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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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OPHTHALMIC DEVICES PANEL

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May 13, 2014
8:00 a.m.

Holiday Inn Express
Highlands Conference Center
20260 Goldenrod Lane
Germantown, Maryland

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M E E T I N G

(8:00 a.m.)

DR. HIGGINBOTHAM: Good morning. I would like to call this meeting of the Ophthalmic Devices Panel of the Medical Devices Advisory Committee to order.

I am Dr. Eve Higginbotham, the Chair of the Panel. I am a glaucoma specialist, a vice dean at the University of Pennsylvania, and very happy to chair this Panel today.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss and make recommendations regarding the guidance documents for contact lenses and care products.

Before we begin, I would like to ask our distinguished Panel members and FDA staff at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And we'll start with Dr. Eydelman.

DR. EYDELMAN: Good morning. Thanks for joining us this morning. I'm Malvina Eydelman. I'm the Director of the Division of Ophthalmic and ENT Devices here at FDA.

DR. JACOB: Good morning. My name is Jean Jacob, and I am a biomaterial scientist and emeritus professor at LSU Eye Center in New Orleans.

DR. ZABRANSKY: Good morning. I'm Ron Zabransky. I am a retired clinical and public health microbiologist and a Professor of Pathology at Case Western Reserve Medical Center, and I've served on a number of these panels over the last 15-some odd years.

Thank you.

DR. LECCA: Good morning. My name is Pedro Lecca. I am a professor and clinical advisor to Howard University; also at Plano College in Texas; also the University of Texas consultant to the international evaluation consortium in Newark, New Jersey, and also a consultant here with the FDA.

Thank you.

DR. SZCZOTKA-FLYNN: Good Morning. I'm Loretta Szczotka-Flynn. I'm a contact lens specialist. I'm the Director of Contact Lens Services at the University Hospital Eye Institute in Cleveland, Ohio, and a Professor of Ophthalmology at Case Western Reserve University.

DR. AHEARN: I'm Donald Ahearn. I'm Professor Emeritus in Microbiology at the Georgia State University, Atlanta.

MS. FACEY: Natasha Facey, Designated Federal Officer, FDA.

DR. HUANG: I'm Andrew Huang. I am a professor at Washington University in St. Louis. I am a cornea specialist.

DR. SUGAR: I'm Joel Sugar, a cornea specialist, Professor and Vice Head of Ophthalmology, University of Illinois in Chicago.

DR. BERGMANSON: Good morning. I'm Jan Bergmanson. I am a clinician and a professor at the University of Houston College of Optometry. As I said, I am a clinician, but I'm also an anatomist with an interest in ultraviolet radiation effects on the eye.

DR. BRESSLER: Good morning. I'm Neil Bressler. I'm Chief of the Retina Division at Johns Hopkins University, Department of Ophthalmology, and a professor there.

DR. OWSLEY: I'm Cynthia Owsley. I'm Professor of Ophthalmology and Vice Chair of Clinical Research at the University of Alabama at Birmingham. My area of research focus is aging-related eye disease, vision impairment, and quality of life.

DR. STEINEMANN: I'm Tim Steinemann. I am a cornea and external disease specialist at MetroHealth Medical Center, and Professor of Ophthalmology at Case Western Reserve University in Cleveland.

DR. LEGUIRE: Good morning. Larry Leguire, retired research director of ophthalmology for 30 years, and I'm a research psychologist by training.

MR. PFLEGER: Michael Pfleger with the Alcon division of Novartis. I'm the Industry Rep.

DR. HIGGINBOTHAM: Dr. Reller.

DR. RELLER: Barth Reller. I'm Professor of Medicine and Pathology at Duke University, in the Division of Infectious Diseases.

DR. HIGGINBOTHAM: We will be joined later by Dr. Steve McLeod, who was delayed in Detroit on his way from San Francisco. But Dr. McLeod is a cornea specialist as well as the Chair of the Department of Ophthalmology at UCSF.

And I failed to add that I'm also a Professor of Ophthalmology at the University of Pennsylvania Scheie Eye Institute.

Members of the audience, if you have not already done so, please sign the attendance sheets that are located on the registration table directly outside of this meeting room.

And as Chair, I would also ask each of the Panel members if you could just tilt your name tags towards me. I certainly have not memorized everyone's first and last names, but this makes it easier throughout the day.

