the questions--

DR. SCHEIN: Yes.

DR. McCULLEY: --I think.

DR. SCHEIN: Yes.

DR. McCULLEY: Would they fit into the question period?

DR. SCHEIN: Yes, I think so.

DR. McCULLEY: Okay; then, we can hold that--

DR. SCHEIN: Okay.

DR. McCULLEY: --until then. Because we don't want to lose any of your expertise.

DR. SCHEIN: Right.

DR. McCULLEY: Okay; so, at this point, if we could have the lights back up, open for questions from panel members for Dr. Schein, and thank you for your presentation.

Dr. Harris?

DR. HARRIS: Well, Oliver, I'm intrigued by your proposal on this

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post-market surveillance, and obviously, a well-designed post-market surveillance should be a part of any approval process, especially something of this nature. I was hoping that you would be spending some time discussing your approach to the pre-market approval, because certainly, we can't just use a post-market surveillance technique to make sure that the products that are being approved by the agency are safe and effective.

We do have to be mindful of the fact that we've made some very costly errors in the past in thinking products were safe and effective and only found out through the postmarketing surveillance and/or incident reporting that they weren't. So, I would appreciate it if you would take this opportunity to discuss your ideas on a premarket approval so that we could put that into perspective in weighing that against the postmarket surveillance.

DR. McCULLEY: So, that's what you were referring to that you had the formal presentation on.

DR. SCHEIN: I had some materials on that and one illustrative calculation but--

DR. McCULLEY: Well, why don't we turn the projectors back on, and if you can stay within the 30 minutes, but if that's the desire of the panel.

DR. SCHEIN: Obviously, you cannot sacrifice one for the other, but we have to realize the limitations of the PMA.

DR. McCULLEY: Before we move ahead--

DR. SCHEIN: Yes.

DR. McCULLEY: --Dr. Ferris has a question.

DR. FERRIS: With regard to your postmarketing assessment, I like the idea in general and have proposed something similar in a different context and have not received rave reviews for these proposals. But with regard to the science of following people up and, in the current milieu of informed consent and so on, have you given any thought to, at the time you register, at the time you bought your contact lenses, for example, signing something that would say I--here's my phone number; here's where you can reach me; I agree to be contacted so that when you want to do your study later, there is some sort of informed consent that you would be called, and are you worried at all about some selection bias as to who will allow themselves to be called and who wouldn't? And what might you do about that?

DR. SCHEIN: Right; well, you're getting into the next level of detail about study design, and the idea of informed consent and registration at the time of purchase is exactly what I've had in mind, and it's analogous to what I've thought through for exemer, where, instead of purchase, it's actually added to the informed consent for the procedure, and I think that the acceptance rates for individuals depends on how it's presented, and if it's presented in a very proactive way with very clear indications about the limited nature of the involvement; I mean, the amount of involvement for a patient to act as a surveillance instrument might be returning a post card at the end of a year and if not returning a post card, agreeing to be called once, you know, to set up a mechanism of enrolling. And if it's put in the right way, I think that the refusal rate would be very, very

low.

Now, let's get back to Mike's question. I don't think that one should choose a sample size so small. That is why I showed you the rule of threes: that if one is likely to see ulcers at a rate that would be considered alarming that you wouldn't see any ulcers. So, you can't go down so far that if the true rate were 1 percent or 0.5 percent or you name whatever you think is important as a threshold, that you wouldn't be able to know that you even had one of them. So, I don't think that we're necessarily lowering from what I believe would be your current expectations of what the study sample would be, but I don't think we should fool ourselves that you can design around the most important adverse event.

So, if you're in the premarket range of 500 patients or 1,000 patients, you get to all of those secondary complication rates that Brien outlined that seem to be occurring at least in a cumulative fashion in the 5 to 10 percent range, but you'll just never get to your ulcers, but you'll be able to make a statement: we had 500 patients for a year; we had no ulcers; we had 95 percent power to detect an ulcer rate of at least 1 in 500, and we didn't have any ulcers.

The other comments that I have have to do with the design, the randomization design, contralateral versus not. I don't know if that's something that--are we doing that later, Jim?

DR. SAVIOLA: Yes; I think as we go into the questions, we're going to present the questions, and since the material is all ready to go, I think you might as well go

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ahead and present that now, and then, it will segue into the opening couple of questions in the discussion.

DR. SCHEIN: Are there any other questions that I should answer?

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: You contrasted sort of premarket approval studies and postmarket surveillance studies, but you said yourself that your best estimate of the incidents of ulcerative keratitis was pretty much the same in the premarket approval studies and the postmarket CLI studies; is that correct?

DR. SCHEIN: That is correct.

DR. BULLIMORE: So, I'll sort of--if you like, sort of a gut reaction rather than our line that we drew in the sand.

DR. SCHEIN: Well, yes, that's true. The perception evolved but also, you know, the number that Scott McRae came up with, simply by pooling very, very different kinds of studies, I think it's useful--I mean, it did give the right impression. It doesn't always do that.

DR. BULLIMORE: One other question: do we have any data on loss of best corrected visual acuity in these studies?

DR. SCHEIN: In the PMA studies?

DR. BULLIMORE: Any of the studies, either the CLI data? Dwight's making hand movements there.

DR. SCHEIN: In the CLI data, we don't.

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DR. BULLIMORE: We don't? Okay.

DR. CAVANAGH: In the premarket data that Scott reviewed of all of the 17,000 or 18,000 cases plus, there was nobody that lost vision.

DR. McCULLEY: What is your pleasure now that--

DR. SAVIOLA: I think Oliver should go ahead and present his study design information. Then, we will get into a discussion. Because that really is our first question for the panel to consider.

DR. McCULLEY: Okay; why don't we go ahead with the?

DR. SAVIOLA: Does anybody want to cut the lights?

DR. SCHEIN: Are they on the second--

DR. SAVIOLA: Yes, they're all set.

[Pause.]

DR. SCHEIN: Okay; I thought I'd run through what I see to be the major design alternatives and what I believe to be the pros and cons of each and then make a few short recommendations.

The classic approach for the contact lens PMAs is a simple cohort: X number of patients for Y number of months with some predetermined outcomes and the use of some historical controls. This is the way it was done in the past; this is the way that the recent exemer studies have all been done. There have been no control groups for the exemer.

The advantages: it's cheaper and easier, and it's similar to what's been done

before, but there really are no adequate comparison groups, and I think that the comparison groups are going to be very, very important, because our knowledge about the rates of these complications in the comparison groups is actually not very good. The knowledge about the secondary level of clinical events, for example, in 7-day lenswear, we don't really know what the rates are. So, the historical controls are not likely to be very good.

The typical, most common kind of design is with the control group would be a randomized design, where the patient is the unit of observation, and patient A gets the control lenses in both eyes, and patient B gets the new contact lens in the eyes, and you follow them forward for predetermined time periods and look at predetermined events.

This is the most common study design. It's certainly the easiest for investigators to organize. It's easier for subjects as far as their behavior and their instructions, and there's no doubt that the control group here is far superior than the historical group. The only con that I can think of is that there is some inability to separate the patient-related versus lens-related risk factors compared to the contralateral design, which I will discuss in a moment.

Randomization, if it is a large enough group, and the randomization is done well, in general, should balance risk factors that may be of interest between groups but not necessarily things between patients, the kinds of things that Brien talked about this morning having to do with, for example, the concentration of staph anagens that may be

related to these peripheral infiltrates.

So, another kind of design is the randomized contralateral design where the eye is the unit of observation, and in each individual patient, one eye is randomized to the new and the other to the control contact lens. The pro is that this is really the most efficient design that I can think of. One would use a matched pair analysis, which would require a smaller sample size, but much more importantly, you have the opportunity to directly compare the technology separate from the ecologic environment, or, put another way, you can control in an optimal fashion for differences between subjects, reducing the compounding effects of variability from person to person.

For example, in lens care or susceptibility to infection, lid margin cultures, other risk factors that we've shown: smoking, all of these things would be optimally controlled.

The con is that it is simply more difficult to manage a study like this. It's more difficult for the investigator to do, and it can be more difficult for the patient to do. And if you have specific questions related to satisfaction with overall vision, it's tough to ask these generic visual questions on a monocular basis. On the other hand, if you're asking questions about lens comfort, there are actually advantages to asking people, individuals, to compare right eye versus left. So, there are some cons; they are mostly management-related issues.

What would I recommend? I would recommend taking very clear definitions, the kinds of things that Brien Holden showed, so that each company and all

companies use the same outcomes, ideally with standardized photographs so that the companies, the professionals and the FDA panel can compare outcomes in an appropriate fashion. Where possible, some of the outcomes should be performed in ways analogous to the way they have been done with eximer laser, so that there is the potential for some comparisons. They may not be the primary comparisons, but it will aid in these kinds of assessments as well as will these measures of patient-reported function, benefit and harms, which I have referred to earlier.

I would like to recommend, I would like to suggest that the panel mandate the use of concurrent controls as opposed to historical controls, but I would also like recommend that they not be so constricting to demand one kind of prospective randomized design over another, because there are pros and cons of each, and I think that it simply would be inaccurate to indicate that there is a right way to do it.

The sample size requirements, I tried to touch on that a moment ago in answering Mike Harris' question, but they have to be based on these estimates of rates of the secondary level of complications and some indication of what might be an acceptable difference in either instance or relative risk.

So, for example, and again, this is example only, because I don't really know what the rate of adverse events might be in the control group, but I've picked 5 and 10 percent just as an illustration, and I don't presume to suggestion what odds ratio the panel and the public should determine is clinically significant. But by way of illustration, if the control group, the control group rate of these peripheral infiltrates and other

secondary adverse events is 10 percent, and you want to be able to detect a relative risk of 2, you end up with a sample size of about 550. That's total; so, about half of that for each group. But if you want one and a half, you're up to 900 per group, and obviously, this will depend tremendously on what the rate of adverse events really is.

So, I'm going to end my comments there unless there are questions. And then, I'll sit down.

DR. McCULLEY: Yes; Dr. Pulido?

DR. PULIDO: Why don't you recommend as the primary outcome results or outcomes that are required for refractive surgery?

DR. SCHEIN: Because they are analogous but not identical, and second, because of sample size considerations. So, the primary outcome for refractive surgery has appeared to be loss of best corrected visual acuity of more than two lines during the study period, and if we were going to design around that, we would have to take the ulcer rate, say, 1 in 500; make an estimate that perhaps one in 20 of these two lines, one in 50, something like that; you'd end up with sample sizes in the probably hundreds of thousands.

The second issue is that there is a presumption that there might be differences in the way the public and patients perceive the use of a contact lens compared to refractive surgery, and this perception goes in both ways. So, for example, there are reasons an individual might assume more risk for a perception of a permanent correction if that is something that is very, very desired by a patient where as much of the contact lens-wearing population may not be willing to assume so much risk for the outcome that

they received, so that events of lesser clinical consequence may be important.

It doesn't mean we shouldn't collect these things, because the public needs to know what the loss of best corrected acuity rate is in the two choices, but you can't design around it.

DR. McCULLEY: Any other questions from the panel?

Dr. Bullimore?

DR. BULLIMORE: This is somewhat unrelated, but is your RSVP instrument sort of freely available now, or is it still under development?

DR. SCHEIN: It will be available to the public by May.

DR. BULLIMORE: And what are your feelings on that being adopted by the FDA for all PMAs?

DR. SCHEIN: I wouldn't ever recommend that any specific instrument be adopted for all of anything, whether it's the VF-14 for cataract or the NAIBFQ. Again, I think that's poor science. You have to fit the particular instrument to the particular need.

DR. BULLIMORE: But you're saying on one of your slides here that, you know, you want a measure of patient reported function benefits and harms. If we're going to be considering a whole range of PMAs on a similar issue--

DR. SCHEIN: Right.

DR. BULLIMORE: --is there any perceived benefit on your part in having the same instrument used on--

DR. SCHEIN: Of course, there is; but I basically can't and won't stand

here and say you have to use something I developed, and, you know, that's not going to happen. But historically, people have--companies have made up a series of questions, and they have differed. So, the issues relating to patient preferences, function and glare, night driving, have been different, and I think it's been problematic. So, the same issues with standardization of clinical findings and patient report are appropriate.

DR. BULLIMORE: Thank you.

DR. McCULLEY: Brien, very briefly, and the reason I say that is we've got to get back on track.

DR. HOLDEN: Isn't that just being a little coy rather than saying yes, you should adopt this, because if you're going to adopt different standards for such a question, you end up with the same problem of objective observations?

DR. McCULLEY: Okay; I think we're going to have to stop right now with this.

[Laughter.]

DR. McCULLEY: We have, by way of everyone's information in this room, we have approximately 2 hours of questions and responses that the FDA has proposed, and we have estimated times for answering each one, and we're going to have to try to address what they've asked us to do. Otherwise, we will get a quarter of the way through the questions. And I would just like to share with you a saying that I heard recently, and that is that if I had had more time, I would have written a shorter letter.

So, what we are going to need to do is give real thought to our responses

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and to try to be succinct and to get to the point, and once we have the answer that the FDA--if you're comfortable; I think our role here, again, is to try to answer these questions to your comfort level. And once you have an answer that you're comfortable with, rather than us belaboring the point, then, please, so indicate. And if you do not have the response or the answer or the information that you need, please also indicate that. And I will try to get things on tap timewise as best I can, and everyone, please: think efficiency of word and to the point.

Sally has suggested a minor deviation at this point, and that would be to ask Dr. Yaross if she has a comment representing industry, and if there are industry representatives in the audience who would like to make a very brief comment at this time, the risk I see here is opening up a can of worms. If it looks like we open up a can of worms, then, I will reverse direction.

So, at this point, I would like to ask Dr. Yaross if she would like to make a comment, and if we have a total of about 5 minutes of any one or ones from the audience from industry who would like to put in a quick two cents' worth, we will recognize you at the podium.

Dr. Yaross?

DR. YAROSS: Thank you, Dr. McCulley.

I do have a few thoughts so far.

DR. McCULLEY: More into the mike.

DR. YAROSS: Sure; a few thoughts so far.

One is that I think a very important point was made by a couple of speakers and seconded by Dr. Bullimore, which is that the original PMA studies have very accurately, it appears, estimated overall rates of occurrence of certain kinds of adverse events, and we need to think very carefully about what level of precision in refining those estimates is important, because as we saw, we can go to tenfold and 100-fold greater sizes of clinical studies, and we need to make sure before anything of that sort is mandated that we are careful to determine do you really need to discriminate between twofold and 1.8-fold, for example.

In addition, I think that we need to also be very careful in terms of study design that we keep in mind the regulatory basis for approval, which is not always comparative. There has been a lot of discussion about comparing differential rates of risk between one product and another product, and that is not necessarily the sponsor's regulatory responsibility to show that their product is safer than another product but that there be a reasonable assurance of safety and effectiveness against some general community standard of what is acceptable risk.

DR. McCULLEY: Is there anyone in the audience who would like to make a brief statement or comment or advise us?

[No response.]

DR. McCULLEY: Seeing none, we will move forward.

DR. ISHIMOTO: I'd like to make a brief comment.

DR. McCULLEY: Then, hop up there.

DR. ISHIMOTO: Bruce Ishimoto, OcuMetrics.

I didn't see anything mentioned in the questions that related to lens design and material evaluation to appropriateness to do a study; that I would like to propose that we consider things like fluorophotometry to see that these new devices are appropriate to do these studies. We are talking about fairly large numbers of patients in these PMA studies and that there should be some evidence on an in vivo basis that are sensitive enough to say that these materials and devices are safe for doing a large scale of PMA study.

Thank you.

DR. McCULLEY: Thank you.

Would the FDA like to comment on that or just let it stand?

DR. SAVIOLA: Well, I will just mention for the sake of the people in industry who discuss these topics with us that we are not, at this point, considering any current materials that have been approved for up to 7 days for studies beyond 7 days at this time. Those are all of the old materials that were out there in the eighties that had the troubles that we all know about and were pulled back in 1989.

And if someone comes to us with a request to study a material to go beyond 7 days' of extended wear, then, you do have to have a Dk/L of about 90 to minimize the overnight corneal swell response and do some corneal swell studies. So, there is a threshold there. The questions for discussion sort of frame up to 7 days on one hand and beyond 7 days on the second hand, and there is that underlying concept which,

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you're correct, we did not articulate in the questions, because that has been our practice for the last couple of years.

The comments that the last speaker made, I think, are worthwhile, and we need to consider that there may be some methodologies out there that we have not recommended to firms to evaluate these materials, and down the road, they may have impact on study designs in general. But at this time, we do have some criteria that companies do have to meet in their work.

DR. McCULLEY: Okay; do you have your questions that can be projected?

DR. SAVIOLA: We have these slides here. Everybody has the handouts available from the doorway.

DR. McCULLEY: Right; okay.

Let's begin with the questions, if we can. Do you want to put your--the first ones relate to study design.

Question number one, has this been adequately addressed to your satisfaction? Would you like more?

DR. SAVIOLA: I would like to hear a few more comments about the first part of question 1--

DR. McCULLEY: Okay.

DR. SAVIOLA: --before we go on to question 1B, because we do have some points to consider, contralateral versus randomized for less than 7 days compared to

beyond 7 days.

DR. McCULLEY: Okay; let me stress again: please be recognized if you wish to speak, and now, we need further comment.

Dr. Cavanagh?

DR. CAVANAGH: When we were trying to put together a study that would get by the NEI's group of statisticians, our IRB, which are really a bunch of tough guys and common sense, taking a group of extended wearers out over a year with one lens in one eye and one lens in the other eye is just not a wonderful way to do it. It just isn't practical to randomize two different lenses in the patients, and you don't need to do it for the science, because, at least if the outcome measures we're looking at are in the biology of bug binding, then, we can certainly do it with much fewer numbers, and maybe some of the other outcome measures are different.

But I can tell you that you are going to have trouble with this in the practical world.

DR. McCULLEY: Patient compliance.

DR. CAVANAGH: Yes, over a year. Now, if it's a one-month study, it's different.

Dr. Holden?

DR. HOLDEN: I would just say that we have, I guess, out of those 2,500 eyes, we have probably run at least 1,700 of them contralateral studies, and you don't have a practical problem if the patient is reasonably instructed, and it is a very good

comparative measure. The problem with contralateral studies in our experience is if one lens is a dog, then, it ruins the study, because it pulls people out of those lenses. But it is a very practical proposition and it's, in fact, the most efficient way of showing one lens is better than the other in our experience.

DR. McCULLEY: Okay; we had differing opinions.

Anyone else like to offer an opinion?

Dr. Harris?

DR. HARRIS: Well, I've done both contralateral and randomized design studies, and in certain situations, the contralateral studies certainly do have a benefit. My concerns with the contralateral study in this particular environment would be basically the management issues that Oliver touched on. But I'm fearful of patients switching lenses, and obviously, that ruins the entire data for that particular wearing session; the effects of one eye on another eye; a patient has an adverse response causing tearing in one eye; it's going to have a potential adverse effect on the other eye.

And the fact that symptoms are often, even though they start out in one eye, you tend to think it's going to the other eye, and indeed, even though one eye may be the one primarily causing the problem, the patient may feel that they've got problems with both eyes. So, I think that there are a number of shortcomings to a contralateral study that would need to be addressed before the agency would approve that as the major way of determining, through a premarket approval, whether or not contralateral studies will work.

DR. McCULLEY: Okay; Dr. Macsai?

DR. MACSAI: I guess I would like to give a different point of view than Dr. Harris', which is a contralateral study, as mentioned by Dr. Schein, does allow you to sort out the difference between the patient-induced problems and the lens-induced problems, and that's an extreme benefit. We are looking at 1,700 patients from Australia and India that have been randomized successfully. You can color lenses; you can color cases; you can do all kinds of things.

But if we have a disease entity such as blepharitis, staph marginal lid disease, staph that lives on all of our skins, and we want to separate out these peripheral infiltrates/ulcers as being related to the lens versus the individual, it's the only way to do that.

DR. McCULLEY: Okay; we continue with see-sawing.

Dr. Schein?

DR. SCHEIN: I just agree with that completely.

DR. McCULLEY: Okay.

DR. LEPRI: I would like to interject, Mr. Chairman.

While you're answering--the panel members are answering their questions, if you would also consider this following question: does your viewpoint differ when considering 7-day studies as compared to studies beyond 7 days? Please address that in your answer.

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: I would agree that contralateral studies are acceptable. The problem is complicated when, for example, you have a patient wearing a 7-day lens in one eye and a 30-day lens in another eye. There needs to be some very serious considerations with that regime and some really sort of supermonitoring on the part of the clinicians and the sponsor in terms of ensuring that there wasn't, for example, a 30-day wear on both lenses.

DR. McCULLEY: Okay; so, there are advantages and disadvantages to each, and maybe a hybrid study would be the best.

DR. LEPRI: And do we have to be mutually exclusive? Can we accept both, depending on the quality of the design?

DR. McCULLEY: I've heard pros and cons from, you know, offering an opinion that sound convincing on each side, and one could possibly do a study that included both components as the ideal or either.

Dr. Holden?

DR. HOLDEN: Could I just say one thing about flexibility of such studies? If you're doing 6 nights in one eye and 30 nights in the other eye with two different lenses, and you instruct the patients well, and they learn to recognize differences in materials because there are, even though they don't necessarily know which is which, there is an important point, and that is what happens if there is an adverse response? Do you switch to two lenses of the same type? Or do you discontinue the patient from the study?

And there are ways of using that without wasting those patients, as it were,

to continue those studies.

DR. McCULLEY: Thank you.

Dr. Ferris?

DR. FERRIS: I started twitching when I heard discontinue the patient from the study.

[Laughter.]

DR. FERRIS: I'll try to calm back down.

[Laughter.]

DR. FERRIS: It seems to me that it's apparent that it's such a giant step forward to go to a randomized design, whether it's randomized contralateral or randomized patient, that we should be delighted that we moved in that direction. As I think has been pointed out adequately, both designs have some pros and some cons, and the investigators ought to be allowed to choose those with the caveat that if they choose a contralateral design, they may shoot themselves in the foot if they've got those problems. That's their problem. That's not our problem.

DR. McCULLEY: Okay; I think--have we adequately addressed that? But have we adequately addressed your issue of 7 versus 30?

DR. SAVIOLA: That will come into play in question 1B here to some degree. I think we've heard the mixed viewpoints on the first question, and by way of clarification, we have been running concurring controls. We've only had one approval for extended wear since 1990, and that was a concurrently controlled study. So, we are

incorporating those in our design.

This next question is part of number one. I think it needs to be touched on just briefly.

MS. WARBURTON: Do you think that the pathophysiology of corneal ulcers and/or infiltrates has any bearing on the study design being contralateral or randomized?

DR. McCULLEY: I think we've addressed that, that there are contact lens issues with some and patient issues with others. So, depending on the pathophysiology, yes; it would point you toward design or another if you know the pathophysiology, and you know what's going to happen.

Dr. Holden?

DR. HOLDEN: Yes; I think we're yet to see any significant adverse event that is provoked by the lens in the other eye in our studies. If we look back on whether--because most of these conditions that we see are unilateral, and here, I'm talking about the obviously contact lens-related problems. And as far as we know, the two eyes are independent in that circumstance. So, whether it's an infiltrate as an endpoint or an ulcer as an endpoint or a microbial keratitis as an endpoint, which is obviously extremely difficult, it does seem as though the two eyes function extremely independently.

DR. McCULLEY: Okay; can we go to the next question then?

DR. SAVIOLA: We're now going to consider safety endpoints. The question is please comment on the suitability of the following safety endpoints in lieu of

the ulcerative keratitis, and comment on an acceptable frequency of occurrence for adverse reactions, corneal infiltrates and slit lamp findings greater than grade two.

DR. McCULLEY: Comments?

Dr. Macsai?

DR. MACSAI: Oh; sorry.

I would like to just address the first part of question 2A: please comment on the suitability of the following safety endpoints. I think these are good safety endpoints, but I think that many of the speakers have alluded to some long-term potential safety problems and contact lens wearers such as endothelial cell loss, corneal warpage syndrome and potentially keratoconus, and in regards to the idea of postmarket surveillance, I think we should keep these in mind as long-term potential complications.

DR. McCULLEY: Dr. Holden?

DR. HOLDEN: Just on those issues, the Japanese have done to death the whole endothelial cell morphology loss of cells, and if you go to the Japanese Contact Lens Society, over a period of 5 years, there are at least three papers on endothelium. And it has been shown, I believe, now that in high Dk RGP and in high Dk soft that the endothelium is relatively unscathed, and it is an enormous amount of work to continue on with those studies.

DR. McCULLEY: Dr. Macsai briefly?

DR. MACSAI: I'm familiar with the Japanese literature, but I still think that the morphologic changes of the cornea, such as warpage and potentially keratoconus

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may be significant and important. We really don't understand, still, all of the biologic factors that make the cornea change shape.

DR. McCULLEY: I would agree. I would just question how we would get a handle on it.

Any other comments on these issues?

Jim?

DR. HARRIS: I think Brien did a wonderful job of illustrating the types of adverse responses that we should be looking for and, indeed, as clinicians, fitting patients with contact lenses, we look for these on a regular basis, and when we see them, we get concerned, and I think the same types of endpoints should be incorporated into any type of approval package in the area of extended wear, and we are looking at the microbial keratitis, the peripheral ulcers, the CLAREs and the infiltrative keratitis. I think you cannot just use one adverse response to measure everything that can go wrong with a patient's eyes, and the stuff that Brien has put together, I think, gives us a lot of good scientific basis for coming up with a multifactorial type of approach to endpoints.