And now Ms. Natasha Facey, the Designated Federal Officer for the Ophthalmic Devices Panel, will make some introductory remarks.

MS. FACEY: Good morning. I will now read the FDA Conflict of Interest Disclosure Statement.

The Food and Drug Administration is convening today's meeting of the Ophthalmic Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and

consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding the guidance documents for contact lenses and contact lens accessories. The discussion will include topics such as microbiological and chemical preclinical testing, revision of preclinical test requirements to address patent noncompliance, modification of rigid gas permeable lens care regimens, and labeling for these devices.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in connection with 18 U.S.C. Section 208.

Michael Pfleger is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Alcon.

Due to unexpected circumstances, the Patient Representative is unable to participate at today's meeting.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and the exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the

official transcript.

Before I turn the meeting back over to Dr. Higginbotham, I would like to make a few general announcements.

Today's meeting is a general issues meeting discussing no specific firm or product. Panel members will not be asked to vote.

Transcripts of today's meeting will be available from Free State Court Reporting. Their telephone number is (410) 974-0947.

Information on purchasing videos of today's meeting and handouts for today's presentations are available at the registration table outside the meeting room.

The press contact for today's meeting is Jennifer Rodriguez.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing session and have not already provided an electronic copy of your slide presentation to the FDA, please arrange to do so with AnnMarie Williams at the registration table.

In order to help the transcriptionist identify who is speaking, Panel members, please be sure to identify yourself each and every time you speak.

Finally, please silence your cell phones and other electronic devices at this time.

I'm going to turn it back over to Dr. Higginbotham.

DR. HIGGINBOTHAM: Thank you.

We will now proceed to FDA's presentation. I will remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

You may now begin your presentation, FDA.

Thank you.

DR. HAMPTON: Good morning to the Panel and to our audience members. My name is Denise Hampton, and I am the Branch Chief for the Contact Lenses and Retinal Devices Branch, or CLRD.

Today you will hear several presentations from our branch with respect to lenses, their interaction with contact lens care products, and advances we have made in the last several years to develop new tools to assess the safety and performance of these devices.

The first soft contact lens was approved in 1971. Since then, FDA has instituted many safeguards such as patient education through our website, participation in national and international standards development, and developing guidance documents for premarket and clinical testing for contact lenses and contact lens care products. You will hear about many of

these efforts later today.

As a result of these efforts, contact lenses and their care products are viewed as safe medical devices, and there are 38 million contact lens wearers in the United States; 12% of the U.S. population.

FDA has written two guidance documents, the titles of which are shown on this slide, for daily wear contact lenses and contact lens accessories, respectively. The last revision to our daily wear contact lens guidance document occurred in 1994, and the guidance document for accessories to contact lenses, such as care product solutions, was published in 1997.

Although the FDA created these guidance documents to provide preclinical, clinical, and labeling recommendations for safe and effective products to be introduced into the marketplace, new concerns have emerged in recent years. In 2006 and 2007, keratitis outbreaks involving two rare pathogens, *Fusarium* and *Acanthamoeba*, were reported, resulting in a voluntary recall of two multipurpose solutions presumed to be associated with these outbreaks.

The two keratitis outbreaks, combined with postmarket experience, led FDA staff to reassess recommendations made in our guidance documents for daily wear contact lenses and for contact lens care products. We have identified new concerns that have surfaced due to the introduction of new lens materials, different and complex product formulations, greater

potential for interaction with these products and contact lenses, and different patterns of use that were nonexistent in the 1990s when the guidance documents were developed.

FDA developed an action plan to address these concerns. In June of 2008, an Ophthalmic Advisory Panel meeting was held in which recommendations were made for improving the safety of contact lens wear.

In addition, in January of 2009, a two-day microbiology workshop was held, in which critical test method parameters for disinfection efficacy tests against *Acanthamoeba* as well as elements that simulate real-world consumer use conditions were discussed. FDA also engaged in several research projects beginning in 2008 that will be discussed on the next slide.

Lastly, we plan to revise our 1994 and 1997 guidance documents to reflect current thinking regarding preclinical and labeling recommendations to be considered for these devices.

The research that FDA conducted focused on the three main areas shown on this slide. Based on our reassessment of contact lens safety and guidance and standards, we chose to:

- Categorize silicone hydrogel contact lenses to address concerns noted with dimensional stability and toxicity;
- Evaluate the efficacy of care product solution in the presence of lenses through a preservative depletion and efficacy study; and

- Development of an *Acanthamoeba* test method.

You will hear from a number of speakers today from FDA who will provide greater detail regarding these research projects and what we have learned since the 2008 Panel meeting.

Based on those concerns, we are holding this Panel meeting today because we wish to obtain input in a number of areas so that, as a result, FDA review staff will have additional information to use in developing necessary guidance for industry. You will hear several presentations encompassing several pertinent areas with respect to these widely used devices.

Dr. Bernard Lepri will discuss patient demographics for contact lens use and continued concerns regarding patient noncompliance.

Dr. Joseph Hutter will introduce our silicone hydrogel grouping system for contact lenses.

Based upon the grouping system, Dr. Angelo Green will discuss implications for preservative uptake on preclinical test recommendations.

Mr. Jeffrey Brocious will summarize our research efforts with respect to microbiology and whether real-world test parameters should be incorporated into preclinical testing.

Dr. Mark Robboy will discuss concerns regarding the use of water as part of rigid gas permeable, or RGP, lens care regimens.

Lastly, you will hear the results of *Acanthamoeba* keratitis

investigations from Dr. Jennifer Cope, an invited speaker from the CDC.

The Panel will then be asked specific questions for consideration.

Shown on this slide are the members of CLRD whom I thank for their hard work and dedication.

Thank you again for your attendance, and thank you in advance for your discussion on these important topics.

Our first speaker for today will be Dr. Bernard Lepri, who will discuss demographics for contact lens wearers and patient noncompliance.

DR. LEPRI: Good morning, Panel members, public attendees, and FDA staff. This morning I will be speaking to you about the profiles of contact lens wearers in the United States, their contact lens care behaviors with respect to noncompliance, and FDA strategies to improve the safe use of contact lenses.

We will begin by identifying some of the key demographics of the contact lens-wearing population. According to data from the various sources identified on this slide, there are approximately 38 million contact lens wearers in the United States. They are predominantly myopic, and half of all of them range in age from 25 to 44 years; 14% are under the age of 18, and 15% are between the ages of 18 and 24; two-thirds of them are female and their median age is 32.7; 80% of this 38 million wear daily wear contact lenses and 15% wear extended-wear soft contact lenses; more than 50% wear

one- to two-week replacement lenses; and 48% wear silicone hydrogels. Of particular note is that the number of daily wear silicone hydrogel lenses has increased eightfold since 2003.

How are contact lens users characterized? Four variables identify almost 9 of 10 contact lens users likely to be using contact lenses on any given day in the United States. They are age, socioeconomic status, age/gender interactions, and socioeconomic status and education interaction.

In a univariate analysis, age and the availability of health insurance have negative associations with contact lens use, while female gender, higher socioeconomic status, and higher educational attainment are associated with increased contact lens use.

In multivariate analyses, age, socioeconomic status, the interaction of age with gender, and the interaction of socioeconomic status with education are associated with contact lens use also.

The products and regimens of care for contact lenses are numerous and diverse. In fact, the care of contact lenses has continued to evolve and in some cases become ever more complicated. Care involves cleaning and disinfecting and at one time also included regular protein removal as well. Contact lens wearers have always had to wash and dry their hands prior to handling lenses and maintain the hygiene of their storage and disinfection cases. And, finally, they have to monitor their own wearing time and replacement schedules.

Considering the millions who wear contact lenses and the responsibility they have in the maintenance and care of their lenses, there are relatively few complications with respect to the number of wearers. However, these complications can sometimes be sight threatening.

What are the sources of these complications? Well, 80% are the result of noncompliance with wear and care regimens, according to Ky et al. And the most interesting finding in this study was that the consumer's perception of their own compliance behavior is fundamental to minimizing and/or preventing these complications.

Medical noncompliance. DiMatteo published this study analyzing general medical compliance. His study revealed a noncompliance rate of approximately 25% for general medical care. Retention depends on a doctor-patient relationship and repetition, and any measures that improve that, improve these two factors, should improve compliance.

Two other studies regarding contact lens compliance reported noncompliance rates ranging from 50% to 79%. The comparison of the contact lens-wearing population to the general medical care population proves to be quite interesting, as we shall see in the next few slides.