DR. McCULLEY: Right; the way I read this question, it was not whether we thought they were of value. I think we would all agree that they are of value. The question was what occurrence rate would be acceptable? Do you want us to try to address that?

Dr. Schein?

DR. SCHEIN: The adjective acceptable is a tough one to deal with,

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because I know people are going to start raising their hands and saying 5 percent or 2 percent or 10 percent. I would approach it a little differently, and I would approach it in relation to the control group. I would assume that the control group is going to be--for any of these studies--in a currently accepted, approved and used lens in an approved fashion. So, I think we have to talk about the difference in risk between the control and the test, assuming a range of potential rates rather than an absolute rate.

DR. McCULLEY: Sounds logical. Other comments?

Dr. Holden?

DR. HOLDEN: Two brief ones. I certainly agree with that, and if we're looking at, say, 30-night extended wear high Dk materials, then, obviously, 6-night hydrogel extended wear. But I have a question for Ollie: it is extremely difficult, is it not, to say this is the same rate or not significantly different. So, we would have to set limits on the differences in rates that would be considered to be similar, and on endpoints in terms of corneal warpage, we have been studying high-Dk rigid lenses for the last 10 years, and I didn't include any of that data, but they do not cause corneal warpage the way that low Dk lenses used to do.

DR. McCULLEY: Dr. Schein?

DR. SCHEIN: The way I think I would go about this issue is to first designate a grading scheme that would be agreed upon, and I don't want Brien to have to be coy in responding to whether we should use his grading scheme.

[Laughter.]

DR. McCULLEY: Brien's never coy.

DR. SCHEIN: So, that's not a risk, huh?

But something of that nature would be appropriate. And then, we would go to the literature or to a Western experience or even an Australian experience to look at the cumulative rate in recent experience in, let's say, 6-day wear for these peripheral ulcers, the acute red eye and the infiltrative keratitis, add them up and see what the range is.

If it's in the range of 10 percent, I would use that as the best estimate. And then, we have this discussion. When we talk about the sample size here, it gets at what's an increased level of risk that would be acceptable. So, presuming that there is a benefit to wearing a list 30 days compared to 6, is that worth a 1 percent difference? Or a 2 percent? That decision needs to be made, and that will generate the sample size.

DR. McCULLEY: Dr. Saviola, did you have a comment?

MS. WARBURTON: I had one comment. One of the reasons for this question was to help us determine what sample size would be appropriate, and, of course, it does occur; I mean, it does depend on the expected occurrence rates and what is considered, you know, an acceptable clinical difference.

As far as trying to tease that out of the literature, I did an extensive search on the past 3 years, anyway, and most of you have that information, and there is not a lot out there, which is why we're bringing it to the panel. And Dr. Holden's information is helpful to us.

But in terms of, you know, time, I don't know when literature studies are going to be in the public domain, where these occurrence rates are actually going to be in black and white. So, if anyone has, you know, general opinion about them, we would really appreciate it at this time.

DR. McCULLEY: Dr. Cavanagh?

DR. CAVANAGH: None of us want to relive the experience of the eighties, where 20,000-plus patients were carefully followed by the FDA and many of us as investigators. And then, when we got them out in millions of people, we started seeing infections on the front pages of the newspaper.

Now, the real question for this panel is going to be the following: all of Brien's pictures here, these are 5 or 10 percent occurrence rates. So, they can easily be addressed what sample size is in the usual range for clinical studies, and in my opinion, they should be and probably, hopefully, the agency will do it that way.

The real thing is when you vote to let a lens be worn, put package approval for 30 days, you're going to be voting with data that will not tell you whether or not there are going to be infections with that 30 days versus 6. Well, I guess the purpose of this meeting, in my mind, is to ask those of you who will be voting on that later what you want to see ahead of time to give you some confidence that you're making a good choice to let something go to 30-day wear, when you're not going to see much difference on 6-night wear or 30-day wear in red eyes; you're not going to see probably worsening with 30-day wear; it may even look better.

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Now, what's your comfort level? To me, the comfort level is if you can put a lens on an eye and measure and show blind, in a blinded fashion, in a random fashion--powerful tools--that you haven't altered that surface. That would then allow me to say that looks good enough to me to allow it to go forward with the caveat that we want to do a followup study that will really tell us that the risk prevalence rates went down.

It's not fair to say that Scott McRae 12 years later went and pulled all of the data in the agency's files and came up with the same number Oliver's study did. Oliver's study was done over a 3-month period one summer, and you need that information and followup on any of these lenses that get 30-day approval. There is not an outcome measure right now that you know will predict future infections and ulcers. The only one that looks reasonable is this difference in binding. All the rest of it: the red eyes, the warpage, the 3:00 and 9:00 staining, you know, change in refraction, blurred vision, microcysts, a little bit of edema: all of these things are important and should be continued to be measured, but they're not really where the money is.

The money is down the road, if you sleep in a lens for 30 nights, are we going to see the kinds of ulcers we saw before? And I don't know any other way to do it.

DR. McCULLEY: Okay; thank you.

Dr. Saviola?

DR. SAVIOLA: I appreciate your comments, Dwight. The people invited here today and the current panel members are the ones who are going to see PMAs for

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these products within the next 3 years. And the way we structured the questions, the overheads really aren't working out as well as we had hoped they might because of the lighting situation and our combinations here.

But these points about what we think, what we want the difference, some feedback from the panel on the significant difference between the test and control groups, alternative endpoints, definitions of terms for adverse reactions and infiltrates, those are things we are looking to hear back from you. We have heard some wonderful information from our invited speakers today, and I could take silence to be an endorsement, but I want to make sure that I am correct in that assumption.

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: I think one of the problems here, and this is no disrespect to Brien, is that the handouts I got before the meeting include the incident rates that were presented at the meeting.

DR. SAVIOLA: That's true.

DR. BULLIMORE: And we had to sort of digest them on a sort of very rapid basis. I would consider personally sort of handling this on a homework assignment where we would have better data presented, but I think at the moment, we're sort of searching for what the numbers might be.

DR. SAVIOLA: Well, there is a possibility that this is like the Jackson cross-cylinder test: there's no better one or two here. Both are the same. There is no real answer to some of these questions.

We weren't able to provide certain information from our PMA database, as Oliver alluded to, because there are, as it comes to pass, some legal considerations for incorporating that information in the handouts. That's why we did the extensive literature search, and Dr. Holden's invitation today was to present that information, which he has, in perhaps a proprietary manner to provide in advance.

So, if you can't give us a less than 2 percent for this or a less than 1 percent for that or something like that, well, that's fine. That's the answer we'll come away with today. And we can follow up with it. But if you do have some thoughts about what your viewpoints are, if you think we really need to look at this on a more cumulative basis for a number of different options as opposed to a single one--

DR. McCULLEY: Other than an immediate gut response to that question with numbers, does anyone have any thought-out response that they would like to make? Because I think I'm hearing and sensing from the group that we probably can't give you comfortable percentages.

Dr. Holden?

DR. HOLDEN: I'd like to say that we--one of the reasons Mark didn't get the detailed numbers was that they were being crunched for this meeting in a great hurry, but we have no problem making the numbers available to the panel for their discussion; in fact, a copy of the presentation is being produced as we speak. And, indeed, all of that material is scheduled for publication over the next year and a half. But it's just a question of timing so--

DR. McCULLEY: So, you will make that available to the FDA for their use.

DR. HOLDEN: No problem.

DR. McCULLEY: Thank you.

Dr. Ferris?

DR. FERRIS: I just have a quick comment to make, and that is as I look at these questions, they're dancing around the main problem, and that is that the event that we really care about is so infrequent that we're not going to measure it with any kind of reasonably-expected prospective clinical trial. The sample size has to be adequate so that we can have relatively narrow confidence intervals around these adverse reactions.

I think some sort of standardization of methodology may be important. As I was looking at Dr. Holden's material, I was thinking, well, those differences between India and Australia, are they related to measurement differences? Are they related to differences between the populations? It's difficult to know for sure. He may know, but just for somebody observing them; so, some methodology is probably important and a sample size big enough to have reasonably small confidence intervals; but in the end, I take Dwight's point that we're going to approve something that we don't really know what the rate of risk is other than it's going to be, as Oliver showed, it's probably less than 1 percent. It may be 1 in 1,000; it may be 1 in 10,000. But I don't know how we're going to know until we have the postmarketing data with the sample size.

And one last comment, and I think that the other thing that Dwight

mentioned and was mentioned about fluorophotometry; it would seem to me that anything else that could be brought with the document to help raise the level of confidence that this material is less likely to cause some long-term problem would be beneficial.

DR. McCULLEY: It seems like there are several issues here. One is ulcerative keratitis is sufficiently infrequent that we're not going to practically get at that; is there a surrogate? And Dwight has proposed that he has a surrogate.

But there are also other issues and other adverse events that may be less than ulcerative keratitis that we would not want to accept: the contact lens-induced red eye; the peripheral infiltrates and so on that are real events that may or may not predict ulcerative keratitis. So, do we have a surrogate is one question; and then, what is the incidence of these other kinds of events that we would be comfortable with? And I think the percentages on that, I think what we're hearing from the panel is that we would like to have an opportunity to look at some of the real numbers and to digest that before making a percentage suggestion or recommendation.

DR. SCHEIN: Jim?

DR. McCULLEY: Dr. Schein?

DR. SCHEIN: I just want to first add to Rick Ferris' comment that this uncertainty about what it would really be is something that you face with almost every device or new drug that comes down the pike, because this situation is certainly not unique to extended wear contact lenses. When you approve a new intraocular lens, for example; when premarket data on rigid anterior chamber lenses came through, it looked

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really good for 500 patients for a year, but the effects were delayed 7 years.

So, you have that uncertainty always, and the point is to put in place a mechanism which does not take 15 years to enact to find out those things that you can't know ahead of time.

On the other issue, Brien estimates that these secondary reactions, the infiltrates, the red eye and the infiltrative keratitis appear at a rate of about 10 percent. So, I think that really, the issue to look at is, I mean, as open gamut, that would be the control group: 10 percent in individuals wearing 6-day, 6-night lenses. So, as an opening gamut, I would say that you would want to design a study that would have sufficient power to compare a group, maybe, with 12 percent, 13 percent, something in that kind of range.

DR. McCULLEY: I guess I would challenge: would we be comfortable with a 10 percent rate of corneal peripheral infiltrates, of acute red eyes with a contact lens?

DR. SCHEIN: Well, this is why I started my discussion that I would not approach this as to what an acceptable rate is but an acceptable difference with a control group that's studied in the same fashion with a product that's already--the market has already accepted it in addition to the FDA. So, the control group would be a 6-day lens, which Brien says has rates of this level.

DR. McCULLEY: Yes; we can do that for the 6-day, but we don't have the extended wear that's on the market here.

DR. SCHEIN: See, that's the anchor at 10 percent. The 10 percent is from the currently accepted products.

DR. McCULLEY: Okay; Dr. Harris?

DR. HARRIS: Jim, I'd like to raise an issue that the panel discussed some years ago, and that is what should be used as a control? Should it be the adverse effects with a 6-day lens? Or should it be daily wear? And I think that that's a discussion that needs to be gone into in more detail, because obviously, this is going to be important to both the agency and industry as they go through and look at the potentials for the various lenses and materials that they're looking at. And I question whether or not we should be using the adverse event rates with the current 6-day lenses as the standard for the future.

DR. McCULLEY: As the gold standard.

One thing we have not done as well as I hope we're going to do in the future, and that's use our consumer representative. And I've seen some head-nodding; so, that's dangerous. I would like to have you make a comment from the consumer standpoint.

MS. MORRIS: Thank you; I appreciate the consideration, but I'm nowhere near ready to give any opinions yet, but I appreciate the consideration. I'll keep listening.

DR. McCULLEY: Okay; I think Dr. Holden had his hand up next.

DR. HOLDEN: Three comments. One is I think it would be bordering on insane to use daily wear as the yardstick when you have 6-night hydrogel extended wear

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not only approved in the United States but used throughout the world. And what we're looking for is something that's as good as that if not better.

Secondly, I think Dwight is relatively uncoy like I am about pushing his test methodology, but it is useful. All of those things that say does this product reduce the physiological challenge from hypoxia, and the best measure for us is microcysts, but you also have overnight edema and Dk/L, but Dwight also alluded to the fact that silicone elastin with a very high Dk/L does cause a high adhesion of pseudomonas to cells. And that brings in that area, and it's useful to have that prediction of adhesion and bacteria.

So, I think both of those things are helpful in predicting whether microbial keratitis might be improved or not, but, as everybody knows, we're not going to know that until new products are on the market.

In terms of the adverse response rates for what we call significant infiltrates, obviously, the comments that Rick Ferris made were very relevant to the whole question, and he used it in the context of India versus Australia, are they using the same techniques, and we spend an enormous amount of time there and with their people at our place standardizing, using grading scales, doing lots of the stuff. But if you don't use standardization, training, all of those things that are written in the manuals from the NEI about how to run a clinical study, then, the rates mean nothing, because the CLPU rate--I am absolutely convinced the peripheral ulcer rate, those little scars in the cornea are occurring at least one in 50 patients on hydrogel extended wear in the United States, and the reported may be one in 5,000 or one in 10,000, because they are small peripheral

scars; events, sometimes, that people don't even recall.

So, the collecting of that information and using it to determine whether one lens is an improvement or equal to what the public is using at the present time has to be done under strictly controlled conditions, and that's been a real problem even for research institutions to agree. I think the FDA has to be very strong about that.

DR. McCULLEY: One thing I'm hearing is the suggestion that it came from the podium, and it's come from around the table, that there may be some tests or some studies that can be done that are not part of the large cohort that can give a prediction or an idea about whether a lens is apt to be safe, and if it looks as though it is, it can then go to the market, but if these other predictors prove to be accurate that it would allow one to screen out lenses that might be not good and, therefore, not subject the public to the trials.

Dr. Cavanagh, last comment.

DR. CAVANAGH: Two quick comments. One is I agree with that comment Dr. McCulley just made and Brien made. It's important to test for lenses in the real world, in real offices that prescribe them in multiple centers and not in ivory towers where everything is controlled to four decimal places, because it doesn't give you data that you can extrapolate to real clinical experience. So, they're not exclusive; they're supportive. And I think you have to do both studies in the future.

The daily wear question has been raised; I didn't raise it, but I think it deserves a serious comment. And we, right now, have a risk which we are tolerating of

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the use of a foreign body in the eye, contact lens and daily wear. It clearly accounts for a quarter to a third to somewhere in that range of ulcers and infections. The real question is are the new materials going to lower that rate as well? And that's the majority of the market, and that's the majority of eyes at risk, and that's the public health problem.

The extended wear outpatients will probably always be a minority of less than 50 percent of wearers. We're backing into it by considering six nights on, one night off versus 30 days as the acceptable study control experimental group, and I agree with Brien; that is correct. But we're going to have to come back and look at some point at the daily wear question.

DR. McCULLEY: Dwight?

DR. CAVANAGH: And when you want to do it and how you want to do it is up to the agency, but it needs to be mentioned.

DR. McCULLEY: Point of order. We've got to stay with the questions that are in front of us. Even though there are many other important issues, we just simply have got to do it. We have three more pages of questions to go through, guys.

Have we dealt with 2A satisfactorily or--

DR. SAVIOLA: Well, actually, we've kind of moved along into more than just 2A.

DR. McCULLEY: Right.

DR. SAVIOLA: B, C, and D as well, sir.

If I may just address Dr. Harris, because he did raise the question, some of

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the points that the invited speakers had mentioned are, in fact, reflective of the current policy. What we had envisioned was at the current time, we are not taking any action to do anything in terms of removing 7-day from the market. So, basically, that is our marker. We've accepted that level of risk, and even though we've tried to encourage companies to show that they are better than that or possibly as good as daily wear, the goal of this discussion was to try to get a handle on where we are with up to 7 days and, therefore, that would then define as a marker what people do as they go beyond that point in time.

And I hope that's acceptable. You may not personally agree with it, but for the sake of what we're trying to accomplish, that is where we stand at the moment on that.

DR. McCULLEY: My impression is that the panel's opinion is that if we're accepting the 7-day rates that we accept the 7-day rates.

DR. SAVIOLA: Yes.

DR. McCULLEY: And that that would be used as the standard to compare--

DR. SAVIOLA: That would be used as the control

DR. McCULLEY: --the 30.

DR. SAVIOLA: Right.

DR. McCULLEY: And that the 30-day should compare favorably to the 7-day.

DR. SAVIOLA: Hopefully better than that.

DR. McCULLEY: Is that a fair summarization of the panel's opinion?

DR. HARRIS: Certainly, I have some significant differences with that, but I recognize the fact that, from a practical standpoint, using the 7-day is a reasonable approach. But I don't think there's any of us who truly believe that we like the fact that the 7-day criteria isn't as strict as we hope it would be.

DR. McCULLEY: Right; and what I was saying is that the panel would not be comfortable with loosening--if we're going to accept that as fact, which we seem to be needing to do, that we would not accept loosening of the complication rate or the adverse event rate beyond what we're seeing with 7 days if we went to 30.

DR. HARRIS: Yes.

DR. McCULLEY: That was what I was trying to state.

DR. SAVIOLA: Before we move along here with the questions, Dr. Bullimore did raise the point about possibly having the information in hand and then trying to give us some feedback afterwards, and we did provide you with a rather exhaustive literature summary. The rates of corneal ulcerative keratitis that we gave you from the published literature do, in fact, reflect the information that was presented by Dr. Schein, 1 in 300, 1 in 500, somewhere there. So, that might take away--that's what we're going to be working with in terms of numbers and crunching is 1 to 300 or 1 to 500 range, in there, rather than letting you off the hook and giving you something to come back with later.

DR. BULLIMORE: Yes; but as we've seen from Dr. Schein's presentation, that presents the sponsor or would-be sponsor with an almost Herculean task of coming up with a sample size in the thousands to show equivalence or, you know, 1 in 200 versus

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a 1 in 400 rate.

DR. SAVIOLA: If I need a number to discuss with people, that's what I'm going to use.

DR. BULLIMORE: Okay.

DR. SAVIOLA: Whether they use that to calculate their sample size is a different matter.

DR. McCULLEY: I don't think we would disagree with that, and I would like to point out that unless you want us to continue to belabor this--

DR. SAVIOLA: No, that's fine.

DR. McCULLEY: --we've got a lot of other questions to get to.

DR. SAVIOLA: I think we've covered it adequately.

DR. HARRIS: Jim, can I just raise one issue that was touched on peripherally? And that is material prerequisites and things that can be done before lenses ever go on patients' eyes? I think it's apparent that before the agency allows a company to start doing the premarket approval with patients that you need to look at certain lens characteristics and certain factors. We've had some presentations on techniques and procedures and factors that need to be evaluated, those that should be considered by the agency. Dk/L is obviously one that is already being looked at; deposit resistance; bacteria resistance; dehydration resistance; movement performance; tear flow; tear replenishment rates; stagnation; biocompatibility; these are all factors that should be incorporated into the types of material testing that's done prior to patient testing.

DR. McCULLEY: Okay; Brien?

DR. HOLDEN: I don't like to keep arguing with you, Mark.

DR. HARRIS: You certainly do, Brien.

[Laughter.]

DR. HOLDEN: But it is very difficult to do what you said other than for the obvious ones that you've mentioned; things like biocompatibility: we have exhaustively looked for any test that would predict lack of performance in the clinic in long-term, and a lot of the things that we see just aren't predictive. These lenses, you know, pass all of the CGI and all of those tests and that sort of stuff, which is sort of standard.

So, it's difficult to do that pre-launch, but I think it's a very good idea to collect information and see if there are correlates with problems as time goes on. For example, deposit resistance: there is absolutely no data in the literature to show that a high level of lysozyme deposits causes more problems than a low level.

DR. McCULLEY: I think, you know, conceptually, we wouldn't disagree. And then, we leave the practical application of it to the agency. But conceptually, I think that there probably would not be disagreement.

2B, I think adverse reactions, corneal infiltrates; I don't think we need to spend any more time on that.

DR. LEPRI: Actually, we've gone all the way up to question number four, Mr. Chairman. In light of the current conversations, I believe we need to rephrase that

question. In light of the discussions that have occurred here today and our conceptions of what events should be considered, do you feel that that is equally applicable to RGP lenses as with extended wear lenses? And do you have any specific safety concerns regarding extended wear RGP lenses as compared to soft lenses?

DR. McCULLEY: Okay; from listening to the panel before, I think that the one comment would be in terms of safety, we would expect any extended wear to perform as well as what is approved, so that there wouldn't be slack cut for an extended wear RGP relative to an extended wear soft. Is that a reasonable statement?

The other question would be would there be any other concerns relative to RGP. I have one that immediately comes to mind that Marian alluded to before, and that would be warpage. Are there any others? Mike?

DR. HARRIS: Well, there's lens binding, adhesion, whatever terminology you would like to use which has been found to be a problem. How much of a problem, what kind of adverse effects this has in the long-term, it's hard to say, but these are issues that those of us who fit contact lenses are concerned about and certainly should be evaluated and reviewed by the agency.

DR. McCULLEY: Dr. Holden?

DR. HOLDEN: Extended wear RGP, I think we have about 500 patient-years with high Dk RGP, and I would agree with Mike that we would have--

DR. HARRIS: That's a first.

DR. HOLDEN: Yes; well, I just thought I would throw that in. I'm just

trying to work out what I agree with you about.

DR. McCULLEY: Now, you just broke his train of thought.

DR. HOLDEN: But adherence, you need to keep an eye out, and if the lenses are inadvertently inappropriately fitted tightly, they will cause peripheral staining. But in that 500 patient-years, we have had no microbial keratitis; no contact lens acute red eye; no contact lens peripheral ulcers; no infiltrative keratitis, and we put that down to the things that were mentioned about less corneal coverage and good tear exchange.

DR. McCULLEY: Okay.

DR. HOLDEN: So, I don't think there's an issue here other than--

DR. McCULLEY: That's good.

DR. HOLDEN: Why aren't they being sold for extended wears is my question.

DR. McCULLEY: Dr. Cavanagh?

DR. CAVANAGH: There is one important issue, though, and that's sample size for measuring binding. Mike, it's an oxymoron that with these better or really high Dk lenses, we haven't seen any binding. We would have to have 50,000 eyes to measure one, probably.

In the old days, with the older Dk materials, the materials in the range I showed you, the RGP materials that it caused increased binding that's in your handout, those had a lot of binding. So, are you going to tell an RGP manufacturer that they have to have 1,000 eyes when really, the binding is not that much of a significant problem, but

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they have to measure a 1 percent rate? Or where are you going to set the percentage? If you set it at 9 or 10 percent, where you're setting acute red eyes for either type of lens, soft or hard, that's fine. But it comes back down to a sample size issue, and I'd like to hear Brien's and Oliver's--

DR. McCULLEY: No, the question is not sample size here. The question is issues that would relate to RGP extended wear vis a vis soft extended wear and those we've stated, and are there any others addressing that specific question?

Marian?

DR. MACSAI: Well, as you said earlier, the corneal warpage or topographical changes, but as a direct corollary to that, it's vision stability which then becomes a labelling issue in these devices.

DR. McCULLEY: Good point.

DR. MACSAI: Because that is what the patients or consumers care about and understand.

DR. LEPRI: We'll be addressing that under our questions about efficacy, Dr. Macsai.

DR. McCULLEY: Okay; now, we have question four in front of us. Does anyone else have a response, anything to add to question four before us?

Dr. Holden?

DR. HOLDEN: If you don't want me to keep making comments, just tell me to shut up.

DR. McCULLEY: I will; you can still talk.

DR. HOLDEN: RGP extended wear binding in prospective studies is about 3 to 5 percent when you see the patients early in the morning. It has no important sequelae in terms of complications as far as the cornea is concerned. In terms of warpage, what has been very obvious as the Dk of RGPs has risen is that from PMMA, and I did my Ph.D. in orthokeratology bending English corneas and distorting them extremely badly.

Over time, as the Dk has risen, the changes that--how Dk lenses are put on corneal shapes are very regular. So, you get a regular shift in astigmatism; you don't get distortion of the cornea. But I'm talking only here of 100 Dk/L materials. I'm not talking of low Dk materials.

DR. McCULLEY: Right.

DR. HOLDEN: So, that issue of edema plus pressure was the one, I believe, that was causing the warpage. If you remove the edema and put gentle pressure on with a modern high Dk RGP lens, it's very rare to see corneal distortion of any sort.

DR. McCULLEY: Irregular distortion.

DR. HOLDEN: Irregular distortion. You can see change in shape, but it is regular and all that stuff.

DR. McCULLEY: Now, the question is we have addressed this issue; now, we're starting to restate. I think we've addressed it. If you have something to say that will move this into another dimension, then, great.

Okay.

DR. MACSAI: I only want to say in respect of Dr. Holden's comments that they are related to lenses that exist of materials that exist. We are talking about new materials, new lenses. So, perhaps the issues, for example, of endothelial cell loss or warpage may be worth considering in a different material in a different lens.

DR. McCULLEY: Okay; all right. We are not--the purpose here is not to debate; it's to offer opinion. So, any other opinions?

Dr. Bullimore?

DR. BULLIMORE: Yes; without wanting to appear like a luddite, I just think we should measure corneal changes induced by the RGP lens in terms of astigmatism measured by refraction rather than trying to wade through 500 topography maps.