Factors affecting contact lens compliance. Donshik et al. identified that complexity of treatment, frequency and duration, and the cost of the regimen are the major factors that affect contact lens compliance. Medical literature has repeatedly emphasized that there is a higher incidence

of noncompliance in conditions that are asymptomatic, prophylactic, or suppressive in nature. Therefore, the factors necessary for contact lens safety appear to be exactly those that contribute to noncompliance.

Hickson-Curran et al. reviewed important aspects of contact lens compliance through an online survey, published in 2010, that assessed contact lens replacement frequency, steps in lens care and hygiene, and replacement of the lens storage cases in a random United States sample of frequent replacement contact lens wearers through sponsor mass surveys.

Lens replacement frequency. They found that wearers of lenses prescribed by their practitioner for two-week replacement reported that only 45% actually replaced their lenses at two weeks, as directed, and only 30% of monthly replacement schedule wearers replaced their lenses at one month, as directed. Eighty-nine percent of two-week lens replacement wearers actually doubled the replacement time to four weeks as opposed to two. About one-quarter of monthly replacement lens wearers replace their lens at eight weeks instead of at one month, as directed.

Lens care and hygiene. Regarding lens care and hygiene, the median reported frequency for cleaning cases was two to three times per week, in contrast to the recommended cleaning directions of each day. Thirty-three percent actually reported cleaning their cases once a month or less. Lens cases are known to be a major source of bacterial contamination and thus contact lens complications.

Lens storage case replacement. With respect to lens storage replacement, it is typically recommended that lens cases should be replaced at least every three months. In this particular survey study, the median lens case replacement time was four to six months. Almost half of the respondents reported that they replaced their lenses annually or even less often. Contact lens noncompliance is nothing new, as we will see in the next few slides from these older studies.

In Oliveira's self-evaluation of contact lens care on college students and healthcare workers, it was found that 54% considered themselves poor wearers. Of these, 44% claimed that they are poor wearers because of their inadequate cleaning of lenses or the lens case. Another 15% admitted to general medical noncompliance.

Regarding contact lens procedures, 79% responded that they failed to implement contact lens care procedures, and another 30% claimed that their noncompliance was due to a lack of knowledge or being poorly prepared to care for their lenses.

Collins found a noncompliance rate of 74% in adult wearers who had worn lenses for an average of 2.6 years. This study also found the components of noncompliance to be a lack of understanding, improper use of lens care products, and poor hand hygiene. This study population had many symptoms and complaints, yet they did not perceive themselves as noncompliant.

Likewise, Turner found a noncompliance rate of 91%. Turner's results focused on multipurpose solutions and found that the failure rate was high despite the ease of use of the multipurpose solutions. So we see that even when procedures are simple and minimal, noncompliance can be very high.

Dumbleton et al. conducted a retrospective study of 500 silicone hydrogel lens wearers in five optometric offices, to evaluate the relationship between compliance with replacement frequency and contact lens-related problems in silicone hydrogel wearers. Of course, one must consider the potential for recall bias in the interpretation of retrospective study results.

However, in this study, 49% wore two-week and 51% wore one-month replacement lenses. The mean replacement frequency was 2.6 times higher for two-week replacement and 1.5 times higher for one-month replacement wearers, with median values of 31 and 37 days, respectively.

Two-thirds of the silicone hydrogel wearers did not comply with the recommended replacement schedule, and two-week replacement wearers stretched the replacement interval of their lenses to a greater degree than the one-month replacement wearers. Failing to replace lenses when recommended and failing to rub and rinse lenses were associated with a higher rate of patient-reported contact lens problems.

FDA, of course, is very concerned with contact lens safety, so it

endeavored to implement several strategies to address this issue. On this slide you will see the various areas in which FDA has endeavored. One of them is safety driven labeling that includes patient labeling, written in enhanced format that provides instructions and the reasoning for each step, and professional labeling that recommends verbal instruction to be provided to patients; outreach efforts through education of both contact lens patients and eye care professionals through safety driven publications and our contact lens website as well as safety alerts for both eye care professionals and patients. There is participation in both national and international standards development and through revisions and updates of both the contact lens and contact lens care product guidances.

Contact lens safety is a continual work in progress that evolves with the technology and the contact lens consumer market. The next few slides will detail our efforts.

Patient and professional labeling. We've added additional warnings and precautions to the contact lens patient labeling, with emphasis on specific contact lens care behaviors that contribute to contact lens complications, such as topping off or reuse, avoiding water exposure, providing a discard date after opening, and updated directions for lens case care.

These topical areas of contact lens safety concerns have always been addressed in the recommended professional labeling package insert and

patient labeling sections of the guidance. They have been upgraded to the newer enhanced format in the proposed revised guidance and in the 2010 patient labeling guidance. This format, known as plain language, is being incorporated into all contact lens guidance-recommended labeling.

This slide presents an example of plain language and how the warning statements have been revised in our guidance. They include instructions for use, the actual warning, definitions, and most importantly the reason for the warning. Where pertinent, our revised warning statements indicate which warnings we believe are necessary for the product carton and the bottle label. Repetition of warnings and instructions provides multiple avenues for disseminating safety information to the consumer.

Publications for patients and professionals. Since the last general issues contact lens panel meeting, FDA has produced numerous publications and outreach efforts to enhance public awareness and thereby increase safe use of contact lenses. These include articles related to contact lens use in children, decorative contact lenses, risks, adverse events published in FDA consumer publications as well as MedScape and WebMD.

This slide presents some of the publications that also include product recall announcements and website notifications.

The next slide shows specific publications by FDA in *Eye & Contact Lens* from the November 2012 issue.

The next slide is regarding our contact lens website updates.

Our contact lens website is continually being updated with new information regarding directions for safe use of not only contact lenses but contact lens care products as well. Special emphasis is given to topping off or reusing solutions and the lens case care, warnings about the use of non-sterile solutions such as water from all sources and saliva, the lens care instructional video, and the MedWatch link for reporting adverse events.

FDA staff are members of various ISO working groups and have contributed to the development of numerous contact lens and contact lens care product standards, as detailed on this and the next several slides.

Guidance. Revisions for both the daily wear contact lens and contact lens care product guidances are integral to our strategies for improving contact lens safety. These are to include recommendations for preclinical testing that include methods that represent real-world testing situations, contact lens grouping, preclinical and clinical testing, and the development and use of an *Acanthamoeba* testing methodology.

The revision of our guidance documents is the reason for our holding this Panel meeting today to seek your expert recommendations.

Thank you so much for your attention this morning.

DR. HUTTER: Good morning. I am Joseph C. Hutter, a chemical engineer and reviewer in the Division of Ophthalmic and ENT Devices.

I will give a brief overview of the interaction of contact lens materials with multipurpose care product solutions, specifically with respect

to lens care product solution compatibility and the research we conducted to develop a grouping system for silicone hydrogel lenses. I will also briefly discuss the implication of this grouping system with clinical test recommendations.

The premarket review of contact lenses and care product solutions include the assessments of the parameters shown on this slide. As noted, lens manufacturers should determine whether lenses are compatible with care product solutions. Conversely, manufacturers of care product solutions should demonstrate compatibility with representative lens materials. Lens solution compatibility testing will be discussed in further detail on the next slide.

As noted in our guidance document for care product solutions, the purpose of solution compatibility testing is to assess the effect of a contact lens solution on contact lens parameters and compatibility under the recommended care regimen. In this test, lenses are subject to the recommended cleaning and disinfection for the care product solution 30 times. The effort is 30 cycle tests. Optical and physical parameters are assessed and compared to parameters recorded prior to the initiation of the test.

Lenses being out of tolerance for these parameters can affect fit and function of the lens. Furthermore, lens solution compatibility issues can result in preservative uptake and disinfection efficacy concerns. This will

be discussed by Dr. Green and Mr. Brocious in their presentations, respectively.

Prior to 1985, manufacturers were required to test each lens with each care product, and any solution incompatibilities were listed in the labeling. In 1985, a grouping system for conventional lens materials was proposed by Dr. Ralph Stone and was adopted by FDA after consensus review.

In these groups, lenses were separated by water and ionic content. Water and ionic content for these materials are useful predictors for preservative uptake/release and interactions with other care product and tear-film components. We have found that in this grouping system, if a care product passed a 30-cycle test with one representative lens from a group, it was highly likely that the care product was compatible with all the lenses in that group, thereby reducing the number of lenses needed for testing of poly(HEMA) materials. We have found that the groups defined on this slide have worked well for conventional poly(HEMA) materials.