DR. McCULLEY: Well, it probably wouldn't be bad to have both. You have refractive change, and you have topographic change.

DR. BULLIMORE: I'm just trying to think how easy it's going to be for reviewers and the panel and the FDA to digest the information, and until we have easily digestible numbers that come out of topography and widely accepted numbers, it seems improvement--

DR. McCULLEY: Did the FDA have a further comment before we move on to the next question?

Dr. Soni, did you have--

DR. SONI: I was just going to comment on this that that's really an efficacy issue rather than a safety issue.

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DR. McCULLEY: Okay.

Dr. Ferris?

DR. FERRIS: Just a quick question or comment. From what Oliver showed and from what we've seen, it would seem to me that you would need a study of--I don't know; what--500 to 1,000? And maybe we can haggle about what the right number is of patients followed for 6 months to a year. You can holler about what that right number is. To be able to find some relative confidence around these infrequent events. And when we start focusing on these individual events, and maybe, we're going backwards here. Maybe we ought to say as a standard, you ought to have 700 people followed for 7 months, just to get around the haggling. And these are the variables that you ought to measure.

And that's what we want to see, and we want to see them in a control group and a treating group, and if your control group rates are very low, then, that's going to raise some questions about the treated group rates as well, and what is the standardization? And maybe that sort of cuts to the chase here. One of the things we want to measure and how do we want to measure them? And the sample size seems to be more or less dictated by the fact that it has to be in that 1,000 range because of the fact that we can't tolerate doubling or tripling of the rate of keratitis.

DR. McCULLEY: FDA comment? Ready to go to the next question?

Okay.

Question five?

MS. WARBURTON: Does the panel think the expected occurrence rates and clinically significant differences should be constant for each study protocol? And this question is intended to address the situation where two different sponsors may pick one or the same, you know, different or the same endpoints as their primary safety endpoint, and, in their protocols, they may have two different expected occurrence rates. It's another reason why we were asking for opinion on occurrence rates. And, as a result, they come up with different sample sizes.

DR. McCULLEY: Would the response to that not be that we would hope that there would be some standardization of appropriate endpoints?

MS. WARBURTON: Yes; that's the ultimate goal.

DR. McCULLEY: Do it.

DR. MACSAI: Yes.

DR. SAVIOLA: It goes back to what Oliver's saying: what's going to be clinically significant difference between the two different groups. We kind of skipped over it as 2D, because we figured, well, you didn't really give us a number. So, it's kind of hard to say what the difference is going to be. But as it stands now, it's sort of a design issue, too.

DR. McCULLEY: And I think that the response from hearing what you said and what the--or you guys said in the FDA and what the panel's saying is that we're kind of accepting, for whatever reason, through the back door, the current rate with 7-day wear. Is that not what I heard you say? And if we're accepting that, whether we like it or

not, then, that's what we're accepting. Or am I missing it?

DR. SAVIOLA: Dr. Ferris, forgive me if I misspeak in this section in terms of a design, but knowing the rate is one issue. Having to decide on what's an acceptable difference between the two samples is a second issue, and this one's getting to that. If you know that the rate is 1 percent or 5 percent or whatever, okay, we've established that, but what is a clinically significant difference you're willing to accept? Is it a 3 percent difference? Is it a 5 percent difference? Is it a 10 percent difference?

DR. MACSAI: Jim?

DR. McCULLEY: Dr. Schein?

DR. SCHEIN: This is an area--ground that we've covered, but we keep going back because there is some confusion.

DR. McCULLEY: We don't understand.

DR. SCHEIN: Yes; the rates that I would recommend are 10 percent in the control group based essentially on what Dr. Holden has estimated from other Western studies. That's a pooled rate of the secondary events. It has nothing to do, Jim, with that rate of 1 in 300 or 1 in 500 of the ulcers. It's just completely unrelated through designing on these secondary issues.

We don't know whether Brien's numbers are correct, and under a different setting, whether 10 percent will be found here, but it may be the best estimate that we currently have. So, start with 10 percent and then discuss the question, whether you're willing to tolerate a new material that has a presumed benefit, and the benefit is wearing it

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for 30 days rather than six. Will you tolerate 11 percent? Twelve percent? Someone hit a buzzer, you know, when we hit a number that--begin to think from a clinical, not a statistical perspective, is intolerable. And that will determine your sample size.

And if you're in that range of going up to 12, 13, 14, 15 percent, then, you're in this range of 600 to 1,200 patients.

DR. McCULLEY: This may be a really dumb question: do we have a handle on the rate of adverse events, negative events, for 7-day wear in the United States?

DR. SAVIOLA: No.

DR. McCULLEY: I understand we then get into a legal issue about what can and cannot be used.

Dr. Rosenthal?

DR. ROSENTHAL: The new law does allow the agency to use data beyond 6 years, but there is an argument with industry as to whether the beyond 6 years is retroactive or starts at the time the new law started.

DR. McCULLEY: Keeps attorneys in business.

DR. ROSENTHAL: Sorry?

DR. McCULLEY: Keeps attorneys in business.

To me, the standard should be if you're saying that you're not--or how did you say before? You're not recalling 7-day wear. So, we're accepting that rate. We need to know what that rate is. If we know what that rate is, then, that sets the standard. That's the logic that follows to me.

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Certainly, the rate in India is different from the rate in Australia and looks like a very unacceptable rate from our standards. I don't know about the Australian rate, whether that would be comparable to the United States rate. If it is, then, we could use Australian data, because it would be legal. It seems like we're shackled here very unfortunately.

DR. SAVIOLA: To go back to what Oliver's saying, though; even if we just, for the sake of discussion, accept that 10 percent aggregate rate as being something to design around for beyond 7 days, then, the phraseology we used here, the clinically significant difference in percentage, is what he was just saying: 10 percent versus 12 percent; 10 percent versus 14 percent. That's where we're trying to get a handle on this question.

DR. McCULLEY: Right.

Dr. Cavanagh? Wait; I'm sorry; Dr. Macsai was in order.

DR. MACSAI: There is no acceptable difference. It's the same. If you're going to put it on your eye for 30 days or 6 days on, you know, one day off, you have to have the same rate. The sponsor has to prove that it's equivalent. Why are we discussing this?

[Laughter.]

DR. McCULLEY: Because the statisticians are going to start to then rip us apart; that's why.

Dr. Ferris?

DR. FERRIS: So, but you can't prove the same.

DR. MACSAI: You take--

DR. FERRIS: You can only prove that it's not worse.

DR. MACSAI: Not worse; you take the--

DR. FERRIS: Not worse.

DR. MACSAI: --what was acceptable with six and one, and you must show--

DR. McCULLEY: It's no worse.

DR. MACSAI: --no worse rate with 30.

DR. FERRIS: Okay; and that's what Oliver was saying; no worse. Are you going to be--

DR. MACSAI: Eleven is not good; 12 is not good. Ten or whatever you set it at but with the same confidence level; you know what I mean; statistically equal.

[Laughter.]

DR. McCULLEY: What I find is that when we get into these kinds of discussions, the epidemiologists start to talk, and I can't understand a darn thing they're saying. So, I think we need to rely on them and trust them, and the point is that we would like to see nothing that is worse by whatever, you know, playing with numbers that you get at that and whatever your limits are, we that don't understand the statistics as well conceptually try to match your statistics to that concept. That would be my response to it.

Dr. Cavanagh?

DR. CAVANAGH: There are no historical controls, and they're useless.

You have to run a control for each new lens you're going to test, number one.

Number two, that control lens: let's call it midwater lens X. It's already approved by the FDA, the panel and everyone else, and people are using it for 7 nights' wear. Unless you're going to go back and rewrite history, you have to take that as ground zero. You then take your control group, and you measure that over time measured in months, and you show that there is no difference, that they're equivalent.

Now, hopefully, the new materials will be better, and the rates will go down. But they can't go up; they have to be equivalent. How do you define equivalence? That's in terms of the way the study is designed for the N and the power and the statistics, and you want it statistically not to be different. And if it is different, and it's worse, you don't approve it. If it's the same or better than, you approve it, and you move on.

DR. McCULLEY: Okay; we're starting to say, I think, some of the same things. Now, one more comment from someone who has not spoken who was wanting to speak.

Dr. Yaross?

DR. YAROSS: Actually, my point was just alluded to. We need to decide are we working towards a historic control when you need to know what the actual data is or concurrent control? If you're saying concurrent control, then, deciding what the current rate and whether you tolerate 10 or 11 percent isn't the issue. The issue is what is the confidence interval around not worse than.

DR. McCULLEY: But we don't have to close our minds to concurrence or historical, and if we have historical data that we can have as a gold standard or as a standard, that can enter into the study as well.

No?

DR. FERRIS: But that gets into measurement technique.

DR. McCULLEY: Okay.

DR. FERRIS: And because it was a 10 percent event rate in the past, if you use Brien's new method of looking harder, your rate goes up. The event didn't go up; it was the ascertainment that went up. So, you have to be careful. That's why it's so important to have the concurrent control group. But I agree with what Dwight said. You've got a concurrent control group. You're better off if the event rate comes in less than the standard rate. If it comes in more, but it's not statistically significant, what I'm hearing is that Dr. Macsai and others are going to say, well, you know, you're going in the wrong direction, and I'm worried that you've got a 12 percent rate rather than a 10 percent rate.

I understand it's not statistically significant, but that's going to be a red flag even though it's not statistically significant, because the other thing I've heard is that there doesn't seem to be a lot of comfort here with the current level. Although it's standard, and although it's current, people are not very happy with it. So, if you come in with something that's equivalent, but the trend is in the wrong direction, that's going to be a problem in getting it approved, I think.

DR. McCULLEY: Okay; let me ask FDA guidance here just for a moment. I know there are several other people who still want to speak. Do you want us to continue to address this issue? Or do you want us to go on to the next issue?

DR. SAVIOLA: Well, in the interests of time, I would like to move along, because we underbudgeted that particular question.

Now, if there is a comment that hasn't been made, if it's not rhetorical, again, reiterative, then, I would--

DR. McCULLEY: Okay; the onus is on you to make a new, completely brilliant, unthought of--and Oliver is in your shadow.

Fire away.

DR. HOLDEN: I would just like to say one thing about this the rates should not be worse. If you have a big advantage in a product, namely, it doesn't cause hypoxia, and patients love being able to wear it 30 nights, and it prevents them from going and getting their corneas cut in half and all of those other things that happen in those places, then, you say okay, the rate is now 10 percent, but it's 10 percent for non-sight threatening, irritating, annoying events.

Now, if it goes to 15 percent, yet, what that means in practice, and what's been going on in our studies, you know, we have about 300 patient years in these protocols of high Dks is that not everybody is going to be able to wear them 30 nights, and you just reduce the people who can't tolerate; they're satisfied and all of that stuff. So, I wouldn't say if it's 10 percent now, it's got to be 10 percent, because that requires a very,

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very large patient study. But you need to take into account that these are not sight-threatening events, and it's a question of consumer satisfaction, and the optometrist and ophthalmologist in practice won't be using lenses that cause a lot of annoying events.

DR. McCULLEY: It has to be a severity rate is--okay--and weight.

Oliver?

DR. SCHEIN: One statement. If the sponsors of these new--the industry sponsors of this new generation of lenses will permit it by, at a minimum, releasing the data on their control groups, we will have better data on the lenses that are worn by millions of Americans through these new studies than we have through any currently available source.

DR. McCULLEY: This is a problem that's come up with the IOL matrix grid and now with these products as well, and it seems like to me, as the politically uninitiated, it seems like we're needlessly hamstrung, and I'll probably get my wrist slapped for saying that. But it would be nice if we could have the data that's available made available to us, but I can't fight law and politicians.

Shall we now go on to question six?

DR. LEPRI: Yes; we're now going to address efficacy endpoints, and I'm going to present several of them all at once, because one discussion seems to flow into the other.

6A: please comment on the suitability of the following endpoints and propose acceptable levels of performance; for example, the proportion of patients

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achieving the endpoint.

Number one, contact lens visual acuity of 20/30 or better compared to that of 20/40 and/or 20/20 or better; two, loss of two or more lines of best-corrected visual acuity; spectacle versus contact lens; initial to final visit and initial to any point in the study.

What is the clinically significant difference between test and control that you would recommend? And does the panel consider duration of lens wear to be an efficacy measure?

DR. McCULLEY: What would you like us to address in that?

DR. SAVIOLA: Well, we'll begin with the end points.

DR. LEPRI: The contact lens visual acuity of 20/30 or better compared to accepting contact lens visual acuity end points of 20/40 and 20/20 or better.

DR. McCULLEY: Who would like to address that question? Dr. Bullimore?

DR. BULLIMORE: Do we have any historical data on this?

DR. SAVIOLA: To use the term "needlessly hamstrung", we were advised to not lead this discussion, and therefore we did not provide a number to you about how many percent in the current PMAs that are approved had 20/30 or better versus 20/40 or better or 20/20 or better. Now, I could say that in your clinical experience, you would expect perhaps greater than 90 percent of the contact lens wearers to achieve 20/20, without leading you too much. We have data, again, proprietary tied up. We're asking

you from a discussion standpoint what your expectations would be.

DR. McCULLEY: Dr. Schein, bail us out.

DR. SCHEIN: I think it's almost irrelevant. Basically, the acuities are important in relation to where they start and in their comparison with previous lens wear or spectacle lens wear in that individual patient and they should just be compared across the case group and the control group.

DR. FERRIS: We've got a control group, and the visual acuity ought to be as good in the treated group as in the control group and it seems to me that's it. The tolerance for a decrease to two-line loss best corrected spectacle vision would be very low, lower than it is for the estimate, which is already pretty low.

DR. McCULLEY: Does that satisfactorily address the issue from your standpoint and does that have panel concurrence? Dr. Macsai?

DR. MACSAI: I can't speak for the FDA, but I have concurrence with it and I would urge the FDA to also consider looking at the best spectacle corrected visual acuity worse than 20/25 if they started with 20/20 for induced irregular astigmatism or visually significant subepithelial fibrosis, any number of things that might cause that. You have a control group.

As far as the duration of lens wear time to be an efficacy measure, that somewhat depends on what the sponsor's claim is.

DR. McCULLEY: Marian, can you wait just a second? Let's try to get one thing buried before we go to the next, and then I'll come right back to you if we have

this one adequately addressed.

Have we adequately addressed 6(a)(1) and (2)?

VOICE: If it ain't broke, don't fix it.

DR. McCULLEY: You say no. Do you want to make it better?

VOICE: No. I said--

DR. McCULLEY: No, not you. Brien was shaking his head.

DR. HOLDEN: I thought you didn't want me to talk.

DR. McCULLEY: Oh, I was kidding.

DR. HOLDEN: I don't understand why one is there, because if people can't see with their lenses, they won't wear them. I mean, what about monovision? You know, it's like 660.

DR. McCULLEY: I think the point--yes. I mean, you're addressing the point further, of where they started, where they get to, and the control group.

DR. HOLDEN: Number two is very important.

DR. McCULLEY: Okay.Ê Do you--

DR. HOLDEN: But number one seems a bit of a no-brainer.

DR. McCULLEY: And the comment that was made about number two was that it should be better than the range that has been accepted for excimer kerorefractive surgery. That was the statement made.

MS. WARBURTON: And with that, are you talking about best spectacle corrected?

DR. McCULLEY: Yes. All right. Now, have we adequately--you have something more to say?

DR. PULIDO: And why does it have to be better than the range that's accepted for PRK?

DR. McCULLEY: Who proposed that, and let's let you answer.

DR. HARRIS: I'll make a stab at it. With PRK, the end result is moderated by wearing either contact lenses or spectacles if it's not as good as 20/20. With contact lenses, that is the end result. That is the mechanism. Therefore, if the contact lenses don't provide you with the vision that you're expecting or close thereto, you're not meeting your own visual requirements.

DR. McCULLEY: Well, but with excimer, it's best spectacle correction, as well, that we're talking about, two lines loss.

DR. HARRIS: I'm sorry. But--

DR. PULIDO: So again, why are we lowering the bar?

DR. McCULLEY: All right. The question is, why does it have to be better than--why is the recommendation that it be better than what is the standard for excimer PRK. Marian?

DR. MACSAI: I can't say why, but I can give you an opinion. The opinion is that the public's perception of permanence in PRK or lasic is such that they're willing to accept a higher rate of complications or incidence of loss of vision.

DR. McCULLEY: For the reward of not having to wear an optical device?

DR. MACSAI: Right.

DR. McCULLEY: Okay.

DR. MACSAI: That's my opinion as to why.

DR. McCULLEY: I would agree with that opinion. Rightly or wrongly, I would agree with that opinion. Are there opinions to the contrary?

DR. SAVIOLA: You have already pretty much answered this question. Why you answered it the way you did, I think is the discussion at hand. I'm willing to accept the idea that loss of two or more lines of best corrected vision with contact lens wear should be at a lower rate than a surgical procedure, simply by nature of being a minimally invasive procedure compared to lasic or PRK, and leave it at that.

DR. McCULLEY: All right. Shall we then now go on to B? I think we've already been beating on that, so let's not unbury that.

Marian, you wanted to comment on number seven, does the panel consider duration of lens wear time to be an efficacy measure. Now--

DR. MACSAI: I would say that that depends on what the sponsor is claiming about the device. If the claim is that the device is for 30 days or 300 days of wear, then the ability or the percentage of patients who can wear it for that long is an efficacy measurement. Otherwise, it's not.

DR. McCULLEY: Dr. Holden?

DR. HOLDEN: It's a very useful clinical indicator if, say, 67 percent of patients, as we found in one study, did not have to remove their lens for a month for any

purpose and 25 percent took it out once and washed it. I think it's very interesting information to collect, but whether it should pass or fail a lens is up to you guys, I guess.

DR. McCULLEY: The question is a simpler one. Do we consider it an efficacy measure?

DR. FERRIS: Why wouldn't you measure it? It seems to me for sure you measure it. What you do with that seems to be a different issue. I think a key here is that we're setting guidelines, aren't we? We're not setting rules. So yes, you need to measure it, and it's going to be relevant. If only five percent of the people can actually wear them for 30 days, that's going to be relevant. But to prejudge what's going to come seems--

DR. SCOTT: I think it's also a safety issue, that if patients in the study, which is what we're using to predict how the long-term results are going to pan out, if the patients in the study don't wear the lenses for 30 days, we're deprived of that data. We don't see the safety component of that. So I think in the study, patients have to be wearing it for 30 days. It's more than just an efficacy issue. If they came in and all of the patients only wore it for 15 days, even though the approval traditionally has been given, I think--is it going to be still worded the same way, up to 30 days continuous wear?

DR. SAVIOLA: Well, if they only get 15 out of it, it wouldn't be. The reason this question was in, we're obviously going to measure it during the study and it was to get the wheels turning in your heads about how you would view the device being able to be labeled for that duration of wear based on what the outcome was in terms of percentage of wearers. If 15 percent, if ten percent, whatever, would that still be in your

mind something which would allow it to be labeled for up to 30 days and then have a breakdown in the labeling, as we get into a later question, about how successful different people were?

DR. McCULLEY: That's a different question. As I understand your question, to restate it, it would be, what percentage of patients would have to successfully wear a lens for 30 days if it's going to be labeled for 30 days wear. Is that not the question you just asked?

DR. SAVIOLA: Well, that wasn't what I was trying to ask.

[Laughter.]

DR. McCULLEY: No? Then I didn't understand.

DR. SAVIOLA: It clearly answers this question, though. If you think there is a certain measure that needs to be achieved in order to gain that--

DR. McCULLEY: Speak up.

DR. SAVIOLA: It must be these government microphones. If there's a certain percentage that needs to be achieved in order to label that claim for 30 days.

DR. McCULLEY: Yes. That's what I tried to say. I guess I didn't say it well. Dr. Rosenthal?

DR. ROSENTHAL: May I make a comment? The issue of asking a lot of questions about end points is that with the new PDP process, the panel is going to be asked for the pass-fail criteria at the beginning of the study, at the beginning, before the study even begins. So we are, in a way, preparing you for what you are going to have to

do when you encounter your first PDP, if you do encounter your first PDP.

DR. McCULLEY: Right. Let me--

DR. ROSENTHAL: If and when you encounter it.

DR. McCULLEY: Let me state a question that I think will get at the heart of what you're asking, I hope. If a lens is going to be labeled for 30 days wear, what percentage of the patients in the clinical trial would have had to have achieved 30 days wear for that lens to be labeled as such, 20 percent, ten percent, two percent, 50 percent, 80 percent, what?

DR. MACSAI: Ninety.

DR. McCULLEY: Now, that, I think, is your question.

DR. BULLIMORE: Does the FDA want a number in that regard?

DR. MACSAI: Do you want a number? How about 90?

DR. McCULLEY: Well, as Dr. Rosenthal said, if we look forward to PDPs, we're going to have to put a number.

DR. SAVIOLA: It was not something that was ever considered when lenses were approved for 30 days originally, and we looked back at the PMA data and really compared the wear times. The percentage of successful patients was really--I'll pick a number--say 30 to 40 percent at best after 30 days, yet they were labeled for up to 30 days. So if you're going to look at this in terms of an efficacy criteria, if you're going to say, they need to have a certain level achieved, then we want to know that.

DR. MACSAI: I still feel strongly--

DR. McCULLEY: Do you have a number?

DR. MACSAI: Ninety percent. If you're going to claim--if a sponsor is going to claim that a device does this, it had better do that. That's it.

DR. McCULLEY: But a counter to that would be that one would have to put in the product labeling that it is approved for 30 days wear, but only 50 percent of those achieve that, 20 percent achieve something else, and so on, and you deal with it in the labeling, I think.

DR. HARRIS: Right. This is a labeling issue because what the agency is going to do is you're going to approve this lens for up to 30 days wear, and indeed, truth in advertising and informed consent tell you that you need to give the patient an understanding as to how likely it is that they're going to be one of those folks who can wear it 30 days versus one of those folks who can wear it two weeks, one week, or what have you, and that certainly is something that we could discuss if the agency feels it's important.

DR. McCULLEY: The number I'm still looking for is what percentage of patients in the trial would have to reach 30 days wear for that to be part of the labeling. Dr. Yaross?

DR. YAROSS: What I think the issue is, if you're talking about wear up to 30 days, you need enough information to be able to say that you can provide the safety profile on that wear up to 30 days, and then if you've shown it's safe up to 30 days and you tell people that these are the results for those who achieve 30 days and perhaps these

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are the results--a sponsor should also have the opportunity to say that for those who achieve 15-day wear, what were their results, so that you have that opportunity to provide good information to the practitioner.

DR. McCULLEY: Have we addressed the issue or do you want more input on this issue, FDA? You're confused, too? You have sufficient input on this?

DR. SAVIOLA: There's a couple more comments that people want to make, so--

DR. McCULLEY: Okay. Let's hear the other comments.

DR. SCOTT: I think that's going to affect your sample size.

DR. McCULLEY: Identify yourself.

DR. SCOTT: Cliff Scott. I think it's going to affect the sample size, that if you're going to have people who enroll as potential 30-day patients and insufficient numbers of them fill 30-day criteria, you're going to be deprived of the safety data that's attached to that 30-day wear. So there's got to be a core number of patients that reach 30 days for the safety issue to be addressed properly.

DR. McCULLEY: That's a good point.

Dr. Schein?

DR. SCHEIN: I agree with Dr. Scott completely, and the corollary is that you can't possibly predict ahead of time because you don't know what the distribution of the data is. You've dealt with this already in excimer, where a company may submit data up to X-diopters, but you find there are very few patients in the higher myopial range, or

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perhaps you have sufficient patients in the higher myopial range but you're not quite satisfied with the data in that group, and so you then vote to approved based on that data and the smaller dioptic range. Those are decisions that you can't make until you see how the data shakes out.

DR. McCULLEY: That works for PMAs. It's going to be a trickier business with PDPs.

Dr. Cavanagh?

DR. CAVANAGH: It is a labeling issue in this regard. If you reach the minimum end to establish safety at 30 days, the approval would work something like this. Fifty percent of patients achieve 30 days. Sixty-five percent achieve three weeks. Seventy-five percent achieved, and so on, just the way you do for laser, but you have to have a minimum threshold.

If you take Marian's minimum threshold, you should immediately stop all seven-day approval for all the mid-water and other thin--low-water hydrogels that are out there because none of them are anywhere near that. They're probably closer to 30 percent, historically, in the past.

So I think--and you've got a control group. Maybe the label should read, compared to a control group of, and as long as the safety issue is there, let the consumer know what they're buying.

DR. McCULLEY: Dr. Holden, the last comment, and then we'll move on.

DR. HOLDEN: In this area, it's a little difficult to have a control group

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because the seven-night doesn't help you with this particular question. But if an approximate yardstick were--based on the experience that we've had, is that, say, 30 percent have absolutely no problem wearing 30 nights over a long period of time and 30 percent maybe have to take them out a couple of times to clean them and all that sort of stuff and 30 percent of them may have to go to seven nights of daily wear, those sort of--there's another ten percent, I realize, but they're rough numbers.

DR. McCULLEY: Lots of good thoughts, and that leaves you guys things to digest that we won't try to digest now.

The next is sample size and study duration. Would you like to introduce that, Karen?

MS. WARBURTON: Sure. I'm almost afraid to.

[Laughter.]

MS. WARBURTON: The recent historical recommendation for a new lens material to be studied for up to seven days has been 400 completed eyes--this is recent recommendations--400 completed test eyes and 200 control eyes followed for 12 months. We had asked our statistician to give us a couple of examples--you should all have a copy of this in the handout that was provided this morning--just to give us a couple of examples of what type of confidence limits we have when an observed--or let's say, the expected rate is three percent and you observe six percent and you have a test of 400 and a control of 200, likewise tests of 300 and 150, and these are the one-sided 95 percent upper confidence limits.

DR. McCULLEY: I don't think this will be difficult if we'll stick to the question. Are there comments?

MS. WARBURTON: Let me go ahead. This was just an example of the types of--

DR. McCULLEY: Your specific question in eight is, as I see it, if we recommended decreasing from 400 to 300 in the test group.

MS. WARBURTON: Yes. Would you consider that acceptable for up to seven-day studies, given that there may not be much more statistical confidence obtained when you have 400 versus 300.

DR. McCULLEY: Right. Now, the statisticians can respond. Dr. Schein?

DR. SCHEIN: I'm not a statistician and not responding based on some calculation, but this discussion now doesn't make any sense to me. I think we've gotten consensus about where we'll have to start with an estimate of what the rate in the control group is, rightly or wrongly, and that's "n" percent, give or take a little bit, something in that range, and you're going to have to show me why it makes sense to pick these numbers out of the air, why it makes sense to have half the number of controls as test lenses, and why you've chosen these particular confidence intervals, because, basically, you need to make that decision about the difference in rates.

MS. WARBURTON: That's true. We just gave this as an example, and that's why we were trying to get a sense of rate and what would be a clinically significant difference.

DR. SCHEIN: This is 6.6 percent of what?

MS. WARBURTON: This--

DR. SCHEIN: What is that?

MS. WARBURTON: As I understand this, this would mean that if the observed rate in the test group was--I mean, I'm--yes. The observed rate in the test group was six percent and you have 95 percent confidence that the true rate would, if you were using 400, would not be more than 6.6 percent. However, if you had 300, the true rate would not be more than 7.6 percent.

DR. SCHEIN: So the first example means that a group of interested people have decided that they're willing to accept a ten percent difference, right, from 66 percent, and if that's the answer, then you get that sample size if you do a two-to-one. But it will be different if you do a contralateral design--

MS. WARBURTON: Right. This is true. This was just meant as a statistical example, and we did not have the ten percent prior to coming in here which we now hear is an acceptable rate for an aggregate of adverse events.

DR. McCULLEY: No. We haven't said that yet. We don't know that yet.

MS. WARBURTON: Well, okay. Well, that's a number that we have heard. We have not heard any other number.

DR. FERRIS: Maybe I'm missing something here. It looks to me, just guessing at what's going on here, is that they're playing this 6.6 and 7.6 off a three percent observed rate in a control group--

MS. WARBURTON: Yes.

DR. FERRIS: --and that if it's about 6.6 percent, then that's going to be too high. In this case, six percent is below both of them. I'd like to get back to how we got down from 400 or 300. I'm driven by what Oliver said in the beginning, that there's some minimum sample size for which I want at least six months', maybe a year's experience to be sure that there isn't some vision-threatening consequence, particularly I want some sort of evidence that the rate of keratitis is going to be low enough that when we unleash this on the public, and they're going to be as unwitting as we are in terms of what the real rate is, that there's no evidence that we have that the keratitis rate is higher than what's currently out there.

It just seems to me off the top of my head--you can do the calculations, but you're going to need 400 or 500 to make me comfortable that there isn't a rate of--an increased risk of keratitis.

DR. SAVIOLA: This question is framed as lenses studied up to seven days of extended wear. It's not for lenses studied beyond seven days of extended wear. So that's why we're giving you as the example what we have currently been looking at. Previously, before 1990, it was 400 eyes with just a prospective cohort, no control, and as I said before, we've done 400 tests with 200 control in the most recent approval, and that's randomized. We're not talking about contralateral as a separate design issue.

So basically, you could say that we didn't really clarify the sample size question adequately because we're not really talking about seven days. They're just up to

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seven days. And in that context, we've recommended people 400 tests, 200 control, and if they come back, well, yes, but if you do the numbers, your statistics are kind of weak and we want to do 300 instead of 400.

DR. FERRIS: Right, and if you do those numbers, we want to do 250 instead of 300--

DR. SAVIOLA: Right. You start sliding down the slope here. And so we brought this back and said, what do you guys think? Do you guys want to stick at 400 and that gives us a little bit more leverage to say, the panel recommendation remains at 400 versus lowering it down?

DR. McCULLEY: Dr. Schein?

DR. SCHEIN: Let me rephrase what he tried to say, because it's this balance between not being able to design around the thing that we're all scared about but wanting to have some assurance that it's not real bad. The slide I showed about the rule of threes, let's say you had a study that had 1,000 patients in it for a year and you have zero ulcers. You could then be very sure, 95 percent sure, that the true rate is one in 300 or even lower.

But if you only get a study that had 300 patients in it and you had no ulcers, you could only be confident that the real rate may be one in 100 or less. And you say, one in 100, that's too high. So you have to move up beyond 300, and maybe 1,000 is too high, but it gets you into this range where you can say something, assuming that you have zero or maybe one ulcer.

DR. McCULLEY: So at this point, we need to pick a number that we're comfortable with, and is that 300 or 400?

DR. SCHEIN: It's neither. I think it's probably more, but it's not done in this way. That method is just not how you do it.

DR. McCULLEY: But this has to give guidance to the FDA and to industry, so what is the target number?

DR. SAVIOLA: Are your thoughts in terms of what we said here? For up to seven days, you're not separating up to seven days versus beyond seven days. You're looking at that as the same thing?

DR. SCHEIN: No. It's the same thing. It's the same thing, because the estimates that Brien has given us are based on seven days and we're looking now to make a determination between what you'll get with seven days and what you'll get with a new product.

DR. McCULLEY: Dr. Cavanagh?

DR. CAVANAGH: Let me come back again and say what I said before in different words. Suppose you're sitting here and you have data in front of you, 400 eyes, 500 eyes, 300 eyes, and it's a seven-day, six nights on, one night off, control group of mid-water lens control versus 30-day high-decay soft polymer. If you have no way to tell the difference biologically between how those eyes behave that will predict ulceration rates, would you vote to allow eyes to be exposed for three weeks at a time more, knowing that all of the available epidemiology data suggests that the ulceration infection

rates increases with number of nights of overnight wear?

And the answer is, I don't think you would. You have to have some other measure that can help you predict, and that's the biology of what happens with the lens on the eye. You can argue about 300, 250, 475, will you take 525, six-and-three-eighths. It isn't going to predict. It isn't going to help you down the road with the big enchilada, which is the ulceration infection rate.

So I think right now, the only thing you can do is to take what you've already approved, compare the new to it. Don't change your basic overall policy. Put in whatever new outcome measures, whether it's counting cysts or counting bugs, and then do an adequate epidemiology study.

I can't help but believe in my heart and in my soul that if you put a lens on the eye and it doesn't alter the surface in any way you can detect, that it's going to have to be at least no worse, and then allow the experiment to be done. But you're never going to get at it with 325 versus 450, 550. It's just not--as Oliver says, it isn't the right way to do it.

DR. McCULLEY: Okay. Dr. Holden?

DR. HOLDEN: I think if you're trying to get some level of reassurance about microbial keratitis, asking people to do 1,000 patients in the expectation that you're only going to get maybe zero or one microbial keratitis and then trying to compare that to what's going on at the present time in a sample group of 500 or 1,000 patients wearing current hydrogels, I think that's impossible.

You either go with the risk factors for infection, which are hypoxia and bacterial evasion or whatever, and improvement or similarity to the current product with adverse responses that can be more easily measured but are not sight-threatening, or you're asking for thousands upon thousands of patients.

DR. McCULLEY: I think the goal cannot be to pick out that microbial keratitis with a sample size that's manageable.

Dr. Schein?

DR. SCHEIN: Right, and the secondary outcomes that we've reached consensus on, in order to study those, you are in the range of 500 to 800 patients, depending on the design. You're in that range to do the studies that I think we would want to do, and if you're in that range, you get some assurance, the kind that Rick has asked for, about not having huge rates of keratitis.

DR. McCULLEY: Okay.

DR. SCHEIN: But you still need the follow-up to answer that question.

DR. McCULLEY: So the suggestion would be to take what numbers we have now from Brien, after you've looked at them and enough people are certain that they're comfortable that they would be predictive of our situation here, and come up with a number, and it sounds like that number, rather than being smaller than 400, is apt to be larger than 400. Dr. Schein?

DR. SCHEIN: Can we put that one slide on?

DR. McCULLEY: Yes, please, if you walk fast. Are there other

comments while Dr. Schein is--yes, Dr. Ferris?

DR. FERRIS: Yes. While he's walking, it seems to me that we're in a difficult position because this is one of those things where more is better. At least from the point of view of reviewers of the FDA, more is better. From the point of view of the company, more isn't better because more is cost. So inevitably, we have to negotiate what's doable for the company and what's adequate for us, and both are going to be pushed to the limit, I think, of what is adequate for us and what is doable for them and probably compromise is appropriate.

DR. SCHEIN: Here is ten percent, all right. Now, if you're willing to live with a twofold excess risk in the new lens compared to the control, you could get away with about 280 patients in each group. Fifty percent excess risk, but again, 50 percent, that means ten versus 12.5, you need 900 in each group with this alpha and beta. So those are basically the numbers that you're talking about if you're willing to accept odds ratios in this range.

VOICE: Those are non-sight-threatening--

DR. SCHEIN: It makes no difference what they are. It's ten percent.

DR. McCULLEY: No comments without being recognized by the chair.

DR. SCHEIN: Ten percent, whatever. It's cumulative. Complications, it's a given complication, but that seems to be the range that Brien would estimate, and this gets you into that range, if you accept this, of this 500 to 1,500 range, it gets you into some comfort as far as the ulcerative keratitis, though it will not answer it.

DR. McCULLEY: That gives information to the agency. Do you need further clarification from panel on this issue? While you're thinking on that, Dr. Scott has had his hand up.

DR. SCOTT: The sample size up there represents--does the sample size up there represent the total study, both the control and--what I'm hearing, and that's assuming an equal sample size, and what I'm hearing, that we're using--they have been historically using unequal sample sizes. What statistical power is lost by using a one-third smaller sample size, which was one of the examples that was given? The control group size, sorry.

DR. SCHEIN: Maybe Rick can do that in his head, but I can't. This is the total sample, so in each group, it's half the size. This is for a traditional design. In a contralateral design, it's more efficient, and depending on the concordance of the two eyes, this might be reduced by as much as a third in a contralateral design.

DR. SCOTT: Well, you realize that if the control group is smaller, that no one will do a contralateral study because the total number of patients entered into the study will be smaller if you have bilateral studies with a smaller control group.

DR. SCHEIN: No, the other way around. It's more efficient to use the contralateral design because the eye is being analyzed, not the patient.

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: Point of--going back to Dr. Holden's line in the sand which was drawn at ten percent, is that ten percent per patient years or ten percent per eye

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years?

DR. HOLDEN: There's two very important points about that. One is it's eye years, which, you know, comes into this discussion. And the other is, I think, probably the most important point, is that the sample has to be specified in terms of neophytes and experience, because if you're going to bias your studies one way or the other, you can drop the rates.

DR. SAVIOLA: I think we've given you a lot of input on a lot of different things for you guys to digest and put together. I don't know that we should do anything more with those issues at this point.

DR. SCHEIN: I think we've addressed the sample size adequately. We would like to, quickly, because most of the remaining questions, I think we've already covered, on post-approval study and labeling we touched on briefly in preclinical, as well, through the course of discussion. But the six months versus 12 months, which gets into patient or eye years versus exposure time, and I'd like some feedback on that, please.

DR. McCULLEY: Okay. Comments on--the basic question is--

DR. SCHEIN: Question 9(b).

DR. McCULLEY: Nine(b).

DR. SCHEIN: Actually, is it 9(a)?

DR. McCULLEY: The question is, are six-month studies acceptable as opposed to 12-month studies? Dr. Sugar?

DR. SUGAR: Brien, did you notice a change? Did you have a higher

incidence in the first six months versus the second six months in your--

DR. HOLDEN: That's a tough question. In some events, probably. In others, not. They just keep happening. But if you're going to cut the study back to six months, you'll need double the eyes.

DR. SUGAR: Right. If the incidence is constant, then if you have half the duration, then you need the twice the numbers.

DR. McCULLEY: Does that answer--

MS. WARBURTON: Let me pose this question. Would you consider your population had an incidence rate of five percent at six months, or is that not true?

DR. HOLDEN: No. Well, the only calculation in our case assumes, firstly, a number of observations, which is also important, to the rates that you see, the number of times the patient is seen. But it assumes that if you have 200 patients at six months, that's a 100 patient years.

MS. WARBURTON: Okay.

DR. McCULLEY: Dr. Schein?

DR. SCHEIN: The eye year assumption assumes that, but I would make a recommendation that you require a year, because if you're looking at a technology that is going to be tried for 30 days, I mean, basically, you're talking about five changes, and I don't think that's enough to assess like that.

DR. McCULLEY: Dr. Cavanagh, last comment.

DR. CAVANAGH: I'd like to second a year, because if members of the

panel will look at that diamond diagram, you find that the larger cells are the most likely to decimate and the ones that desiccate and are larger are more likely to bind. I, for one, would really like to know that over a year's time, shutting down a lot of epitosis on the cornea wouldn't lead to cells at six, eight, nine, 12 months where we might see binding levels going up. I think that we have to do those kinds of studies.

The biology is what's important here. How many times a patient comes in with a red eye, which is totally reversible and non-sight-threatening, is--I think it's interesting. It's important. But I think the biology you need here.

DR. McCULLEY: There seems to be unanimity. Is there disagreement?

Dr. Ferris?

DR. FERRIS: Well, just a slight disagreement, and that is no study recruits everybody on day one. I would think that it would be reasonable to say that there has to be--the majority have to have finished a year and there has to be an eye year's worth of experience on the total population. So again, 18 months on a third and six months on a third and a third had one year, that that would be equivalent to one year on all of them.

DR. McCULLEY: That, to me--

DR. FERRIS: Well, you have to be--I just think you have to be practical as to what you say. I mean, the alternative is that you say everybody has to be followed for one year. That's okay, too. That means that you're going to have a year-and-a-half's follow-up on some. That's fine.

DR. McCULLEY: Not necessarily. They could be exited from the study.

What we want is a year's data on the population.

DR. FERRIS: Okay. I mean, it's--I just think we have to be specific if you're going to make a recommendation.

DR. McCULLEY: Yes. That was my--I thought in my mind it was a specific recommendation, that the patients in the study, whatever that "n" is, are followed for one year.

MS. WARBURTON: Can I ask for a clarification? Is this for both less than seven-day and greater than seven-day studies?

DR. McCULLEY: Yes. Dr. Holden?

DR. HOLDEN: You have to be careful with two issues. One is specifying the number of patients who are going to finish the study as opposed to start the study, and the enrollment time is important, whether it's three months to enroll 500 patients. It doesn't make sense to make it long.

DR. McCULLEY: Other comments?

[No response.]

DR. McCULLEY: I think we will adjourn the morning session at this point, if that's your desire.

DR. SAVIOLA: Before we do, if anyone on the panel does have any comments regarding the last three general topics, which are post-approval study, pre-clinical, and labeling, if we could just take a few minutes and see if there's any comments people have on that, then we can adjourn promptly, within five minutes of our

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scheduled time.

DR. McCULLEY: Presumably, everyone has read these questions. Are there any very strong opinions that you would like to share with the FDA, and presumably, if you have lesser strong opinions, the FDA would be happy to receive those verbally or in writing.

Dr. Harris?

DR. HARRIS: Now?

DR. McCULLEY: Now.

DR. HARRIS: Well, one of the issues that was raised earlier had to do with the whole idea of doing post-surveillance evaluation, and that had to do with tracking patients. Obviously, some type of an informed consent document, some type of a registration is going to be important as part of whatever labeling goes on, similar to what's done in the UK with their extended wear patients. I just raise that as something for consideration.

DR. McCULLEY: I think that was stated before by a couple of people, as well, and you bring it up, as well, and my sense would be to endorse that concept.

DR. SUGAR: Number 12 is a definite, strong yes, the answer to number 12. Would it be necessary for each material to have a post-approval study? Yes.

DR. McCULLEY: Okay. Dr. Schein?

DR. SCHEIN: I have one comment on that. I think the most important issue would be whether there's substantial similarity between the product. Let me give an

analogy, because I don't know much about the chemistry of these products.

It would not be unreasonable to have Bisex and Summit do a combined post-market surveillance on excimer laser and all of its progeny, because they are substantially similar even though there are some technical differences. I think there are advantages to doing that, as I've outlined. So yes, it has to be done for each company, but not necessarily as a separate stand-alone effort.

DR. SAVIOLA: I would like one point of clarification. If the opinion expressed regarding number 12, the post-approval study, is also there for RGPs as well as for hydrogels.

DR. McCULLEY: Oh, yes.

DR. SAVIOLA: Thank you.

DR. McCULLEY: Are there other strong opinions or thoughts that one would like to share on any of these latter questions that we did not specifically address?

[No response.]

DR. McCULLEY: Before turning it back to Sally, I'd like to thank the invited experts. You did a great job. You brought a lot to us and we very much appreciate your very thoughtful and valuable participation.

DR. ROSENTHAL: May the agency also express their appreciation.

MS. THORNTON: Before the panel goes to lunch, I would just like to make you aware of the fact that in the back there are blue bins in which you can deposit papers that you would like to part with and they will be corrected and shredded. The

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room will be locked. The materials that you have been given today are not considered confidential, but if you would like to just go home a little lighter than you came.

DR. SAVIOLA: If I may, Sally, some of the slides were considered potentially confidential.

MS. THORNTON: Could you give me those?

DR. SAVIOLA: Dr. Cavanagh's presentation.

MS. THORNTON: Okay. Then that presentation does have to go to the back.

I would like to express, again, my appreciation to our three guest speakers for today. I think it's been very valuable for us to have you. This has been a rather new experience to bring on folks from so far away and we appreciate your willingness to participate with us. I know Jim and Bernie and Karen got a great deal out of it, as well as the panel and the rest of the group, and I thank you again. We'll see you back here at 1:30 promptly.

[Luncheon recess.]

AFTERNOON SESSION

DR. McCULLEY: We will begin this afternoon's session with an open public hearing, and Sally has a few things to say.

MS. THORNTON: I just wanted to reiterate for the record that the speakers who will be making presentations before the committee are doing so in response to the panel meeting announcement in the Federal Register and that the FDA has not invited them to speak nor are their comments, data, or products endorsed by the agency.

Each scheduled speaker has been given a five-minute limit, as this morning's group had, and Dr. McCulley will recognize unscheduled speakers as time allows. He will also possibly, as he sees fit, as for questions that the panel may have for the individual speakers.

We can begin now with Dr. Joseph Winberry, who will make his presentation. Dr. Winberry?

DR. McCULLEY: And let me just warn the speakers, we do have five-minute limits and we will adhere to that, but we won't start until you actually get started.

MS. THORNTON: We're not talking about the guest speakers. We're talking about the open public hearing speakers. I saw a little consternation over there.

DR. McCULLEY: We really do have limited time and need to move forward. Would you like for us to go to the second speaker?

DR. WINBERRY: Hi. I'm Dr. Joseph Winberry from Camp Hill,

Pennsylvania, and today, I'm going to talk about the risk of extended contact lens wear in orthokeratology. I'll talk about what is orthokeratology, how safe is the procedure, wearing retainers, a little bit about cornea anatomy and physiology, a definition of extended wear and extended wear therapy, and I'll recommend some clinical signs and symptoms and recommendations for successful extended wear.

Ortho-K is a non-surgical corneal molding technique for reduction of nearsightedness, farsightedness, and astigmatism in children and adults. Retainer lenses are worn at the end of the program to maintain results of therapy. An optimal retaining wear schedule is prescribed for each patient to maintain the best visual acuity.

This is an example of an OK-3 lens fitting well on the eye. It's centered and lose about two to three millimeters on blink. That's the key to orthokeratology, to keep the lenses centered on the cornea.

This is an overview of traditional ortho-K, which used to be done with PMMA lenses. That limits it up to about two diopters of nearsightedness. Ortho-K is done with common RGP lenses. It usually could be done probably in about four to six months, and more of the overnight accelerated ortho-K can be done up to four diopters and it can be done on an overnight basis, such as the VMC lens.

How safe is the procedure? Well, four university studies and over 40 years of clinical experience have proved that this contact lens technique is as safe as wearing any type of rigid gas permeable contact lens. There's no clinically significant side effects, provided the lenses are fit, maintained on a regular basis, and annual examination and

follow-up visits are important to maintain the results. And in some cases, it can be reversed.

Retainer wear lenses vary in type and amount of refractive error that the patients have. Retainer wear should meet the patient's needs and provide the best vision possible. Retainers are worn on a straight, split, alternate, or night schedule, and the known factors that affect retention are ocular rigidity, IOP, measurable shape factors. Retainer lenses should be worn long enough to maintain the effect, that's visual acuity, but not cause blur upon removal.

What is extended wear? Extended wear means wearing contact lenses for 24 hours or longer, including a period of sleep. Extended wear is prescribed for correction of ametropia, aphakia, and therapeutic purposes. The FDA has established guidelines for extended wear soft hydrogen lenses, but not for rigid gas permeable lenses.

Here is an example of some materials available of the low, medium, high, and super-RGK lenses. What we're interested in today is talking about the hyper-DK lenses, those are above 80 DK.

This is an example--this slide is about two years old. It's some of the lenses that were available, the Menicon SFP lens and also the Advent lens itself, so these are some of the materials that were available at the time. The Menicon Z lens is approaching, I think, some of the VK values of approximately 250.

Moving about the cornea, you're familiar with this. It consists of the epithelium, Bowman's membrane, stroma, Descemet's membrane, and as you all know, the

transparency is maintained by a sodium pump in the endothelium, typically. Over time, those endothelial cells, if they're lost or aging, trauma, damage through surgery, disease. Water enters the stroma from the aqueous humor if the endothelial pump is defective. Stroma edema is the major cause why there is decreased vision and a need for transplantations and corneas. Again, you're familiar. This is a cross-section of the cornea, the lower portion being the epithelium, the stroma itself, and there's the sodium pump pumping water in and out of the cornea itself.

Cornea edema or central cornea clouding is very rarely seen in modern day daily wear or extended wear RGP lenses. The presence of vertical striae may or may not be an indication of a hypoxic condition or a thickening of the cornea, so it's not definite.

Holden and Mertz in 1994 established a clinical standard. They said 18 percent EOP during open eye wear of contact lenses limited to overnight or four percent, the level experienced when contact lenses are not worn overnight. So that's the clinical standards.

Epithelial microcysts are sometimes seen ortho-K, can be avoided. The extended wear in the open eye is at least 17 percent EOP level and developed epithelium and three to four percent that caused that condition.

In cases of more severe deprivation, you see polymegathism in the endothelial layer, and most of the high DK lenses today meet the needs of the cornea itself.

This is an example of central corneal clouding. This is a typical example of an RGP lens overnight. You can see the swelling of about 6.5 percent as measured on a

pachometer, as opposed to soft lenses, which you see more of a swelling here because you get a higher DK with the RGP lenses.

This is an example of vertical striae in the cornea itself. This is an example of different types of contact lens, A, B and C and D, and the oxygen tension levels on the cornea as you go through the cornea.

This is an example of corneal microcysts. They're not sure what causes them. This is microcysts. The larger one is the corneal vacuole. An example of the endothelium. That's a normal endothelium there, but when they have oxygen deprivation, you see some of the endothelial cells get larger and weirdly shaped.

Dr. Stuart Grant in 1992, he developed the concept of night therapy, where patients wear contact lenses first on a daily wear basis and progress to extended wear and night therapy wear only. This particular therapy works well on myopes of less than 150 and extended wear on these patients above 150.

DR. McCULLEY: You have one minute.

DR. WINBERRY: The advantage is little or no lens adaptation. Wearing lenses during sleep allows for a quicker adaptation. And ortho-K lenses create greater changes with no deterioration of vision itself.

Night retainer wear as opposed to night therapy is utilized for successful orthokeratology programs and patients who wear a greater than diopter 50 myopes can attain 20/20 vision placed on a schedule.

These are examples of some of the common complications that you see in

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RGP extended wear lenses. This can be alleviated through different mechanisms.

Some of the areas that we want to examine are the hypoxia, typically seen microcysts and vertical stride. Some of the staining is SPK is not important. You do see some other staining, three to nine o'clock staining. You don't typically see that in particular ortho-K chases.

I'm going to cut to the chase here real quick.

DR. McCULLEY: You need to summarize in about ten seconds. Your time is running. I'm sorry, but we have a great deal of ground to cover and we have to be equitable with everyone.

[Pause.]

DR. McCULLEY: I'm sorry. I think we're going to need to--

DR. WINBERRY: Let me just get through this.

DR. McCULLEY: If you don't have it right now, we're going to have to move ahead.

DR. WINBERRY: I have it right here.

DR. McCULLEY: No, you've said that before. I'm sorry. We're going to have to move ahead. Thank you. No, I'm sorry. I'm sorry. Your time is way over. I'm sorry. Please. What we would ask that you do, if you go over any written material that you have, please provide it to the FDA and they will include that.

DR. WINBERRY: Thank you.

DR. McCULLEY: Thank you.

The next speaker is Michael Russell, and please do identify yourself and who sent you, who sponsored you.