Technological advances after the implementation of conventional poly(HEMA) lenses included silicone hydrogel lenses. The first silicone hydrogel lens was made of balafilcon A and was introduced in the U.S. in 1999 and was characterized as a Group 3 lens. By 2008, six additional silicone hydrogel lens materials were introduced into the U.S. market. As of today, there are 13 silicone hydrogel lenses on the market. It should be noted that all the lens materials passed all our premarket tests at the time.

Shortly after the introduction of silicone hydrogels, some lens care product incompatibilities became evident. Balafilcon A was found to be incompatible with the peroxide solution, and galyfilcon A was found to be incompatible with the PHMB solution. We determined that the lens grouping system was inadequate to evaluate these silicone hydrogel incompatibilities in the setting of increasingly complex care product formulations.

In 2008 the Ophthalmic Advisory Panel recommended that three representative silicone hydrogel lenses plus a Group 4 conventional lens be tested to address these compatibility issues.

To initially address differences between conventional materials and silicone hydrogels, standards organizations initially separated silicone hydrogel lenses from conventional lenses by creating a high oxygen permeability lens Group 5 as part of the conventional lens grouping system. We realized that this was an interim step and that more groups were needed to fully characterize the material differences.

In 2008 the Ophthalmic Advisory Panel recommended that the groups be revised. We subsequently began an internal research effort to characterize the silicone hydrogel materials and their interaction with care product components. This work and its findings were published in *Eye & Contact Lens* in November 2012.

Reports from the literature also revealed that silicone hydrogels differ from conventional lenses with respect to their interactions

with preservatives. Shown on this slide is a figure from Powell and colleagues which shows uptake and release for two preservatives, PHMB and Aldox, shown in circles, from various lens materials, shown as boxes in the center of the figure. Thick arrows denote uptake into the lens, while thin arrows represent preservative release into the tear fluid.

PHMB, for example, is rapidly absorbed but slowly released from acidic poly(HEMA) material, shown at the top of the figure. The PHMB dynamics are much less robust in a typical silicone hydrogel, shown in the middle. In the high water lens, shown at the bottom of the figure, relative uptake is less compared to the acidic material, but release is maximized.

Aldox, which has a positive charge as well as a hydrophobic tail, has its strongest interactions with the silicone hydrogel materials and is less absorbed and readily released from poly(HEMA) relative to PHMB.

Silicone hydrogels also interact differently with other care product components as well as the tear film.

As a basis for a new grouping system, we measured PHMB uptake on various lenses. We found that this property depended on water and ionic content of the lens materials. As ionicity and water content increases, uptake increases similar to the results for a conventional lens.

Note that the version of polymacon we tested had a high concentration of methacrylic acid, which made it behave more like a Group 4 lens and hence the higher uptake levels better fit on the right side of the

graph.

A new grouping strategy also needs to account for new behaviors of silicone hydrogels and interactions with care products. We found that the basic water content and ionic charge division used in the original groupings still predicts preservative uptake/release for charged hydrophilic components.

We have also found that some surface treatments limit access to the internal pore structure of the material for large molecules. Surface-treated and non-surface treated materials also absorb different relative amounts of tear-film components, proteins versus lipids, as well as some surfactants.

Lastly, we have found in premarket tests that some semi-interpenetrating network materials are more vulnerable to swell outside of tolerances in some situations. We have accounted for these effects in our new grouping strategy.

We have proposed that previous Group 5 lenses could be further subdivided into the following five groups to account for the known interactions of silicone hydrogels with existing care products:

- No water specification, ionic group
- High water content, nonionic group
- Low water content, nonionic surface-treated group
- Low water content, nonionic, non-surface-treated,

containing hydrophilic monomer group

- Low water, nonionic, non-surface-treated, semi-interpenetrating network group

ANSI has proposed a grouping system which is in line with our proposal. The ANSI proposal has additional subgroups with which, currently, no lens materials exist.

The Panel will be asked the following question: Do you believe that FDA's proposed grouping scheme for the silicone hydrogel lenses is adequate to mitigate concerns regarding dimensional tolerance and compatibility? If not, what recommendations and modifications would you make?

I will now briefly discuss the clinical test matrix for conventional lenses and the implication of the grouping system for silicone hydrogel lenses on clinical testing.