MR. RUSSELL: Before I start my five minutes, I want to see if everybody has this. I had handouts at the front, and there's more at the back, and you'll need it to follow this presentation.

I'm Michael Russell. I'm with Dynamic Resources. I'm the owner of an FDA-registered specifications developer, repackager, relabeler, and exporter of specially designed lenses. I'd like to also acknowledge my longtime friend, colleague, and tutor, Al Blackburn, the owner of Metro Optics, an extensive expert on all types of specialty lenses, including orthokeratology.

My two primary objectives for today are to recommend the FDA establish a formal clinical protocol for practitioners to follow when recommending overnight or extended wear use category four orthokeratology lens designs and fitting procedures by both manufacturing labs and by optometrists. I'll explain the four categories momentarily.

This protocol should include mandatory patient follow-up exams the first and the fifth morning after initial lens dispensing in order to protect the safety and corneal health of patients. These follow-up exams should also include slit-lamp evaluation to determine the incidence and the magnitude of lens adhesion in order to protect the efficacy of the category four orthokeratology procedure.

The follow-up exam should also include a corneal topography exam. Without detailed and recorded corneal topography information about the specific location

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and the impact of lens adherence, the practitioner and/or the lens design consultant are flying blind with regard to making any improvements in the performance of the lens.

I also would like to publicize the fact that the FDA is not now enforcing their existing guidelines and regulations regarding the production, distribution, promotion, and dispensing of class two and class three RGP contact lenses and lens materials.

Without specific performance by the FDA on these issues, there will continue to be unapproved applications and aggressive promotions of RGP lenses recommended for overnight and extended wear for the purposes of orthokeratology both here and abroad.

This will be to the detriment of patients worldwide, because often the practitioners who get involved in category four orthokeratology lens designs are inexperienced RGP contact lens fitters who accept advice from groups of optometrists who export their extraordinarily aggressive fitting philosophies together with finished RGP lenses without FDA oversight, without the required FDA pre-sale certificates for export, without the required facility registrations as repackagers or relabelers, and without the record systems and the lens material lot number tracking systems which are required in the event of an FDA-directed recall.

These American optometrist exporters often recommend category four orthokeratology lens designs for overnight wear. Their patients are not within their practices and their promotional efforts do not qualify as an off-label use of RGP lenses.

FDA proclamations on these issues would have a big impact internationally, which would serve to reduce this new danger to international patient safety

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which is directly related to the application of category four orthokeratology lens designs for overnight wear. The potential threat to patient safety started here in America and can, with FDA oversight and diligence, be ended here by the establishment of a defined clinical protocol, including morning-after follow-up when category four orthokeratology RGP lenses are dispensed for overnight wear and by the enforcement of existing FDA regulations at both the lab and optometry level.

Skip to page three, if you will. Category one has been used for some 30 years, single vision spherical and aspheric designs. Notice from the photographs that there's a lot of fluorescein and tears behind the lens, a relatively loose fit.

Category two orthokeratology designs also have been in use for 25-plus years. Also notice from the fluorescein pattern relatively loose fit, rarely recommended for extended wear.

If you would now skip to page seven, you'll notice category three orthokeratology designs. Category two was reversed spherical designs. Category three are reversed aspheric designs. Notice that it's an ideal fit. It includes a lot of tear behind the lens, a relatively flat fit. Even when it's relatively steep, a half a diopter steep, there's still a lot of fluorescein behind the lens.

Category four, notice on page eight, it's a very tight, very tight fitting lens, very little fluorescein behind the lens, very little tear behind the lens. When the lens is fit half a diopter steep, there's virtually no tear behind the lens. This lens has a high probability of adhere, and contrary to what Brien said this morning, up to 35 percent of

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patients in this category adhere and have lens binding, lens adhesion, and run the risk of the complications associated with that.

The last page, if you'll print to the Wall Street Journal reprint, I would like to agree with Dr. Cavanagh that was here this morning that extended wear includes extended risk. I'd also like to say that versus surgical procedures, category one, two, and three orthokeratology are completely reversible in their effects, virtually no incidence of losing best corrected visual acuity, but with category four, which is a far more aggressive, far tighter fit, physical fit than anything that's been done in the prior 25 years, prior to the last two years, there is a significant risk of lens adhesion, lens binding, and the complications that are incident with that.

Thank you for your time. Are there any questions?

DR. McCULLEY: Thank you. You hit that right on the button.

DR. SAVIOLA: I do have a question.

DR. McCULLEY: Yes, Dr. Saviola?

DR. SAVIOLA: At the risk of displaying some ignorance on this topic, even though I've read a lot of the published articles recently, I'm not someone who subscribes to Contacto, nor does our library. Would you be able to tell me where this category designation is derived from?

MR. RUSSELL: I created this category designation for this meeting.

DR. SAVIOLA: So it's not been published?

MR. RUSSELL: That's not been published.

DR. SAVIOLA: Thank you.

DR. SUGAR: You mentioned the complications that go along with category four lenses. Could you tell us what they are and what the frequency is?

MR. RUSSELL: Well, again, the major complication, the number one complication directly results from a very tight fit. It is independent of DK. These lenses are all made in EW approved materials and lens adhesion is up to 35 percent, and, of course, you all know as well or better than I what undetected chronic lens adhesion can do with regard to the potential complications. In fact, Dr. Snyder here has published articles on it and would be better qualified than I to describe the immunological response and the physical response of the cornea to the desiccation that is incident with lens adhesion, and the hypoxia, as well.

DR. McCULLEY: Thank you.

The third speaker is Dr. Newton Wesley.

DR. WESLEY: My name is Dr. Newton K. Wesley, Chairman of the National Eye Research Foundation. I'm honored to be before your panel. I developed keratoconus conical corneal or myopic ectasia when I was 21 years of age. I hasten to state I am 80 years of age now and, thankfully, seeing well, right eye 20/20, left eye 20/20--I'm sorry, 20/25 each eye in both.

I've not had a corneal transplant and I am told that I do not need it. I saw 50 eye doctors before they diagnosed the condition. Dr. Eric Fantl found it and he prescribed molded sterile fluid lenses and I could only wear them for a few hours without

halo and discomfort.

Through my own research, I found that my eyes got worse if there was a space between the eye and the cornea and the fluid was absorbed into the eye. They were Feldman and Gilman's solutions and my keratoconus progressed very quickly. The cornea would move up to the back surface of the lens because there was a vacuum space.

It was difficult to go against the accepted techniques in these days and Dr. Jessen and I developed contact lenses for myself so that I could see. I have still Fleischer rings and slight scarring, but I, as I said, don't need an operation, and I recently had a cataract operation on my right eye. I am thankful to be seeing.

In the latter '40s and early '50s, Tuohy lenses and micro-lenses were created and they made the vision better because they flattened the cornea. The microlens was about 2.5 to four diopters flatter.

Since so many doctors worried about abrasions and so forth, I created the Sphercon lens so that the eyes would not distort. The condition was spectacle blur, because the cornea changed shape. We did animal research, 36 rabbits wore their lenses for 36 months and then an ophthalmologist and an optometrist checked them on a regular basis and there was not harm done, and in those days, we could do microscopic dissection and there were no problems there.

Based on this animal study, Dr. David Sloan with the Foundation fitted 61 patients and they wore their lenses night and day just as the rabbits did and checked as regular patients, and no harm came and the program was closed.

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Orthokeratology is a section of the NERF, as we call it, National Eye Research Foundation, and it was formed in 1962. I want to pay credit to people like Dr. Stuart Grant and Dr. Charles May and all that have--because they gave tirelessly of their information and worked hard on the Orthokeratology Section.

Our objective as NERF is to be dedicated to research, education, and communication of the information to the professionals and the public in eye care and related health care. NERF's mission statement is, what is best for the patient is excellent for the public and all of us.

There have been a lot of uses of contact lenses, but there are many that have been skipped, especially in the areas of mesopia, middle-age sight, presbyopia, and strabismus, and there are alternate methods there that have not been applied and we're busy trying to get this out to the public. The Foundation also is interested in eye care and related health care and the sensitivity of the retina and we hope to use that in color mapping, visual color fields.

The optometrists and ophthalmologists must do their share for the total benefit of their patients. The government through the people are the great regulators and the National Eye Research Foundation will help in every way possible.

I wish to thank you for letting me talk to you and I want to keep under my five minutes. Thank you.

DR. McCULLEY: You've made. Are there questions? We do have 30 seconds remaining in the time.

[No response.]

DR. McCULLEY: Thank you very much.

If there are those in the audience who have not spoken who wish to speak, we have a few minutes that we can leave the open session open and allow you to come forward.

[No response.]

DR. McCULLEY: Seeing none, the open session is now closed.

We will move now to the heading for this portion is "Topics for Overnight Orthokeratology Studies" and Dr. Saviola, would you like to introduce this?

TOPICS FOR OVERNIGHT ORTHOKERATOLOGY STUDIES

DR. SAVIOLA: Thank you, Dr. McCulley. As you get ready, I'll just make my introductory remarks.

We have invited two speakers to present information on orthokeratology this afternoon. Dr. Harue Marsden will be the first speaker and also Dr. Roger Tabb.

In regard to introducing this topic for the panel, the question may very well be asked, why are we interested in this particular subject now? As you heard from the last speaker, there have been practitioners doing this for the last 30-some years. At the October '97 panel meeting, I did state our policy regarding orthokeratology. It is considered to be a type of alternative vision correction treatment, and like other types of alternative treatments, we are interested in evaluating them from a scientific standpoint and determining the true degree of safety and efficacy regarding how this is used in

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contact lens devices.

There is interest in the Federal Trade Commission regarding the promotional practices of some orthokeratologists and FTC did request that we make available at the back table a pamphlet, "Facts for Consumers, Vision Correction Procedures Alternatives."

We also have included in the panel packet a proposed draft of clinical trial formats. If people are interested in obtaining that and sending in comments to us, we would be more than happy to take your address and send it out. It is not specifically going to be a topic of discussion this afternoon. We do want to go through the speakers' presentations and the questions we posed to the panel.

We will take back from this discussion this afternoon the comments we receive and determine the proper course of action. In all likelihood, we will be finalizing a draft for comment regarding clinical testing protocols for these types of lenses.

Having said all that, I'll lead into Harue. Dr. Marsden is on the faculty of Southern California College of Optometry. She's conducted research in orthokeratology and authored a number of literature publications on the topic. She has been asked to present general information on orthokeratology, and in particular the newer reverse geometry lens designs utilized for this procedure.

While she practices orthokeratology, she generally does not practice the overnight fitting approach. She generally is a daily wear type of orthokeratologist and she has been asked to present her rationale for her viewpoints on this topic. Dr. Marsden?

DR. MARSDEN: Thank you. Certainly, it's an honor to be here and I want to kind of precede it with a little bit of history because it's rather obvious by some of those that preceded me that this does tend to create a lot of emotion for practitioners and it probably has been historical for, as I joked once before when I did a presentation, longer than I've been alive. In some regards, it is not a method that's new.

In the early days, a lot of the information was very anecdotal and was perceived more as a religion as opposed to a fitting methodology, and I think it's important that we clarify that, that this is not a religion, it is a fitting method with which practitioners choose to provide as an alternative for their patients.

What has gained greater notoriety is certainly we now have an alternative to refractive surgery, and with the increased interest in refractive surgical options, certainly the contact lens options have been revisited and newer lens designs have facilitated some of the effects that we were able to experience previously.

So the big terminology that comes about is this term "reverse geometry lenses". Conventional lens designs and conventional orthokeratology incorporated the use of what we contact lens folks call tri-curve lenses, a base curve that is to fit the contour of the center part of the cornea, a peripheral curve system that is somewhat flatter to better approximate the flattening that occurs towards the periphery of the cornea, and then a third curve to enhance to facilitate tear exchange beneath the lens.

The historical research in orthokeratology and that has existed conventionally used these tri-curve lens designs, and in so doing and in preparing some of

the book chapters that I've written, I come to find nearly a dozen different fitting methods even within orthokeratology, from an apical clearance or a slightly steep fit to a dramatically flat fit. And by having this huge variation, obviously, from a practitioner's standpoint, it gives great variability into which avenue a practitioner was going to pursue to obtain their orthokeratology effects.

What we did know and what the research that Kern did back in the '80s certainly showed us that we could take very flat lenses, get very dramatic changes, yet unfortunately, it was not predictable and oftentimes was associated with corneal distortion, warpage, and induction of astigmatism.

The biggest criticism of that study was the fact that the lenses did not center well and, therefore, manufacturers went into this reverse geometry lens design, where contrary to having a secondary curve system that was flatter than the base curve, they decided to use a steeper secondary curve system which enabled the flatter-fitting lens to center better on the cornea and, hopefully, then, enhance the ortho-K effect. So by having that improved lens centration, we were able to get more dramatic ortho-K effect as well as the same magnitude which was reported in earlier literature.

Just a flashback about what the fitting looks like, this is a conventional tri-curve lens and we see that we've got a very flat bearing area. The probably more applied tradition of fitting for orthokeratology using a conventional tri-curve lens is what's called the MGM or May-Grant method of fitting orthokeratology, which is about a half a diopter flat. The limitations and what their study showed is that they were able to get the

greatest effect within the first 18 months of enrolling into an ortho-K program, and so from the standpoint of outcomes, they were able to get myopia reduction but at the length of a very long duration of treatment and therapy.

Some practitioners then chose to go flatter, and here, we're looking at about a diopter to a diopter and a half flat and we start to see that the edge starts to lift up more dramatically, which leads to some problems with peripheral corneal desiccation, and even more problematic, the lens now rides high. Oftentimes, what we started to see, and unfortunately, during the time that these were being applied we did not have topographical means to assess this, we were actually shifting the apex inferiorly, so it wasn't really giving us the control that we thought we were able to achieve using the flatter-fitting contact lens.

By going to a reverse geometry lens, what we have here is that steeper secondary curve which enables the lens then to center better, yet keep that dramatic one and a half, even two diopters flat central apical relationship.

Now, what is very difficult about orthokeratology is there's still a lot of philosophies and theories as to what the mechanism is with regards to the effect or what gives this myopia reduction. Common philosophy or theory is that there is a massaging action of this flat lens over the apex of the cornea, and what this lens design or the reverse geometry lens design is supposed to do is then facilitate the movement of the cornea into that steeper secondary curve area.

What is important no matter which orthokeratology you choose to pursue,

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the lens has to center well. When it does not center well, we start to see these shifts in the corneal apex which then can, in turn, lead to unwanted corneal redistribution that can create visual problems for the patient.

Now, I want to somewhat digress to a presentation about these category four lenses because there are even newer lens designs that I don't even think many folks are even aware of. These classic reverse geometry lenses have a secondary curve system with one secondary curve value given. It's a single curve, secondary curve system, generally between two and six diopters steeper than the base curve.

These newer lens designs are actually going to dual secondary tier reservoir systems or two secondary curves, one with which has about a ten diopter--I think between six and ten diopters I've heard reported--secondary curve system, and then another reservoir slightly less steep, more comparable to what we conventionally have.

These, again, as has been reported, tend to be a little bit more aggressive and yield different results, and so I think it's important to probably keep some of these things clear when we talk about whatever category system you want to use or whatever term you want to use, that there are some differences even amongst the newer lens designs, and that certainly raises a whole another issue of efficacy and safety with these lenses.

As far as the background, I wanted to present my opinion on overnight versus continuous wear. I think it's important that we do separate that phraseology or that terminology, because as a person who practices orthokeratology, I was completely

aversive to any type of sleeping in the lenses, just based upon the complicated associated with sleeping in the lens.

It then dawned on me that if I--and typically when we go to overnight, and it's very rarely that I've had to do this, but we certainly have patients that are better served by being able to sleep in their lens at night and then function throughout the day without their lens. Therefore, we have taken this type of modality to allow them to use the lens as what we call a retainer.

So when we go through orthokeratology, there is a session or a period of time with which we are treating the patient to reduce the myopia to its maximum ability. Once there is no longer any myopic reduction or change, we then move them into a retainer, very comparable to braces, where after the braces are removed, a retainer is used to maintain that shape change following the orthokeratology session.

So when we go into retainer schedule, it is not uncommon for orthokeratology practitioners to enable their patients to sleep in the lens overnight and then allow the patient to function throughout the day without the lenses in place. The big benefit of that is that they get added oxygen because of their ability to work throughout the day without the myopia.

The limitation, however, is that if you are a high myope and it reduces you the standard two to three diopters of myopia, you are still running around uncorrected throughout the day, and oftentimes, many practitioners will then go to a sustained modality for some of the higher myopes. Sustained also tends to be utilized more for

treatment phase as opposed to retainer phase. So it's important to kind of differentiate those issues when we look at orthokeratology.

They are not equal, and I kind of want that as a take-home message, that unfortunately, based on the way that the definition looks at extended wear, any time a patient sleeps in the lens, whether it is for an eight-hour period or they wear it continuously for six days, they're all viewed as an extended wear modality, and unfortunately, that's not necessarily going to have the same impact, although the complications are very similar and very comparable in its results.

As far as the endpoints, I tried to gear this presentation towards the panel discussion, so that, hopefully, this could facilitate the discussion once we come to some of these topic areas.

So in the panel questions, the issue of safety endpoints was raised, and typically, as a practitioner, we would discontinue orthokeratology when central SPK arises and it does not resolve with solution change, because we do typically find that either a solution toxicity will create central SPK or if the lens is too flat. So oftentimes we will back off a quarter or a half a diopter, steepening the base curve slightly to see if that does not alleviate the central SPK.

In the last ten years that I've been doing this, I've only seen it in one patient, and on the same side, I've seen it in one daily wear RGP patient. So it's not something that's unique or more commonplace in orthokeratology, but it certainly does exist.

As far as overnight wear, we do have a few patients that are wearing it on a retainer basis overnight and the biggest problem that we tend to experience is lens binding. As the issue was raised earlier, there was a rather low percentage that was dictated as lens binding with overnight wear rigid lenses. Even the literature tends to be somewhat variant, between about ten to 43 percent incidence of lens binding in conventional extended wear RGPs, and certainly, I do tend to see it more so--well, I should strike that.

We do not have very many extended wear conventional RGP wearers. We do have overnight ortho-K RGP wearers, and I do typically see this as a complication as a result of them sleeping in their lenses. What we typically do, if the lens is bound and does appear to create a compromise to corneal physiology, we then place the patient on a daily wear schedule.

This is the central SPK that we talk about, and a couple of things as I mentioned earlier that we certainly try to rule out and the first thing is solution possibility, the second being generally a tear, or the lens is too flat, creating excessive bearing along that central portion of the cornea.

This patient that the slide was taken from was actually debris that was deposited on an old lens, and so certainly that is another issue, that if you have a soiled lens, that that can then impact upon the physiology or the health of the cornea. So again, not a real typical finding, but it can happen.

I contacted John Mountford down in Australia, because overnight therapy is the standard down in Australia, and so, like we found out this morning, they tend to do

things a little bit more progressively, perhaps, than we do here. I do tend to be a lot more conservative about overnight wear, just because of my natural aversions. I don't ride a motorcycle, either, but I do scuba drive. So we all have these risks that we're willing to take with ourselves and the same thing happens about the way we want to practice contact lens fitting.

So the pictures on the right are simulations as well as photographs of actual fluorescein patterns of what I call the conventional reverse geometry lens, so I will show you what a map or what the tear film profile looks like in some of these dual reservoir lenses.

But what we see here is the degree with which there are still tears beneath the surface of the lens. Now, you have to take this with a grain of salt. There is no way to be able to actually measure what the layer of tears are behind the lens surface, but some of the newer topography systems can simulate that.

One of the criticisms about the tear films and one of the things that is speculated to contribute to lens binding is the fact that there is an inadequate tear lens layer beneath the edge profile and it typically occurs right there, which is confluent with that third curve, secondary curve junction, and what happens, if there is not an adequate amount of tears there, overnight wear with tear evaporation and tonicity changes that occur, the lens tends to stick or bind in that portion.

Classically, with extended wear RGPs, the binding tends to occur, or the lens tends to ride low and then bind off towards the periphery. However, with ortho-K,

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we tend to see the lens tuck up a little bit higher and that may be due to the flatter fit, and again, we do tend to see a more peripheral binding that tends to occur.

John Mountford indicates that the optimum tear layer that you would want to see is about 20 microns, given that the accuracy of this measurement is probably plus or minus ten microns. So even at this point, we're right at 20. If I was to guess where this lens is going to bind, based upon the narrowness of that tear layer, it's going to bind somewhere off towards the periphery, off in that region where the tear film does tend to be a little bit thinner beneath the lens surface.

This is the dual tear reservoir lens that I was talking about, and you can tell that there's two because of the way that it peaks here and there, and that's where we can see a larger degree of steepness in the two different secondary curves that are on these tear lenses. But the biggest impact that these lenses tend to demonstrate is a far tighter tear lens layer off towards the periphery. So it does indicate that these may be a little bit more predisposed to binding.

Again, I've only got one patient in this and so I'm not real comfortable saying that with an "n" of one that this is good research, but certainly it is something that we do experience, not only with just the dual tier reservoir lenses, but we do also experience with single reservoir lenses, that if a patient sleeps in it, they do tend to bind.

This is what lens binding looks like, and fortunately, the biggest complication that arises from a lens binding is that the patient tries to remove the lens. It looks like the lens is still there, and that's what happens. The lens makes an impression

onto the cornea. As the patient tries to diligently remove this lens, unfortunately, they tend to remove epithelium with it.

Now, during the daytime, if they take the lens off, that enables adequate, so long as it's not too deep of an epithelial defect, but it allows adequate time for the epithelium to heal before a lens goes on again. Unfortunately, it does leave that open wound for pathogens to make access into the cornea. So again, there arises that concern as to whether or not you want to put your patient at risk of the potential for this to occur.

What we've typically done is order lenses with fenestrations. Now, the fenestration is about a half a millimeter in diameter. It tends to be in that secondary curve region. It does not prevent lens binding, but what it does do is enable the tears to exchange upon awakening so that the lens will unbind much more rapidly during the morning.

What was mentioned earlier is probably the most important thing, is that the follow-up needs to be at the appropriate time. If we know that the lens is going to bind, the issue is how fast is it going to unstick, and when it does unstick, how is it impacting the corneal epithelium, and that needs to be assessed. The patient also has to be much more aware of their contact lenses and the fact that the lenses are moving adequately before they try to remove it in the morning, or as was demonstrated previously, they do tend to remove the epithelium as they remove the lens.

As far as the efficacy endpoints, generally, when we pursue orthokeratology, we take it to a point where no further refractive error reduction occurs.

Now unfortunately, that's not a very good endpoint for a lot of patients, but they do realize that there is individual variability and fluctuation from patient to patient.

Typically, what we do is make a measurement, make a subsequent flatter lens change, and then follow them through, and if no consecutive changes occur once the lens has gone flatter, we call that the endpoint and move into retainer schedule.

The other alternative is to use measured corneal eccentricity value where "e" equals zero. Now, unfortunately, or fortunately, I suppose, depending on how you want to view it, with some of the newer, more aggressive lens designs, the "e" values are now reaching negative proportions, or indicating that the cornea is reaching an oblate curvature, very comparable to what we see with refractive surgery endpoints. So "e" equals zero may not be the appropriate end point, depending on the type of orthokeratology that you practice.

The unfortunate thing is that we always have to remember that these topographical instrumentation uses value is based on "normal" corneas, which we are no longer dealing with.

DR. McCULLEY: You have two minutes.

DR. MARSDEN: Thank you. Again, efficacy endpoints, we look at the uncorrected visual acuity and we know that that's going to be variable. We talk about these numerical values, and unfortunately, we do have a number of high refractive errors or moderate refractive errors that pursue this lens option. Knowing that they'll need to wear lenses all of their life, they'd rather wake up in the morning during a California

earthquake, be able to see in order to be able to get out of the house in an urgency or an emergency, and so being a three diopter myope as opposed to a five or six diopter myope tends to be an option that they're willing to deal with. So it's important not to use restrictions of uncorrected visual acuity without taking into account the initial refractive error.

As far as other efficacy endpoints, you need to talk about best corrected acuity with or without lenses, because there is some reported incidence that there is corneal distortion that occurs. With the corneal distortion, you do lose acuity. Clinically, I don't believe I've lost any greater acuity than two lines, generally one line, and mostly no lines, but it is important to differentiate between spectacle acuity and contact lens acuity because the contact lens does allow the tear film to fill in any irregularities and oftentimes yields a much more inflated visual performance.

Again, on efficacy endpoints, magnitude needs to be somewhat dependent upon where we're looking at. With regards to historically, we've seen one to three diopters in the nice compendium that was put together with the orthokeratology studies. We get very comparable results with the single tear reservoir lenses. However, with the dual reservoir designs, they are getting higher magnitudes of refractive error reduction. So again, we're kind of dealing with different items.

Again, stability of the visual acuity needs to be defined, and it is difficult because it is dependent upon the starting refractive error. That variability is something that we haven't been able to come to terms with and be able to evaluate at this point.

Again, clinically significant difference between test and control groups, and that's hard to define. And again, one of the items came up about the type of study, and I think we learned this morning that sample size is certainly dependent upon what we're looking for as the outcome. There is no statistically significant difference with conventional RGPs and orthokeratology. You probably have to take that to the next step, because that has not been demonstrated with reverse geometry lenses.

As for coming up with a study design, I truly don't know. John Mountford has done quite a bit and he reports two in 2,000 incidence of ulcerative keratitis and only one person in 2,000 lost one or more lines of best corrected visual acuity.

As far as retrospective data, the problem is you commented upon topography, and most, or I shouldn't say most, but quite a few practitioners do not have that data available and that could be difficult. The best thing is that it does give ease of data analysis, but unfortunately, I don't think it's been really proven to give usable information, and so that's again a very difficult thing. Probably visual acuity and safety events tend to be a little bit more reasonable items to look at, and that may not always be documented appropriately by practitioners.

Product labeling, these are probably the big issues about product labeling, is what are the realistic expectations? The patient cannot be given a guarantee, and unfortunately, we have seen that occur, and then certainly risks versus benefits.

I will open it up to questions.

DR. McCULLEY: As with this morning, we would like 15 minutes and up

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to 20 maximum--we hit a little over 20--presentations, and then the remainder of the allotted 30 minutes for each of you for questions and answers, and then you will be involved in our discussions when we're discussing the questions that have been posed to us.

So at this time, we have time for a few questions from the panel. Dr. Macsai?

DR. MACSAI: I was wondering if you could--I have two questions that you could educate me on. One is the diurnal variation of patients' vision with this technique and the second is longitudinal studies on patients who have undergone this. In my review of the literature, I really didn't see longitudinal studies, but I may not have been complete.

DR. MARSDEN: No, you're absolutely correct. Both of those areas tend to be somewhat deficient in the literature. Very few--in fact, I can't think of any peer reviewed articles that look at the fluctuation of vision, although I do stand back a little bit. Polse did look at that up at Berkeley and showed that--you know, primarily the bottom line was that there is variability and that it is not permanent, but nobody has quantified the degree to which variability occurs.

From a clinical standpoint, it truly depends upon the rapidness or the malleability that the cornea demonstrates during the process. So somebody who gets rapid results also tends to digress more rapidly. But again, that has never been demonstrated, proven, or put into a prospective study to confirm.

The same issue about longitudinal data. It does not exist, although I think many practitioners and perhaps Dr. Tabb can comment upon that. I've only been doing this for the last ten years, and so of the patients that I have, it's difficult to say.

My gut reaction is I don't see them any more frequently on an urgent care basis. I don't see higher risks. They tend to follow the same follow-up schedule as we do with our conventional RGP wearers, although I do recall them more frequently just so that we can ensure that there isn't any induced complications.

As far as the other issue with longitudinal, the fact that this is not a permanent solution. We often find a lot of patients discontinue by choice and go back to conventional contact lenses. I haven't heard of any, but I'm sure that there will be those that start to consider refractive surgery options, as well.

DR. MACSAI: Can I follow up with one more question for you?

DR. McCULLEY: Yes.

DR. MACSAI: In your personal experience, and Dr. Tabb, perhaps you can address this, too, after discontinuation, how long does it take for refractive stability?

DR. MARSDEN: For refractive stability or to return back to baseline?

DR. MACSAI: Both.

DR. MARSDEN: That is a variable. Generally, within a week's time, they're back to baseline, but I've seen people go back as quickly as three days and as long as nearly a month. So it, again, tends to be more of an individual response and not necessarily--and again, we've looked at predictability factors and things for the effect and

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my guess is we probably find very few predictive indicators as far as who will and who will not return and what their time frame will be. Hopefully, with some of the studies that we're trying to develop now, we'll look at some of these issues and be able to have more information.

DR. McCULLEY: Dr. Pulido?

DR. PULIDO: I'm sure many of these patients are relatively young and middle-aged patients that want to do away with glasses. Some may be pilots. Some may be mountain climbers. What is the effect of altitude to the stability of the refractive changes? We know with radial keratotomy, it can be disastrous.

DR. MARSDEN: Right. Unfortunately, I'm at sea level, so it's very difficult for me to address the issues with regards to altitude, and certainly there are practitioners that provide this type of care. I believe there was literature presented with regards to the Air Force and its impact there, but I truly don't recall there being a statistically or dramatically significantly different performance.

But we certainly know--and I think a lot of what we see or what we don't understand about orthokeratology is at the cellular level. There is argument now down in Australia as to whether the effect is truly based upon keratometric changes or if it's compression of the epithelium. Those are issues that we have not quite fully investigated with regards to what the results are, and even down there where they're looked at this data, there's argument among the camps of individuals that are reviewing this.

So certainly those are useful data so that you can warn patients, because if

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they are doing it, for example, to get a commercial pilot's license and we send them into a point where they lose cabin pressure, we could end up with some complications that we really didn't anticipate and probably didn't educate the patient about.

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: I guess this is sort of infringing on the practice of optometry or medicine, but would you personally sort of fit someone, a Federal Aviation Administration pilot?

DR. MARSDEN: That's an ethical--that's an ethical dilemma, because at that point, you're trying to squeak by, and personally, no.

DR. BULLIMORE: Do you think it's something that, were the FDA to start labeling these devices, that should be considered to be in the labeling?

DR. MARSDEN: I'm sorry, considered to be in the label?

DR. BULLIMORE: Yes.

DR. MARSDEN: I suppose no more so than whatever restrictions exist with exchrome lenses for color vision deficiency. So again, not knowing what the intent is--

DR. PULIDO: Excuse me. You just told me, though, you'd have no idea of the effect of elevation.

DR. MARSDEN: Exactly.

DR. PULIDO: So how can you say it's similar to something that may or may not be of value, and here's--

DR. MARSDEN: And that's just it. Since I don't know, it's very difficult for me to say, yes, you need to put that on the label, unless you want to use a labeling very comparable to what they do for pharmaceuticals, where it says, "Has not been tested on children." It's very difficult for me to say, yes, indeed, you need to put that down as a restriction or limitation. The data isn't there. The studies aren't there. So it's difficult to endorse that type of labeling without the science to back it up.

DR. McCULLEY: We have one to two more minutes. Dr. Higginbotham, I think you had your hand up first.

DR. HIGGINBOTHAM: Based on your ten-year experience, can you give me an idea of what optimal age range responds to this therapy?

DR. MARSDEN: You know, I'll be honest with you. We have had a huge influx of children whose parents are seeking this, and probably the biggest reason, and I think it was mentioned earlier that this has gone outside of this country and gained huge interest, primarily in the Asian community. So I'm not saying they're optimum, because, unfortunately, as they are growing older, their axial length is elongating, and so we've got two things that are competing against each other, and so there has been a theory to evaluate it as a form of myopia control as well as myopia reduction.

I'm trying to think of our studies that we have done. We really didn't find an optimum age. I think that's been looked at with refractive surgery. So certainly it would be something to consider, but from a standpoint of who is better served by this, the people who pursue this tend to be in their 20s and 30s, although we do have patients that

are much older, but we certainly enter issues with regards to presbyopic correction that this does not address.

DR. McCULLEY: Dr. Sugar?

DR. SUGAR: You're not doing a study, but what do you consider entry criteria for your therapy? In particular, what do you feel about corneas that are not regular, like keraticona corneas, and--

DR. MARSDEN: We did not pursue that. We--

DR. SUGAR: --and what ranges of myopia and astigmatism?

DR. MARSDEN: Okay. Typically, and like you said, it's not a study, and frankly, the patients are rather surprised that I try to talk them out, and I do a darn good job trying to talk them out of it, because the primary success factor is a motivated patient. So when I have a five-diopter myope, I will tell them things differently than I would a two-diopter myope. I know that the data confirms between one and three diopters. Personal study that we conducted found two-and-a-quarter diopter of myopia reduction.

So I feel very comfortable that if a two-diopter myope came, I'd never make a 100 percent guarantee, but I'd indicate that we have a very good likelihood of being able to obtain uncorrected visual acuity comparable to what you have through spectacles. However, that's not a guarantee. A five-diopter myope, however, at best, based upon the data in the studies that we did, is going to end up about 1.75.

So if I'm looking at visual outcome, I try to give them, to the best of my knowledge, and again, when I look at average of two-and-a-quarter, that means that we

had folks with no change and folks with greater than two diopters of change, and so it's difficult to--and again, the literature tends to endorse that there isn't a predictive measure to determine who's going to reduce by how much.

DR. McCULLEY: Dr. Soni?

DR. SONI: If you believe in the procedure and you're carrying out the procedure on a number of patients, why do you talk patients out of it?

DR. MARSDEN: Because I want to make sure that they're motivated, and I've learned that--as part of my residency, I worked with a refractive surgeon and it tended to be the patients who found value and that appreciated the surgical outcome, whether they were 20/40 best corrected or not, it was based upon what was explained to them prior to undergoing the procedure.

The patients that we deal with, we have a lot of practitioners that their patients are very frustrated and end up coming to us and the biggest disappointment that they have is that they were not made aware of or they did not understand the restrictions or limitation of the procedure. So if I can ensure that I educate them to that level, to the point that if I try to talk them out and they still want me to do it, I can rest pretty easy that they'll be happy. It's like that formula about expectations minus outcomes equals success. If they have low expectations, no matter what outcome I have, it's going to be a successful outcome.

DR. McCULLEY: I think I would tend to think of this more like I would as a surgeon and a surgical procedure, that one weighs risk in not doing the surgical

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procedure, risk in doing it, and benefit in doing it--

DR. MARSDEN: Right.

DR. McCULLEY: --and not the way that you approached it, I think, because you're intervening here. It's a little bit different mindset.

DR. MARSDEN: Right. Right.

DR. McCULLEY: We're past the 30 minutes. I think we need to go on to Dr. Tabb for presentation.

Let me state what I think is the obvious, or what I'm understanding, just so I have my mind clear and I can stop thinking about it. We are addressing this because in the past, orthokeratology has been done as a practice of medicine, a practice of optometry, issue, and that we are being asked to look at this and the FDA is looking at it because sponsors, the outside world, is wishing to market this, and in order to be able to market and promote it, it must have been looked at and determined to be safe and effective by the FDA, and that has not been done so that the FDA is taking this as a charge to look at this and will develop a guidance document for those who wish to pursue this so that they know what to follow in designing their trials.

DR. SAVIOLA: You're 98 percent there.

VOICE: What's the two percent that he left out?

DR. SAVIOLA: The two percent is that the very first overnight orthokeratology application that comes in as a class three PMA will be brought to the panel for discussion and recommendation because we're bringing--it's a first-of-a-kind

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device. There hasn't been an overnight type of device reviewed before.

The first daily wear orthokeratology application that comes in will not be brought to the panel. It will be dealt with as a class two application under 510(k). So we will review that one in-house.

So this is a session which is getting the panel acquainted with the concept. It gives the industry some idea of what the expectations will be in terms of the type of rigorous study which will be evaluated by the panel under PMA and does it in a sort of generic context rather than on the back of a PMA at the end of the whole session.

DR. McCULLEY: Thank you. That was an important two percent I left out.

Dr. Tabb?

DR. TABB: Thank you, Mr. Chairman, and thank you, Dr. Saviola, for inviting me to come speak and all of the panel members here. I have been practicing orthokeratology for over 30 years and I was one of the old original diehards that felt we really had an exceptional procedure and I've stuck with it and I've been extremely conservative through the years. I also deal with a great deal of keratoconus and so I've had an opportunity to see both directions of attempting to change a cornea and attempting to keep a cornea from changing any more.

Orthokeratology, the facts as we know them today really are that it's about a 40-year-old subspecialty of optometry. There are only a handful of optometrists who have practiced and developed this specialty over the years. Recently, we have had

dramatic increase in the number of practitioners who practice orthokeratology.

The older methods were slower. They were less predictive and less retentive, which created low acceptance among the average practitioners and sometimes some animosity, and definitely animosity from other professions.

Reverse geometry designs were first introduced into the literature by Dr. Al Fontana, who died last year, bless his soul, and was an extraordinary giant in the orthokeratology field. He developed the very first reverse geometry lens, as far as reported in the literature. I had designed some back in 1968, but there were no lathes to manufacture them and I didn't build my first one until 1975. Even then, it was difficult because it had to be done on double-compound lathes, and now with the new DAC lathes [ph.] and the new equipment, we're able to generate these curves much more effectively. And the laboratories, there are some really exceptional laboratories out there who can generate these curves.

These designs were really not manufactured on a high level until about 1989. Dr. Richard Waddaga [ph.], who wrote the first article on what he called accelerated orthokeratology, more or less kick-started the use of reverse geometry lenses, and since 1989, the reverse geometry designs have spread rapidly because they do work. I think everybody that has ever done orthokeratology or even hasn't and watched the results have to say it definitely works, no question.

Beyond the initial reverse geometry designs now, we have advanced, or what I call advanced back-surface control designs. They create rapid orthokeratology,

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larger potential changes, and clinical-level research has demonstrated safety to be much, much better than refractive surgeries.

Improvements in designs create a demand for better tracking, better designed equipment for manufacturing, and better designed equipment for measuring, and all of these things have been overcome. We have tighter controls of parameters, more complex mathematics in designing of manufacture. We have a better understanding of corneal structural analysis.

Just recently, as early as last Saturday, I heard Dr. Caroline, who is a professor of ophthalmology for the University of Oregon Health Sciences Center at the Casey Eye Institute in Portland, Oregon, make his first orthokeratology presentation in Arizona, and he started by saying, "You all know me as having avoided this topic like the plague for the last X-number of years and today I embrace it because now I understand how it works."

He based that on the subject that Dr. Marsden alluded to earlier. Dr. Helen Sworbuck [ph.], I believe is the name, from Australia, who is really a mathematician, demonstrated, according to Patrick, beyond the shadow of a doubt that it's epithelium movement rather than actual corneal change. I don't know that I necessarily buy that, but I do know that we only have to change the cornea a few microns. It's not like we're shoving heavily on the cornea.

With the newer reverse geometry lenses, as far as I'm concerned, we have control of the mathematics in terms of elevation data and calculating what these end result

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lenses are and that's why the results. They're so much faster, so much more effective, so much more lasting, and, frankly, in my practice, I'm not seeing a great many problems. I have seen no ulcers. I have seen no ulcerative keratitis. I've seen decentered lenses, which can be corrected by the change in design. If it can't be corrected by change in design, we go to day wear lens and go to a different type of lens. So the problems that come up are reversible and very correctable.

One of the things that was in demand, in my opinion, all the way through orthokeratology, my lens, originally, back in the '60s, the late '60s, was what I called a hydraulic lens and it was an apical clearance lens in which I actually controlled the peripheral part of the lens with modification and I was able to effect about two to two-and-a-half diopters of corneal change, not a great deal.

It was fairly fast, and I have a letter from Dr. Coon that was written in 1977 to Dr. May in California, describing to him what had transpired in the research that he did and published in the American Optometric Journal in 1981 and 1982. The study was done from 1975 to 1980, a five-year longitudinal study.

He found it was completely safe at that time with that hydraulic method and he was stating that the periphery did seem to be the magic, and that's what we find in these new reverse geometry lenses and that's why we can effect these changes so much more effectively. It's not the crunching push in the middle. That doesn't really exist. It's the control of all the curves to change the direction of the cornea, because we have a confined structure that can't be collapsed or stretched, but we can bend it and change it in

certain places which will change other curves and that's how we affect the orthokeratology. From an engineering standpoint, and that's what I was originally, before I became an optometrist, it all makes perfect sense to me.

The ranges that we seem to be able to use with these reverse geometry lenses now and what I would call more back-surface engineered lenses are in myopia from about minus a quarter to minus four diopters. I have been able to move five-diopter myopes to 20/20 literally overnight and they held 12 to 15 hours and do hold, but they're rare. Up to four diopters is much more realistic. These, we can do a much greater percentage of the time. Up to two diopters and three diopters, we can do this almost consistently.

As far as astigmatism, realistic ranges are from around a quarter to minus two-and-a-half diopters. I even have a case here that's a two-and-a-quarter and a two-and-a-half diopter to show what happens with those, if we want to look at that.

Hyperopia, we're now investigating that. That's much shorter ranges with that. We're being very cautious with that. But at this point, we have been able to effect changes up to about two-and-a-half diopters, and the advantage with doing hyperopic-orthokeratology seems to be that if the individual is also presbyopic or they can't see up close as well, after they go through the orthokeratology, they not only can see at distance but they can also see very well at near. My wife is an example of that.

Mathematical and physical principles that we have to be adherent to are, in my opinion, hydrodynamics, because we have a thin fluid, a film that is very thin. It's

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about eight microns thick. we have to fit in that tear system a mechanical contact lens system that will stay within the tear system, and that's why some of the old lenses from a long time ago didn't really perform well. The May-Grant type system which were flatter had a tendency to hang out of the tears and go up.

The first generation reverse geometry lenses did the same thing. You could put the lenses on and we had great performance, but if you had more than a couple of diopters to move, they'd start to go up because they'd lose their hydraulic containment. They started to become a mechanical structure. And once they become mechanical, there's very little control. If you have the mechanical as well as the hydraulic control, you can center the lens and move the lens very easily with modification, if you understand how to do that.

Which brings up a point, and that point is, I believe that this process needs to be done by experienced practitioners or the individuals need to be trained by experienced orthokeratologists that understand modification as well as lens design and performance.

The cornea can be reconfigured dimensionally within certain limits. As I described before, we have a certain shape that the cornea might have and there's no such thing as a normal shape. You can take 5,000 normal-looking corneas and they'll all look different on a topographical device. They'll all look a little different.

So the key is, what do we want to have happen for that patient, and in my opinion, one of the things, especially with the enthusiasm of being able to wear the lenses

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overnight and wake up, take their lenses off, and be able to see sharply all day, that's extraordinarily exciting for these people and they send other folks in to have that checked out to see if they're possible candidates.

At any point that we see adverse reactions, which is very rare, by the way, we will take steps to correct those with modification of the design or modification of the existing lens itself. Many times, it's a matter of three months down the line and the lenses have to be resurfaced.

Gas permeable lenses have a tendency to absorb some protein into the very outer matrix because gas permeable lenses absorb about 0.02 percent moisture by volume, and so they have a situation, in my opinion, in which we have to resurface the lenses at about every three months to get rid of the protein. Bacteria lives on dead protein.

That's one of the reasons soft lenses are a problem and why I've never really fitted soft lenses much. I see lots of soft lens patients, but I don't fit a lot of soft lenses. Ninety-eight percent of my contact lens practice would be gas permeable lenses.

We have proven clinically, in my opinion, in the United States here in a few practices that eccentricity is not the limiting factor. Dr. Marsden alluded to that, that we do produce some oblation, and it has to do with the actual change in shape that we can produce in the cornea with these lenses.

One of the things that was mentioned earlier was that these lenses are fitted very, very tight. I don't agree. That's what I thought when I first saw one on. I almost panicked when I looked at it, because I'm used to seeing lots of movement. I've been an

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advocate of at least two to three millimeters movement of contact lenses, and day wear, that's absolutely true and it still holds true with these lenses.

So these overnight lenses, in my opinion, should not be worn during the day, and the folks who have produced these lenses agree that they should not be worn during the day. They should be worn strictly at night. They are designed on a different level of engineering than the previous reverse geometry lenses. They're designed on what I call a visco-elastic molding principle in which the cornea is a visco-elastic structure and we simply remold that at night.

In terms of edema, when you close your eyelid at night, there's about three percent edema which is produced every night, and when you wake up, within a few blinks, that edema goes away.

With soft lenses, years ago, I believe Dr. Holden did a study and Fat and possibly Richard Hill were involved in that study in which they found that the edema is much, much higher in soft lenses, sometimes up to 13 percent. Many times, that edema would not go away all day long, and so I asked myself why that occurs and it turns out the soft lenses really don't have fluid underneath them. They don't move much. And so the cellular debris and metabolic debris does not really go away until you take the lens off, and that's probably why we end up with sub-epithelial filtrates and filtrates with extended wear soft lenses.

With gas permeable lenses, I have never seen this. I was in a study in 1988 with Syntex in which RGP lenses were used as extended wear lenses. I still, out of the 30

patients I fitted, see about 20 of those patients after all these years. I have yet to see a problem with any of those patients, other than they go too long. Sometimes they need to come in sooner to have the lenses resurfaced. When they don't come in and the lenses are very built up with protein, we see stain. We resurface them, check them the next day, the stain is gone.

How are we doing on time?

DR. McCULLEY: You have been talking for 15 minutes.

DR. TABB: Okay. Can I have about five more?

DR. McCULLEY: Five more max, yes.

DR. TABB: Okay. In terms of the ranges of acuity that can be produced, some of the preliminary clinical studies that have been done have shown that from plain-O to minus two, 81 percent are able to reach that. From minus two and a quarter to minus three, 62-and-a-half percent are able to reach 20/20. Minus three and a quarter to minus four, 60 percent. And minus four and a quarter to minus five, 21 percent. So you can see as the power goes up, the effectiveness of the device goes down and that's something that I believe you folks will need to address in terms of how far the individuals can go before it loses its effectiveness.

When you get down to the level of 20/40, it's 98 percent for up to minus two, 97.7 for up to minus three, 96 percent for up to minus four, and for up to minus five, 84.2 percent. So at the levels of the study at 20/40, it still doesn't do bad. It matches up pretty well, I would say.

I'm going to just put a few overheads on because I'd like to demonstrate that even if individuals--I have had a few individuals who we've had in orthokeratology for three years. They've decided that they don't want to continue with orthokeratology.

DR. McCULLEY: We have about three minutes remaining.

[Pause.]

DR. TABB: This first individual was a flight instructor. He insisted on orthokeratology and I explained that the best we could possibly do is possibly 20/400. He was 20/1600 at the time and I felt that there would be no real purpose in doing orthokeratology other than to possibly give him better aided acuity because it reduces the amount of nearsighted prescription he might look through and that had worked quite a number of times for other individuals who had optic amblyopia.

He was a minus 7.75 in one eye and a minus 6.50 on the other eye and we were able to move him down to an uncorrected acuity of 20/200. After three years of orthokeratology--could we go to the next one after that--he decided he'd like to just go back to regular contact lenses and that's what his corneas look like now, and you'll notice that date on the bottom is fairly recent.

So you can see that the corneas do go back. He had been out of the lenses, the original lenses, for two months and there are no ill side effects. His refraction now is back to 7.75 in the right eye and minus 6.50 in the right eye.

So the question is, is it permanent? No, it is not permanent. In individuals up to about a minus four range, is it lasting? Yes. It lasts fairly consistently up from

about 12 to 15 hours. Sometimes it can be down at an eight-hour, eight to ten-hour level. But it allows these individuals to function at a 20/20 level, sometimes in a dusty job, without glasses or contact lenses, which is an incredible boom to them.

The next one, this is an individual that we started about a year ago. The top is a picture of what her corneas looked like before we started. And then after we started with what we call T-compression orthokeratology, the first generation orthokeratology lenses, and we went to a--and this was several months later. Let's see, I can't see that. I think we have one more on that, don't we? Good. This is after one night wear, the bottom picture--no, go back one more. There should be three there. Are there three?

DR. McCULLEY: We are over time. We need to find what we need real quick.

DR. TABB: No, that's the other one. At any rate, you would be able to see that the lenses moved down in the third slide, if we had that, because we used an overnight lens. She wears it overnight. She has up to three days' acuity with 20/20. I have a letter from her here that demonstrates that she still is maintaining that after one year. She was originally minus three in the right eye, minus three in the left, and minus three-quarter in the left, and so she maintains at about plain-O in the right eye and minus a quarter in the left eye.

My point being, I find it very safe in my practice. I have not seen the adverse results that sometimes I hear reported. I am a fairly cautious practitioner, and by

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the same token, I'm not afraid to, if I can figure out how something works, check it out and see if it's going to perform.

I have a lot more, but obviously I'm out of time, so any questions?

DR. McCULLEY: Well, thank you for your presentation. It's possible that you will have the opportunity to share the additional information during the questions that we might have over the next ten minutes and then when we're attempting to answer the questions the FDA has posed to us.

Dr. Harris, did I see your hand, or was it Marian's hand?

DR. HARRIS: My official job is to hand her the microphone.

DR. McCULLEY: Oh, okay.

[Laughter.]

DR. MACSAI: Dr. Tabb, thank you for your presentation. I have a few questions for you.

DR. TABB: Certainly.

DR. MACSAI: Before you remove that overhead, how long after contact lens removal were those maps made?

DR. TABB: Immediately after removal.

DR. MACSAI: Okay. Secondly, you talk about resurfacing the lens every three months.

DR. TABB: Yes.

DR. MACSAI: The contact lens, you resurface every three months?

DR. TABB: That's correct.

DR. MACSAI: In the office?

DR. TABB: In my office.

DR. MACSAI: With just a buffering agent, or what do you--I don't understand that.

DR. TABB: Well, that's okay. Let me explain it. I've been doing this for all my RGP wearers and PMAA wearers since I started practice in the '60s. With PMAA, I used to resurface the lenses every six months and I still noticed that patients would have problems relating to mucal protein buildup, and so I dropped it to five months, and then four and then three, and at three months, I found they very seldom had these problems show up like SPK, edema, et cetera.

So in the event of the RGP lenses in 1973, about, I did a study at Pacific University for them, a study on a couple different types of RGP lenses, and I found that I had to resurface these lenses at about three months to keep the protein out of the outer matrix of the lens. I found that the incidence of problems was dramatically reduced over years, literally.

So as a matter of routine in my practice and with my orthokeratology patients, as far as I'm concerned, it's even more important.

DR. MACSAI: So you don't mean chemical resurfacing, like with an enzyme, or--

DR. TABB: No.

DR. MACSAI: You actually are physically resurfacing--

DR. TABB: It's a mechanical--

DR. McCULLEY: What we used to call polishing.

DR. MACSAI: Polishing? Is that what I think of as polishing?

DR. TABB: Well, I think of polishing as putting a little polish on a lens and rub it in your fingers. I have a spinner which you put the lens on. You put it on a--

DR. McCULLEY: You buff the surface.

DR. TABB: You get the sponge tool and you can call that buffing. You can call it what you like. I call it resurfacing.

DR. McCULLEY: Okay.

DR. JURKUS: Dr. Tabb, do you have any information regarding a measurable topographic change that could relate to a visual acuity from, say, morning to evening? You had mentioned a few times that your people were able to not wear lenses for 12 hours. Is there a measurable change other than just their acuity?

DR. TABB: Topographically, you can see that the corneas are still changed, yes, and sometimes you can see that the regression is very little from what you found in the morning. When my patients come in, I see them after the first night of wear, and if everything's going well, I see them after the first week of wear. If things aren't going well, we make changes in the design, and if things are going well at one week when they come in, I like to see them possibly in the morning after they've removed the lenses, but some of them can't make it in the morning and so I see them toward the evening and

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these topographic changes are still there and still show and we do take those topographies. So topographically, the changes are there. Refractively, the changes are there to a certain degree.

DR. JURKUS: Could I--

DR. McCULLEY: Go ahead.

DR. JURKUS: What I was trying to get at is, for example, if a person were to remove their contact lenses and have 20/20 acuity immediately after they took their lenses off and 12 hours later their acuity had become 20/30 or 20/40, is there a measurable way of charting the corneal change that is coincident with that refractive error or that acuity change?

DR. TABB: I believe there is an instrument that may do that now. We haven't had a way with the placebo disk-based systems. But the new elevation data systems have a more direct measurement of elevation and I believe we're probably going to be able to come up with that information.

DR. McCULLEY: Dr. Sugar?

DR. SUGAR: A simple question that should require just a very brief answer. You presented 98.1 percent, 20/40 or better, and so on. What are your "n"s? How many patients "n"? What does all-day uncorrected visual acuity mean? Did you measure them in the morning and in the evening to get those data?

DR. TABB: The individuals were measured sometimes in the morning, but when we were measuring data for all-day wear, they were measured primarily at the end

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of the day.

DR. SUGAR: Just once? And what's the "n"? How many patients? You have a table here.

DR. TABB: Yes.

DR. SUGAR: What's the number of patients?

DR. TABB: That specific table started off at 400-and--400 to 500, between 400 and 500, and had dwindled to 386 patients, I believe, through the study.

DR. McCULLEY: Dr. Bullimore, last question.

DR. BULLIMORE: That small table on, I guess it's page four that we were faxed during the week, this is the same patient data set that's in the what seems to be an Excel or Lotus spreadsheet that was also circulated?

DR. TABB: Yes.

DR. BULLIMORE: Is that the same cohort of patients?

DR. TABB: Yes.

DR. McCULLEY: Dr. Higginbotham?

DR. HIGGINBOTHAM: Thank you, Mr. Chairman.

DR. McCULLEY: We can't leave you out.

DR. HIGGINBOTHAM: At least one of your patients, I noticed, in one of your flow diagrams had a decrease in corneal thickness as measured by pachometry in one eye. First of all, do you routinely do pachometry on your patients?

DR. TABB: Yes.

DR. HIGGINBOTHAM: And secondly, is that something that's statistically seen in many of your patients, or--

DR. TABB: No. Statistically, I see very little difference over the long haul over years, and that's why I'm having a little trouble with the Australian individual, although she is a brilliant mathematician and I don't doubt that she's done the work and it may be very significant, I still have not seen the--I've seen very slight variations, but as far as any major variation in pachometry, I haven't seen it, and I've been doing pachometry since 1975 in my practice.

DR. McCULLEY: Thank you.

Dr. Soni, last of the last.

DR. SONI: Over the 30 or so years that you've been using this procedure in your practice, can you give us an idea of how many patients you've seen for this procedure, and let me just finish, one other thing. Based on that particular experience, what sort of safety concerns should we be interested in? What sort of safety concerns should we be looking at?

DR. TABB: Over that 30 years, I haven't done a tremendous number of patients, as 30 years would--you'd think I'd done 30,000, about 1,000 a year. I've done about 1,000, maybe. I never kept track, and so I apologize for not having those statistics. I did start to--when I talked with Dr. Saviola, I did start to go back and count at least the ones I could dig out quickly, but I was preparing for two other seminars, so I fell short of that. I'm sorry. Probably about 1,000.

As far as safety concerns, when the lenses are fitted well and designed well, I really don't see major safety concerns, other than hands of individuals who aren't trained to look for the problems and recognize when some of those problems exist. The problems are very minor and they're about the same type of problem that you see with ordinary contact lens wear--with RGP, I'm sorry. Thank you. But if left for long periods of time, I think they can become problematic.

So I think the safety concerns are primarily that the doctors are trained, that the designs are checked out so that they truly are endpoint lenses, and at least a scientific study or an FDA study done to demonstrate that they are safe and efficacious and follow it for six months or whatever you need.

The point is, we've been doing this for 40 years and reverse geometry lenses have been around a long time, too. The newest one on the block is simply the visco-elastic molding lens, and frankly, the overnight wear I'm finding safer than day wear as far as--because it's taken off as soon as you get off in the morning, and they do bind.

Thirty percent, if they come in and they haven't taken the lens off, you'll see the lens maybe stuck on about 30 percent of them. You can literally just touch it with the lid and it starts to move and they'll blink and it continues to move when you take it off. Those effects, when you check them toward the end of the day, are not there.

DR. McCULLEY: Thank you, doctor.

DR. TABB: And it doesn't create the stain.

DR. McCULLEY: Thank you. Thank you, and thank Dr. Marsden. If

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you both will stay there, we will involve you in our discussions as we move forward.

I think what we need to do at this point is move directly into the questions that the FDA has posed to us. We have on the schedule a closed session beginning at 3:30. We do not necessarily have to begin that exactly at 3:30, but I think we need to aim for that.

The first question you have to project, or would you like for me to read it? Are the safety end points identified for sustained RGP extended wear the same as those for the interrupted overnight wear for orthokeratology lenses? If not, what are the additional concerns?

Dr. Macsai?

DR. MACSAI: I would add a few additional concerns. One is the issue mentioned before, I think, by Dr. Jurkus and myself of diurnal variation or stability.

A longitudinal evaluation, because we know--well, we don't know. We hypothesize that keratoconus is the result of a genetic predisposition and a second hit of potentially trauma, and if that trauma exists to the cornea and these lenses where we're talking about potential epithelial loss, et cetera, is this a problem?

The third issue is reversibility. Is it reversible and how long does it take?

DR. McCULLEY: One question I had from Dr. Marsden's presentation with the epithelial defects, were you only seeing those significant epithelial defects when the lenses bound, or were they seen with all of the lenses?

DR. MARSDEN: The epithelial defects are primarily seen with bound

lenses, and so there is peripheral corneal desiccation that can result, but at no greater rate than we saw with conventional RGPs. So probably the magnitude or the nature with which the epithelial defects were experienced tend to be more noticeable or more dramatic with lens binding, or associated with lens binding.

DR. McCULLEY: And binding is at about 30 percent?

DR. MARSDEN: For my experience? I don't have very many patients. I probably have about half a dozen patients in overnight and all of them have experienced binding, so that's--

DR. McCULLEY: All of them have?

DR. MARSDEN: All of them, so that's--

DR. McCULLEY: Okay. So it looks like.

DR. MARSDEN: That's not a good end , though.

DR. McCULLEY: It looks like 30 percent to 100 percent of patients with these lenses have binding and, therefore, develop epithelial defects.

DR. MARSDEN: No, that's not true, either. They bind. It depends upon the aggressiveness with which they remove the lens. Most patients are educated--well, I shouldn't say most. Our patients are educated not to remove the lens if it's bound, so that they consciously look in the mirror to see if the lens is moving appropriately before they try to remove the lens. If not, they're instructed to use lubricants or apply gentle pressure, as Dr. Tabb said, to reduce that adhesion prior to removal of the lens, and generally, the only thing that's there is compression, which tends to resolve within an hour.

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DR. McCULLEY: Let me be sure I understand. Sustained means 24-hour use, wear?

DR. MARSDEN: No.

DR. McCULLEY: What does sustained mean?

DR. MARSDEN: In my definition, sustained is over, I'll say, six nights continuous wear, which is overnight.

DR. McCULLEY: Six nights?

DR. MARSDEN: Yes.

DR. McCULLEY: Day and night?

DR. MARSDEN: Day and night. That's sustained wear, versus overnight, which is they wear it from the time they go to bed and in the morning they remove the lenses.

DR. McCULLEY: Okay. In terms of concerns here, I think, as a cornea person who sees the complications of a variety of things, when the epithelium is not kept healthy, there is a real risk for a variety of things, not the least of which is infection. So in any study that is done, I think it's going to be important that vital staining of the cornea be done so that we assess the health of the epithelium at a minimum, if not going to other things like we talked about this morning.

DR. MARSDEN: Yes. I think we'd have to concur on that.

DR. TABB: May I add a comment? I have seen what I call compression staining, which is the SDK, more with daytime lenses that have gone past the limit of what

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the cornea can change, and changing the lens back, or bringing it into a more hydraulic containment system will alleviate that problem. I don't see these stain problems with overnight wear unless we've gone past the limit of the cornea, and I believe it's a design problem. I think this is a design function as opposed to necessarily a material function, primarily a design function.

DR. McCULLEY: Dr. Bullimore and then--

DR. BULLIMORE: Just a point of clarification here. I'm correct that we're not trying to establish whether this is less safe, more safe than any other modality that exists. We're just trying to establish guidelines for what we might look for? I think it would be better if we kept our responses in line with that rather than making comparisons at this stage.

DR. McCULLEY: Rather than doing--you tailed off. I didn't hear what you said. Rather than making--

DR. BULLIMORE: Rather than comparing them to other treatment modalities, I think an acknowledgement of things that we need to look at is sufficient at this stage and delving into too much of years of clinical experience is interesting as a fellow sort of clinician, but--

DR. McCULLEY: I think there was a question down here about retrospective and I think the mindset is going to be prospect.

Dr. Lepri?

DR. LEPRI: Dr. McCulley, when you were referring to evaluating the

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health of the epithelium, were you recommending rose bengal [ph.] staining and fluorescein or rose bengal just for vital staining?

DR. McCULLEY: Well, no, not just fluorescein. I would prefer a vital stain, rose bengal, lisimine green [ph.], but something that is a vital stain that is going to be more sensitive than fluorescein staining. It wouldn't hurt to have both, but fluorescein staining, to me, alone would not be enough.

DR. LEPRI: Thank you.

DR. McCULLEY: Dr. Pulido?

DR. PULIDO: Excuse me. This question is somewhat nebulous to me because it says, are the safety endpoints identified the same as those for interrupted overnight. We haven't identified the safety endpoints for either type of lenses yet, so what are our safety endpoints?

Are they going to be, number one, development of ulcerative keratitis? I think that's important.

Number two, I am still very concerned about the problems of altitude changes, and likewise, the diurnal variations, and those weren't things that we were worried about with regular contact lens use, but I think they have to be concerns in this type of process.

DR. McCULLEY: And temperature, probably.

DR. PULIDO: Correct.

DR. McCULLEY: Temperature and altitude. Thank you.

What we're addressing now are things that we would want to be concerned about, one to the other, and just for either one, I think. Dr. Higginbotham?

DR. HIGGINBOTHAM: I would add the corneal thickness to the list. I don't think that was on the original list for RGPs, but certainly, considering that in the document that was provided there was also a pressure, a perceived pressure change of two millimeters, which may or may not be real, but could be related to some corneal thickness change.

DR. McCULLEY: Okay.

DR. SAVIOLA: There's one thing I'd like the panel to keep in mind as they discuss this topic. The materials that these lenses are designed out of, assume for the discussion purposes that they are materials that have already been approved for overnight use, for the prolonged extended wear from one to seven days. So there has been addressed the fundamental safety threshold for the lens material itself.

And as we talk about designing these type of orthokeratology lenses out of that material, the safety questions we're trying to get feedback from are the ones that deal with the design aspects, and if there are additional safety questions concerning the material, some of those may already have been addressed by the fact that the material is approved for overnight use already.

DR. McCULLEY: Okay. And I think the things that we have brought up so far would relate to the difference in design.

Dr. Harris?

DR. HARRIS: Well, I think it's important that we look at corneal topography changes associated with overnight ortho-K, and I don't think the keratometer is an adequate way to do this and we need to have corneal maps. I think that we need to do a measurement of refractive error change, including any astigmatic changes, any distortion that may have been involved, and visual acuity changes. After all, that's the specific reason why people are undergoing this particular procedure. If that's not part of the measurement of efficacy, then we're missing the boat.

DR. McCULLEY: Thank you. Dr. Pulido?

DR. PULIDO: Dr. Harris, I have just a question for you. How would you grade the corneal topography changes? How would you follow those? That question came up this morning, so I'm just boomeranging at that.

DR. HARRIS: Well, at this point, I don't have an easy answer for that question, unfortunately, but I think that we need to establish somewhere along the line what kind of changes are going to be acceptable, just as we are in other endpoint criteria. I don't have a guideline at this point to present.

DR. McCULLEY: I think we're starting to see a regular astigmatism when we start to see that--

DR. HARRIS: Certainly.

DR. McCULLEY: --then translate it into visual acuity changes, that we would have the two together.

DR. HARRIS: I could certainly see that there is a point at which it's totally

unacceptable, but I'm not sure that there's a place somewhere between okay and unacceptable where you can draw the line.

DR. McCULLEY: And a real risk, to restate what Dr. Macsai said earlier, if contact lenses are associated with the development of keratoconus in genetically susceptible individuals, that we might see changes here in a larger percentage of the population, so that that would be another concern to watch.

There was another hand over here that I saw. Dr. Jurkus?

DR. JURKUS: One of the things in terms of the safety I would also be concerned about is stability of the lens itself, the lens design. I would assume that the initial studies were of conventional lens designs, and here, with differential thicknesses, since there may be a warpage or change in lens curvature which would then adversely affect the corneal change.

DR. McCULLEY: Yes?

DR. MARSDEN: One of the things that I'd like to hopefully reinforce what Dr. Saviola said, is the fact that we've got lens designs that are constantly being upgraded and modified and these criteria really need to address the potential for some of those.

So, for example, I received a phone call a week or so ago that said, oh, do you have any patients with this double tier reservoir lens, and I only have one, and I was asked, look for microcysts in the secondary curve region. It was so subtle that I never would have probably detected it had somebody not said, "Look for it."

And so I think it's important to probably think a little bit more futuristic, that there are going to be newer, better, bigger designs that come about and are these going to be adequate enough to address those when that time comes.

DR. McCULLEY: Thank you. Other comments on this first question?

Yes, Dr. Tabb?

DR. TABB: I'd just like to make a comment. The concern about keratoconus, it's my understanding from Dr. Nessburn [ph.], who is in California and has a keratoconus research center, that keratoconus primarily comes from a type six collagen that isn't quite right and it allows the layers to slip--that's not true?

DR. McCULLEY: No. Let me state something I said this morning. The purpose of these deliberations are to offer opinion and information to the FDA, not for us to debate and resolve.

DR. TABB: Okay.

DR. McCULLEY: Yes?

DR. LEPRI: Does the panel feel there is any merit to evaluating shifts in magnitude and access of cylinder with keratoconus? You want that evaluated, too?

DR. McCULLEY: With orthokeratology.

DR. LEPRI: Yes, with orthokeratology.

DR. McCULLEY: Absolutely. Yes.

Do you have any additional questions, or have we dealt with this question to your satisfaction?

[No response.]

DR. McCULLEY: Okay. We'll go on to the next question.

DR. PULIDO: That was an efficacy endpoint, not a safety endpoint.

DR. LEPRI: Yes, that would be efficacy, induction of cylinder, like limiting a certain proportion of patients--

DR. McCULLEY: The proportion of patients that would have cylinder of more than two diopters induced, such as we do with refractive laser procedures.

Okay. The next question, 2(a). Please comment on the suitability of the following efficacy endpoints and provide an acceptable level of performance, such as percentage of patients achieving the endpoint: Uncorrected visual acuity, 20/30 or better, compared to 20/40, compared to 20/20. Mike?

DR. HARRIS: Am I understanding this question correctly as to what should be the end point of doing this procedure? Is that what you're asking?

DR. LEPRI: Yes. In other words, we would like, or we want your opinion about what would be beneficial. When results are presented from a sponsor, do you feel that it would be in the best interest for labeling purposes especially to delineate how many patients with a certain preoperative--not preoperative, pretreatment refractive error achieve 20/20 vision, what percentage achieve 20/30, et cetera?

DR. HARRIS: I think that's very valuable. I think what you should be doing is twofold. Number one, indicate, since this particular procedure is refractive error dependent, and certainly individual variations, you should come up with a grid that shows

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how much refractive error change is likely for what percentage of the population and what associated improvement in visual acuity goes along with that refractive error change.

Coming up with what percentage has 20/20, 20/30, or 20/40, even though that is useful information and it's something that I would like to see in the labeling, that may not be the end result that the patient is looking for. So I think that if a patient is a five-diopter myope, they might be satisfied ending up as a two-diopter myope seeing 20/100 and that's fine with them, as long as they understand that from the get-go.

So I'd look at both end result as far as actual end result acuity, but I'm more concerned--I shouldn't say more, but I'm equally concerned with the actual amount of change and improvement of acuity that can be gotten.

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: I actually like Dr. Tabb's table. I think it's intuitive. I guess it was on page 20 or 19 of the fax that we had circulated. I think stratifying patients by the entry refractive error deals with what Dr. Harris was just suggesting, so I would encourage the FDA folks to use that as at least a first template.

DR. McCULLEY: Does that answer your question?

DR. LEPRI: Yes.

DR. McCULLEY: Yes? Substantial additional comments?

DR. SONI: Yes. I'd like to also include reduction of astigmatism in there.

DR. McCULLEY: That was Dr. Soni speaking. Please always identify yourself, if I haven't done it. Dr. Macsai?

DR. MACSAI: I would also like to see included, as we spoke about this morning, the best spectacle corrected visual acuity less than 20/25 if originally it was 20/20, and an alternative way to look at this, the attempted versus achieved in the event that this minus five example might want to be monovision and be happy at minus two.

DR. McCULLEY: Good points. Dr. Higginbotham?

DR. HIGGINBOTHAM: Considering the variability of this outcome, does one want to consider taking more than one visual acuity as an endpoint and maybe have two consecutive visual acuities or three consecutive visual acuities be an endpoint and maybe taking the median? I'm just throwing this out as a suggestion.

And the other consideration--oh, okay. I'm jumping ahead. And the other consideration would be whether or not there's an age influence here. I don't know--

DR. McCULLEY: Possibly a morning and an evening visual acuity, in the studies, anyway, to give some idea of stability.

DR. HIGGINBOTHAM: Number four.

DR. McCULLEY: Is that number four? Good. We don't have to answer number four now.

Dr. Pulido?

DR. PULIDO: I would like to see--I agree, but going back to what we had mentioned before, I think that stability of uncorrected visual acuity should actually be a safety concern, not an efficacy concern.

DR. McCULLEY: Okay. Other comments?

[No response.]

DR. McCULLEY: Then we will go to loss of two or more lines of best corrected acuity. What you want from us there is a comfort level of a percentage that would lose two or more lines, or what is your question?

DR. LEPRI: Yes. What we would like to know is the percentage that the panel recommends of loss of two or more lines of BCVA as a safety issue.

DR. McCULLEY: Dr. Harris?

DR. HARRIS: You're talking about loss of two lines best corrected with any type of correction spectacle or contact lenses?

DR. LEPRI: That's correct.

DR. HARRIS: So is it, as an end result--the patient started out seeing 20/20 with correction.

DR. LEPRI: Yes.

DR. HARRIS: They go through orthokeratology. At the end of the procedure, their now best corrected acuity, regardless of what you try, is 20/40.

DR. LEPRI: Correct.

DR. HARRIS: To me, that's unacceptable for any patient.

DR. LEPRI: Well, what limit? For example, in refractive studies, you have a certain percentage that is considered tolerable. I see a zero coming in from the back.

DR. HARRIS: Since this procedure is not a permanent procedure, it

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should not make a permanent change. Therefore, any permanent change that reduces best corrected acuity is unacceptable in my view.

DR. LEPRI: So zero loss. Zero percentage of loss.

DR. McCULLEY: Zero tolerance is what you're saying.

DR. SAVIOLA: Excuse me, Mike. You mentioned permanent loss.

There's the issue that if they start treatment at 20/20 with spectacles, they get ortho-K fitted. After three months, they're 20/30 with spectacles. If they go out of orthokeratology, they return back to 20/20, 20/25. That's a little of a different thing than if they permanently remain at that level.

DR. HARRIS: We're talking about best corrected acuity. We're not talking about whether it's with--

DR. SAVIOLA: That's with the spectacle--

DR. HARRIS: No, but that's not what it says here, Jim. We're talking about best corrected vision, whether it's with spectacles or with contact lenses. I would assume that with one of those two devices, that their best corrected acuity is going to be as good as it was or better than what it was when they started, and if it is reduced by two lines, this to me is unacceptable.

DR. McCULLEY: Dr. Pulido?

DR. PULIDO: I have to disagree with that, because for contact lenses, we are accepting a small loss for extended wear and daily wear contact lenses. We accept a small amount of infiltrative keratitis and it looks like maybe 1/20 of those do have some

best corrected visual acuity loss. So we need to be no harder than regular contact lens wear.

DR. McCULLEY: There really can be zero because all you have to have is one adverse event and everything's gone. So what we said, I think, with the contacts was that it should be less than what the guidance was for keratorefractive surgery, and I would think that that statement would hold here, as well.

Dr. Macsai?

DR. MACSAI: Are we only talking about myopia, because if we're talking about hyperopia, it's going to be different, you know, because if you correct it with a magnification change, you might lose vision, but that's okay? I mean, do you understand what I'm asking?

DR. McCULLEY: Yes, I do, but you're not talking about a range of hyperopic correction and I think that that's going to be a major point.

DR. MACSAI: Dr. Tabb was talking about hyperopic correction.

DR. McCULLEY: He was, but very low ranges of hyperopia. I don't think we're going to get into a major magnification difference. If we do, then we can deal with that.

DR. MACSAI: Just keep it in mind.

DR. TABB: that's very experimental at this point. Very few people do that procedure--three in the United States that I'm aware of, and we're very cautious with it. I don't think it's anything that we need to worry about at this point.

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DR. McCULLEY: Okay. We're past 3:30, so we need to stick with it.

Two-A-three, magnitude and distribution of myopic reduction. We've already said that we think that should be stratified.

Stability of uncorrected visual acuity, we have mentioned with morning and evening vision, and I would think refraction, as well. So refraction and uncorrected visual acuity, morning and evening, for a measure of stability.

Yes?

DR. JURKUS: In regard to the morning and evening, I would think that it would be more appropriate, the number of hours of not wearing lenses as opposed to in the morning and evening, particularly if they have been wearing their lenses during the day and then take them out in the evening. So I think we need to be consistent on the acuity measurements after lens removal.

DR. McCULLEY: That was the intent, so if there was some way to mess around with that, we don't want it messed around with.

Two-B, is there a clinically significant difference in percentages between test and control groups that would be acceptable? Now, what's the control group?

DR. HARRIS: Jim?

DR. McCULLEY: Yes?

DR. HARRIS: Can I ask your indulgence, since I have to catch a flight.

Can I make some comments on some of these others and let those stand?

DR. McCULLEY: Can you start with this one?

DR. HARRIS: I don't have any comments on this one. That's why I want to move on.

DR. McCULLEY: Yes. Please do.

DR. HARRIS: I'm concerned about the length of the study. I think it should be at least a one-year study. I don't think six months is long enough.

All of the information on orthokeratology to date, except for a few studies, has been anecdotal. There are very few clinical trials, very few controlled studies that have been published in referred journals, so that we need to start from base one. We should not use retrospective data. It should all be prospective, and I think a 12-month study should be used.

I also think that the labeling issue is extremely important. This is where I have most of my concerns. Obviously, we've talked about the refractive error changes and the visual acuity that can be achieved and some type of a grid that shows that is important. The fact that visual acuity is going to be variable and that the end result visual acuity is going to change during the day or during the week when you're not wearing contact lenses is something that I think a patient needs to understand.

The patient needs to also understand that they are going to have to wear a retainer lens for a period of time, sometimes overnight, sometimes during the day, depending on the procedure. They have to understand that there are some safety concerns obviously with this and the same kind of safety concerns as we have with extended wear.

I want to raise another issue which I have some real trouble with, and that

is the fact that many of the patients who seek this procedure are parents looking for something to help their children and I'm really concerned about minors being involved in an overnight study. I don't think that any of the approvals we've had so far for overnight wear have included minors. If they are, I'm not aware of it. But I think we need to be very, very cautious about including minors in this kind of a study, certainly at the initial study, anyway. I think that that can be extremely dangerous.

DR. McCULLEY: I was very bothered by that statement, as well.

Would you comment on the study size, 100 or larger?

DR. HARRIS: I'm not the statistician in this group. I think that we can use the same kind of insight we got from Dr. Schein this morning and others. I think we need to decide, first of all, whether you're going to go with a contralateralized study or whether you're going to go with a controlled randomized clinical trial. You've got a--

DR. McCULLEY: Well, it's hard to have a control group in this--

DR. HARRIS: Well, there's--

DR. McCULLEY: --that's going to be taking this to what our standards are.

DR. SAVIOLA: Excuse me. Since we're jumping ahead, we did have a slide prepared from our statistician to address sample size for uncorrected VA pre-treatment versus post-treatment, and if you wanted to react to that, this is what it is.

DR. McCULLEY: Okay. That's going back to 2(b). Dr. Harris, are there other areas before we go back to where we were that you'd like to comment on?

DR. HARRIS: No, but I think the area of product labeling and informed consent is extremely important and I want to urge that the panel give that due consideration.

DR. McCULLEY: I certainly feel the same way, so if you're not here, I will state those concerns.

DR. HARRIS: Thank you. And again, my apologies. Unfortunately, in order to get home, I have to leave now.

DR. McCULLEY: Thank you.

So we'll go back to this slide.

DR. BULLIMORE: Mr. Chairman, if it pleases you, this is Dr. Bullimore. I don't think this is a useful way to think about it. I think we should look at the proportion of patients reaching a certain visual acuity level and I think we should look at the mean reduction in myopia.

DR. McCULLEY: Any disagreement?

[No response.]

DR. McCULLEY: Good. Three, the "n" and the duration. The duration, to me, seems like that ought to be really easy. Anything less than a year, I would think, would not even be worth talking about. Agreement?

DR. BULLIMORE: Well--

DR. McCULLEY: Are you going to disagree?

DR. BULLIMORE: Yes, I'm going to disagree with you, Mr. Chairman.

DR. McCULLEY: All right.

DR. BULLIMORE: But only in the fact that we don't really have the data to think that the shorter might be doable or possible. It's very possible that subsequent studies could be done within six months and be perfectly satisfactory, but at the moment, in the absence of any data, I would reluctantly agree.

DR. McCULLEY: Okay. Good. I would, too, and I would think that if we found data to the contrary down the road, that we could consider going shorter, but as a starter, that we would start with a year. So we agree. Good.

DR. MACSAI: Dr. McCulley?

DR. McCULLEY: Are you going to disagree, Dr. Macsai?

DR. MACSAI: I'm only going to point out that in other refractive procedures, we've requested two-year follow-up.

DR. McCULLEY: Initially.

DR. MACSAI: So since we're talking about initial studies, why the difference? Sorry.

DR. McCULLEY: Dr. Tabb?

DR. TABB: I would say there's a major difference. This procedure has been done for over 40 years. We have changed the design of the lenses, but the safety issues are not anywhere close to the safety issues that would be in an invasive technique. It is not an invasive technique.

DR. McCULLEY: That could be debated.

Dr. Soni?

DR. SONI: I have a question for Dr. Marsden and Dr. Tabb as far as the duration is concerned. What's your estimate on how quickly can the procedure be done? Does it need to be more than six months? In the past, the best studies show that it takes about 12 months to 18 months for it to be effective, but if you think it can be done in three months, then I think six months may be possible, but I agree with--

DR. MARSDEN: The current literature supports a shorter period of time for treatment, but one of the things that the data certainly is lacking is the issue of retainer wear, and that's what we don't know and what we can't predict what the longitudinal effects. We had said that the stability, those issues have not really been published, and so we do get results far sooner, and generally within six months' time, we're already in retainer wear. So now the issue becomes, are you just interested in the therapy portion, which my guess would be not, you would want to take it out a little bit further to find out what the ramifications--

DR. McCULLEY: So would you recommend two years?

DR. MARSDEN: I'd still feel comfortable with a year because the variability doesn't seem to be there, and that, again, is anecdotal, so it's difficult to say. It may be something that as we come along that we might have to come back and revisit.

DR. McCULLEY: One of the things we did in the guidance document in terms of--for refractive surgery relative to stability was stability at two successive times, at least a specified length of--pardon?

DR. SUGAR: One diopter at three months.

DR. MACSAI: One diopter at three months.

DR. McCULLEY: Right. So I would think a year or establishment of stability, at a minimum. Dr. Macsai?

DR. MACSAI: Dr. Macsai. The reason I brought up two years, Jim, is that in Dr. Marsden's presentation, they talked about an 18-month period of therapeutic before the patient reached a retainer lens, and if that's the case, then a year will not be enough.

DR. McCULLEY: Dr. Tabb?

DR. TABB: The 18 months was from literally almost 30 years ago. We're talking about reaching the end result literally overnight for many individuals and within a two-week to a maximum of two-month period. As a matter of fact, many individuals, if we haven't reached where we want to go in a couple of weeks, many times we'll discontinue because it isn't going to be satisfactory.

DR. McCULLEY: Dr. Rosenthal? Into the microphone. You're being called upon.

DR. ROSENTHAL: I'm not supposed to be asked scientific questions.

[Laughter.]

DR. ROSENTHAL: What percent discontinue? What percent are you not able to fit by two weeks?

DR. TABB: I've had one that I discontinued and he actually went from

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20/600 to 20/20 overnight. The difficulty was--and he had been a patient of mine for 27 years, since he was a little guy--

DR. ROSENTHAL: Excuse me. You said that within two weeks, if you don't get them within two weeks, you don't have to go any further. What percent are you not successful by two weeks?

DR. TABB: I have one that I--

DR. ROSENTHAL: Just one?

DR. TABB: I literally went two months. The other, I discontinued after one week.

DR. BULLIMORE: We have a table here which suggests that the three-month discontinue rate is 20 percent. We all have that data in front of us.

DR. McCULLEY: We're suffering from absence of good controlled scientific peer reviewed data, and we're having to rely on memory.

So I think what we've said is that a year is the minimum or stability established, no more than a diopter of change, three successive visits three months apart.

DR. SAVIOLA: I have one hand over there for two years.

There are two phases to this, and I guess it really wasn't emphasized that much during the presentation. There is a treatment phase and then there is the retainer phase, and what we're hearing from our invited speakers is with these newer designs--the 18 months was the old method of fitting, the category one, as you heard from the one public speaker. The treatment phase can be as rapid as six to eight weeks in some

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cases--in most cases, perhaps. If the treatment phase goes beyond this immediate three-month, couple-month period, then it's not going to be a good candidate for this procedure.

So if you're saying you want one year or two years or whatever, I'm going to interpret that as you're looking to get information about not the treatment phase exclusively but also the retainer phase and the stability of the procedure over time.

DR. McCULLEY: Yes.

DR. MACSAI: Right.

DR. McCULLEY: Safety and effectiveness, right.

Dr. Rosenthal?

DR. ROSENTHAL: Mr. Chairman, the reason I'm pressing the issue relating to those who will not complete the course of the treatment is because in defining the number you need at the beginning of the study, you have to know the number that will drop out so that you have enough people at the beginning that you're able to make your evaluation on it.

DR. McCULLEY: It's a major onus on a sponsor to figure that out.

DR. MACSAI: Not only that, but to include why those that drop out do from a safety point of view.

DR. McCULLEY: Right, from a safety and efficacy standpoint.

Dr. Pulido?

DR. PULIDO: There is some data. The Paragon, et al., that we were

given, the 1990 paper, 100 myopic children--now, this is kids that were involved in this one, unfortunately--and there was a 50 percent dropout rate.

DR. BULLIMORE: This is Dr. Bullimore. That's not an ortho case study. That was the use of a conventional fitting of RGP lenses for the control of myopia in children. While it's included in there, it's not considered RK.

On that topic, I do think it's important in terms of labeling, planning these studies, and any information we give to our patients that we distinguish from the potential effects of RGP in controlling the progression of myopia and the use of ortho-K in temporarily reversing myopia or temporarily treating myopia. I think that's an important distinction and I share the other panel members' concern at the use of ortho-K in children.

DR. McCULLEY: Good. I'm not sure that that actually will be there in these other questions. Is there disagreement among the panel that this should not be a procedure for children? Is that statement clear enough from the panel? We think this is for consenting adults. I shouldn't say that in Washington, D.C., is that it?

[Laughter.]

DR. McCULLEY: Until proven safe for consenting adults, and then to be shown in children.

DR. PULIDO: What we did with IOLs, and now we're using children.

DR. McCULLEY: Right.

DR. PULIDO: To do similar with what has been done with intraocular lenses. Once shown in adults, then it can be tried in clinical trials with children with

informed consent.

DR. McCULLEY: Right.

DR. SAVIOLA: Could you articulate your basis for that concern, please?

DR. McCULLEY: Children?

DR. SAVIOLA: Specifically, yes.

DR. McCULLEY: Well, I think to subject a child--for many of the same reasons we don't do other things in children that we're not certain about, is that they would have something potentially done to them by a guilty parent who feels like, gee, my kid inherited myopia because of me. I feel bad about it and I'm going to try to do something or I want to do something for my child. When the child cannot consent, when we don't know what the safety of the approach is, I think it's just inappropriate.

DR. SUGAR: Also, all of our refractive procedures, we've talked about having stable myopia prior to initiation of therapy. You're going to have a moving system where you can't judge the change if they're actually elongating at the same time.

DR. McCULLEY: So you've got a philosophical and a scientific response.

DR. SAVIOLA: I'm asking for specific reasons so that the industry can hear your concerns.

DR. MACSAI: I would also want to really reiterate Dr. Bullimore's comments that there's no evidence that this decreases the progression of myopia and that that in children, and that that be very clearly made out as all labeling, et cetera.

DR. McCULLEY: Well, at this point, we're recommending no children.

Number four, I think we've already made a very strong statement that retrospective data is not for consideration. It's prospective. Is there any disagreement to that?

[No response.]

DR. McCULLEY: Okay. The last question, what is the panel's viewpoint concerning outcome information and product labeling for this type of device. If you think it should be provided, are there any specific recommendations, such as stratification by amount of myopic reduction.

I think Dr. Harris addressed that well and it's a clear yes. We should have data by myopic degree. Are there any other comments about the labeling that either one wants to make or that you want us to make? Ms. Morris?

MS. MORRIS: Well, actually, I have a couple of non-technical questions, not for the speakers but really for the panel, and I wasn't sure where they fit and this seems like the most likely place.

Patient information, the brochure that was distributed earlier today, I actually have three questions. The first one, I think got answered, but I want to check if I understand the answer correctly. It says--first of all, I understand ortho-K to be a procedure, so I was confused why this panel is looking at that. But I think I understand the answer, is that there'll be newer designs coming on the market and, in fact, FDA will be regulating these new designs, is that correct? That's why we're currently discussing this--

DR. McCULLEY: More or less.

MS. MORRIS: --in order to give information to FDA staff for when sponsors come forward and we will be dealing with that issue, is that correct?

DR. McCULLEY: Ralph, would you like to answer that?

DR. ROSENTHAL: I think Jim can answer it.

DR. McCULLEY: Jim?

DR. SAVIOLA: Well, yes. The whole purpose of this discussion is for the industry so that they can structure their studies in a manner that would be consistent with what the panel would view as being valid scientific evidence for an application. As I said earlier, the very first overnight application will come to the panel for review--

DR. ROSENTHAL: An overnight--excuse me, this is Dr. Rosenthal--an overnight lens is considered a class three device, so while they were doing it during the day, they did it as off-label use. When they do it at night, they can do it as off-label use. But once they advertise it, then they have to come in.

DR. SAVIOLA: Right. As a practitioner, like Dr. Tabb has been doing it for 30 years, if the practitioner designs their own lenses in conjunction with a manufacturing lab for those specific patients in his practice and fits the patient, then that's a procedure done as an off-label use for that particular device, that contact lens.

What's happening now is it's going beyond the scope of the practitioners designing lenses. It's being marketed by labs, by firms, and so those are truly manufacturers. There is no off-label issue there. It's strictly a regulatory issue and that's

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why we are regulating it.

MS. MORRIS: And that's what's coming here. Okay. Thank you.

DR. McCULLEY: You said you had a couple of points.

MS. MORRIS: I have two more, because I'm a little nervous about this brochure that I'm looking at. It also says in the brochure that because the operation is performed on a healthy organ, as a result, the surgery usually is not covered by health insurance. So I guess from a consumer perspective, if, in fact, this is an effective procedure and we're going to be dealing with new designs and so on, why isn't this covered by health insurance?

DR. McCULLEY: This is not--as I would understand it, the appropriate response to that is this is not the forum in which that would be appropriately addressed.

MS. MORRIS: Okay.

DR. SAVIOLA: If I may address that question--

DR. McCULLEY: Oh, good.

DR. SAVIOLA: The part you're reading from is--this brochure, again, is an FTC brochure that they updated from last year that originally was to discuss RK and PRK, and with their actions they took against claims regarding orthokeratology, it included orthokeratology within this brochure. If you look on page two of this brochure, the part you just read is not related to orthokeratology. It's related to the surgical procedures of RK and PRK.

DR. McCULLEY: But RK and PRK typically aren't covered, either.

DR. SAVIOLA: Right.

MS. MORRIS: Okay. And then my third question is, and again, it's for the panel, if, in fact, these claims are rampant out there, and I know earlier we looked at one on the screen, is FTC currently following up on this false advertising?

DR. McCULLEY: That's a good question. What is being done with--

DR. SAVIOLA: FTC took action against one particular doctor in Tennessee who was actually marketing this technique to a variety of different optometrists and the claims he was making were unsubstantiated beyond the scope of what had been published in the literature. I'm not a lawyer, but they took some legal action. They enjoined him or whatever they do to prevent him from continuing with those practices.

The organization, the National Eye Research Foundation, really, the section that Dr. Tabb is Immediate Past President of which specifically is interested in orthokeratology, they are working proactively with FTC in terms of the types of claims which are acceptable to the Federal Trade Commission that can be made for this procedure. So there is interaction with other Federal agencies besides FDA.

DR. McCULLEY: Thank you for your input.

Are there any other issues relative to labeling before we conclude? Dr. Higginbotham?

DR. HIGGINBOTHAM: Not specifically related to labeling, but in our discussion, we didn't really address quality of life or patient satisfaction issues, and I think, considering these patients come back as often as my glaucoma patients, about every three

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months or so, every four months, and they're in their 20s and 30s and they're wearing overnight contact lenses, we might want to consider some kind of instrument to try and capture the impact on their lives.

DR. McCULLEY: So a patient satisfaction survey along the lines that we have requested and seen for refractive surgical procedures? Good point.

DR. MACSAI: To include symptoms, also, of, you know, glare, night driving--

DR. McCULLEY: All in the questionnaire. Right.

Dr. Ferris?

DR. FERRIS: Rick Ferris. I just want to make sure I have this straight. At the end of the day, we're going to have a study brought to us that would have outcome variables similar to the refractive surgery outcome variables plus a couple more with regard to a variation in vision over time during the day and we're going to review that data and it will be a smaller sample size than we looked at for the surgical procedures?

DR. McCULLEY: That is something that we--

DR. SAVIOLA: You might have missed that part because we put that up while Mike Harris was on his way out the door, but that was one we were going to go back to when you asked us, did you answer all our questions. Question 3(a) was the sample size question. The rest of that is correct, Dr. Ferris. You will be reviewing this.

DR. McCULLEY: And where we ended up recommending--boy, it's getting late in the day--on sample size for contact lenses, you questioned going from four

to three and our response, I think, was would push it four up, and it seems like in a study such as this that we would have to recommend the same thing.

Dr. Macsai?

DR. MACSAI: If you're looking at the procedure and looking at it as a refractive procedure, I think that initially we asked for other refractive procedures 500 to 700 eyes and why would you ask for less?

DR. SAVIOLA: Well, if we can go through this discussion right now. As I said earlier, these lens materials have already passed a threshold, being approved for extended wear. So there's a threshold of safety that exists for them. That's one point.

The second point is that if it's an overnight only type of fitting procedure, that is fundamentally different from this type of sustained extended wear, where the lens is on the eye continuously, 24 hours per week [sic] at a time, and that's a point that really hasn't been tossed around here. So those are two factors of why it's going to be different.

The third factor why it's going to be different here is with the patient acting as their own control, uncorrected visual acuity pre-treatment compared to uncorrected visual acuity post-treatment, and the numbers play out to be relatively small for that type of analysis if you're designing your study around the efficacy issue.

DR. FERRIS: I guess that's the issue. Are we trying to figure out whether this does anything? I mean, I would assume that if it didn't do anything at all, this would have died out long ago. It does something. The issue if we're reviewing it must be as much or more that we're concerned about side effects than we are about whether it does

something. I'd be willing to stipulate today that it probably does something. I just don't know how to balance the risks and benefits because I don't know what the risk side is. I assume there are benefits. Otherwise, people wouldn't be fiddling with this. People wouldn't do this if it didn't do anything.

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: I think you're using efficacy to drive your sample size calculation. So what you were trying to say was you want to have reasonable narrow confidence intervals around whatever your estimate of the number of patients reaching 20/20 or uncorrected 20/40 or whatever. In terms of efficacy, I think you would reasonably end up with somewhere around 100 such that you had confidence intervals of the order of five percent or so on either side of whatever number you pulled out of your hat. I think that's reasonable.

Regarding additional risks, I don't think we've clearly identified what the additional risks might be, and unless we do identify what the additional risks might be, it's perhaps premature to inflate the sample size on that basis.

DR. McCULLEY: I think that there are identifiable potential risks that are principally related--at least one of them, a major one related to the health of corneal epithelium and susceptibility to infection. So I think that, to me, is as big a question as the efficacy.

DR. BULLIMORE: Yes, but to reiterate what Dr. Saviola was saying, this is a material and the modalities all but approved for extended wear based on previous

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studies.

DR. McCULLEY: But that's with well-fitted lenses and these are not well-fitted lenses relative to the corneal curvature.

DR. BULLIMORE: Yes. I mean, I--

DR. McCULLEY: They are distorting the corneal curvature, and I have trouble envisioning anything that is significantly going to distort the corneal curvature to induce a refractive change without it significantly adversely affecting the corneal epithelium and I'd really like to see data to give me comfort that it does not do that.

DR. BULLIMORE: Yes. I accept that. I'm just asking you to state that clearly, so--

DR. McCULLEY: Okay. Well, thank you for the opportunity.

[Laughter.]

DR. McCULLEY: Dr. Rosenthal, you had your hand up.

DR. ROSENTHAL: If, in fact, these lenses stick and they do come off and sometimes bring epithelium off, that can be a significant safety factor. If it's 30 percent of the time, you don't need more than 100 lenses. I mean, of course, if one of those get an ulcer, then you're going to have to study five--so, I mean, you know, it depends on the magnitude of the frequency of at least the one obvious complication you've already spoken about.

DR. McCULLEY: Dr. Macsai?

DR. MACSAI: Not only the epithelium coming off, but the adhesion

properties with this lens. If it requires polishing, buffing, whatever, every three months and if it's not buffed every three months, what's the additional increased risk of microbial keratitis in a poorly or an alternatively-fit lens that's got increased adhesive properties due to increased protein build-up.

DR. McCULLEY: Dr. Marsden?

DR. MARSDEN: Yes. I think one of the things that needs to be kept in mind is that reverse geometry lenses in and of itself have been utilized and fit on a daily wear basis, that part and parcel, you also have that material that has been approved and tested for extended, continuous wear, whatever terminology you want to use.

So bearing those items in mind, you know, one of the reasons for utilizing the Australian data is to show that if you're going to use microbial keratitis or ulcerative keratitis as your safety endpoint, the incidence is so low that you'd have to have a phenomenal "n" to be able to get something of significant, and I am by no means a statistician, that yes, there are safety concerns and health concerns. However, you almost have to look at what are the issues from the two independent things and pulling those two things together, is there greater risk or greater--

DR. McCULLEY: Right, and we had trouble with surrogates with conventional lens wear earlier. I don't think we have so much trouble with a reasonable surrogate with a lens that is going to significantly alter the corneal surface. You start mucking up the corneal epithelium, you've got a pretty good surrogate that you're going to get microbial keratitis.

DR. BULLIMORE: Okay. So I'm just trying to sort of keep the level of science at the same level as we had this morning. If we're going after ulcers, let's state what we think the percentage might be. If we're going after corneal staining, let's state what we think the percentage might be and then base our sample size on that rather than just saying 100, 500, 1,000, and that be it.

DR. McCULLEY: I agree. So I think that at least my sense is that you would need to look carefully at the numbers, keeping not only efficacy under consideration but safety, and personally, I would like to see 400 or 500 sample size, but I don't know the exact number. I need the statisticians to help me.

DR. SAVIOLA: You do have the situation here with this particular type of product which is a little bit different in that since people have been practicing these types of fitting techniques and using overnight wear lenses, that while retrospective data may not support a PMA application, retrospective data certainly gives you information regarding the procedure and from that data you may be able to determine a basis for a smaller prospective study.

DR. McCULLEY: Boy, I tell you, I have real trouble with that from a scientific standpoint.

Dr. Pulido?

DR. PULIDO: I think this might be a very nice situation where "fellow eye" type of a follow-up might be better than a randomized multiple patient type of follow-up, because one eye could be fitted with an extended wear lens and the other with

one of these ortho-K lenses and seeing what happens to the corneas in the two eyes would be a good way of doing this kind of a study.

DR. McCULLEY: Interesting thought. Did you guys note that?

DR. SAVIOLA: I don't know if you'd be able to recruit any patients in that study.

DR. McCULLEY: Okay. Dr. Jurkus?

DR. JURKUS: Yes. I was going to say I disagree with you, in that patient recruitment would be almost impossible in terms of getting people to--in terms of quality of life, if they are trying to compare having a contact lens on one eye and not having the lens on the other eye.

DR. McCULLEY: Okay. Dr. Soni?

DR. SONI: Going back to sample size, and from what Dr. Rosenthal just said and also what Dr. Holden said this morning about RGP lenses and adhesion with the RGP lenses, he said they see something like 30 percent adhesion with RGP lenses. And to take your argument further, which is to suggest that these are poorly-fit lenses compared to the normal RGP extended wear lenses, we'd see a lot more adhesion with these lenses, say 50 percent. So 50 out of 100 is going to give us incidence of problems, a lot more than any of the other things we're looking at.

So I think our numbers--you're looking at the numbers being larger to be able to prove that. We don't need to go larger. We need to actually--everything will wash out in a smaller sample size, actually.

DR. McCULLEY: Okay. Dr. Ferris? We're going to have to start to wrap up, but not to cut you off.

DR. FERRIS: I have no idea what the complication rate is, but I assume that it's probably low. If it's low, then in order to have any kind of confidence around that complication rate--if what we're going to be doing at the end of the day is providing information to patients about safety and efficacy, we're going to have to have some ability to address the safety issues, so that although these lenses stick, I don't know what, 30 percent, whatever they stick, it sounds like most of the time you wiggle it around a little bit, pop it out, and the next day you're fine. So what?

But some percentage of that time, it may lead to something significant, and if that's going to be--I heard earlier sort of a low tolerance of serious side effects, and if they're going to be low, then the sample size is going to, by necessity, have to be fairly large to be able to capture them. If they're going to be in the five percent range, you're going to need a fairly big sample size to be able to capture that.

The FDA has dealt with unusual side effects before and what sort of sample size is necessary to capture it and I would leave it to them to define a big enough sample size to capture a five percent event rate.

DR. McCULLEY: Thank you. That was a very good statement. If there is a statement that can help resolve this issue and you're confident that it is going to help resolve the issue, I will recognize you. Otherwise, we are going to have to wrap up. You're on thin ice.

[Laughter.]

DR. TABB: I'd just like to say that in my practice, and that's all I can speak from, the incidence of these epithelial problems is extremely rare. It's when a lens is not calculated correctly, when we go back and recalculate it, these problems aren't there. The 30 percent adhesion occurs after they first wake up, and just either drops or movement, if they blink a few times, they can take the lens out. The corneal problems simply aren't there. I see it with--

DR. McCULLEY: Thank you. That pushes the sample size higher.

DR. SAVIOLA: Well, actually, what I'm hearing from the panel in terms of summary is that we do have some safety-related concerns, which we did expect. Our viewpoint had been to consider this to be a design modification type of issue and to design the study around efficacy issues, not specifically around safety issues, and I'm getting feedback from some of the panel members here that that's not consistent with what--

DR. McCULLEY: Well, let me make sure that we have consistency, because I certainly feel extremely strongly that there are safety issues here. Now, if I represent the minority, then I represent the minority, but if I don't, you need to hear it that I don't, because you seem to be thinking that those of us who have expressed safety concerns would represent the minority.

DR. SUGAR: I don't think we know what the safety issues are and I think we need numbers to find that out. People are being fit with techniques that apparently have only been developed in the last couple of years in terms of the tighter and tighter

fittings. So the tighter and tighter fittings, you are talking about a lens design you fit one patient with, with the two peripheral curves. So we need numbers. We're starting from scratch. The plastic itself isn't the issue. It's the fitting.

DR. McCULLEY: Is there disagreement with more or less what I said and what Dr. Sugar said?

DR. MACSAI: No.

DR. McCULLEY: So I think you're hearing that we have major safety questions, if not concerns. Fair enough?

Do you have any further questions, queries for us?

[No response.]

DR. McCULLEY: I thank both Dr. Tabb and Dr. Marsden. We appreciate your coming and helping to educate us. It is greatly appreciated.

With that, I'll ask Sally in just a moment if she has any concluding remarks. We will conclude the open session, and by popular demand, we're going to have a seven-minute break before we begin the closed session. Please check your watches.

MS. THORNTON: Again, I would like to add my thanks of the FDA to our two guest speakers and I would also like to tell the panel, anything that you would like to never see again, please put on the table. If you've brought with you something that you need tomorrow, please take it back to your room with you. The room will not be secured until tomorrow.

[Whereupon, at 4:09 p.m., the open session of the meeting was adjourned.]