The on-eye clinical performance of silicone hydrogels was found to differ from conventional lens materials. For example, silicone hydrogel wear resulted in less corneal staining and swelling and injection. Silicone hydrogels tend to favor lipid deposition over protein deposition more commonly observed with conventional hydrogels. Significant levels of relative asymptomatic corneal staining were observed when subjects used a PHMB-based system, with 37% of subjects demonstrating a level of staining consistent with the classic solution-based toxicity reaction.

Clinical study recommendations were developed based on the original grouping system for conventional materials. For a new contact lens care product for intended use with conventional hydrogels, a total of 60 subjects, stratified as shown on this slide, was recommended. Our 1997 care product guidance document then recommended that a care product be tested with a contact lens from FDA Groups 1 and 4, as they represented the extremes of the four groups with respect to water content and ionicity.

With the advent of three silicone hydrogel lens materials from 1999 to 2008, the Ophthalmic Advisory Panel recommended testing all three silicone hydrogels plus one Group 4 conventional lens, for a total of 180 subjects.

As previously stated, there are now 13 silicone hydrogel lenses that have been cleared for marketing. As with the initial test recommendations for conventional lens materials, we currently recommend that a representative lens from each group be tested clinically, for a total of 270 subjects for testing. It is possible that once information is obtained over time regarding the behavior of these lenses, representative lenses may be tested.

The Panel will be asked the following question: Do you believe that the proposed clinical test matrix for silicone hydrogel lenses is sufficient to address the clinical performance issues? If not, what additional testing would you recommend?

The next speaker will be Angelo Green.

DR. GREEN: Good morning, Panel members, FDA staff, and guests. My name is Angelo Green, and I am a chemistry reviewer in the Contact Lens and Retinal Devices Branch.

Today I will discuss how we plan to modify our care product guidance to evaluate potential incompatibilities regarding preservative uptake by lens materials. Your feedback will be sought on the criterion that will be used to evaluate these incompatibilities and the way to communicate these incompatibilities to patients using labeling.

Uptake is the removal of preservative by the lens from the lens case solution, resulting in a decreased concentration of available preservative for disinfection. This is a depiction of a lens that, after being immersed in a care product solution for a given soak time, absorbs a significant amount of preservative from the solution. Lens materials absorb preservative both on the surface and in the bulk of the material. The material properties influence the rate and extent of preservative uptake.

Preservative uptake and release is assessed for new solutions according to ISO 11986, which was first published in 1999. Uptake of preservative is measured at different time points until a concentration plateau is obtained. There are no acceptance criteria established in the standard, and compromised disinfection efficacy by preservative uptake by the lens material is not evaluated.

Reduction in disinfection efficacy has been implicated in clinical cases of *Fusarium* keratitis, especially where solutions were reused after being stored with lenses.

This table from Levy et al. shows data for two solutions, Renu MoistureLoc, which was voluntarily withdrawn from the market, and Renu MultiPlus. Both were subjected to a level of simulated noncompliant reuse of solution, a practice that is not in accordance with labeled instructions. The solution was sampled for biocidal efficacy against *Fusarium solani* before or after one, two, or three simulated cycles of contact lens disinfection and wear with no additional fresh solution added. Each cycle consists of 10 hours in test solution in the lens case to simulate the process of disinfection, and 14 hours in saline solution to simulate wear.

In addition, in the simulated reuse experiment, concentration of the disinfectant alexidine was determined for MoistureLoc. No disinfectant content was determined for the other solution. After a single use or a cycle, the active preservative concentration decreased significantly. The solution failed the ISO standalone biocidal efficacy test after two cycles.

It is important to note that both of these solutions were subjected to tests currently recommended in FDA's guidance in the past. The data demonstrates that topping off or reuse of the solution can compromise disinfection efficacy.

There are numerous examples in the literature which

demonstrate that decreases in preservative concentration caused by preservative uptake by the lens material can reduce disinfection efficacy. Mr. Jeffrey Brocious will later outline some of the research that FDA has conducted in this area.

In addition, lens material properties can influence the rate and extent of preservative uptake, and therefore can influence whether the disinfection efficacy of solutions are compromised.

Two of these material properties, as Dr. Hutter pointed out, are water and ionic content, and this graph demonstrates that these properties may influence the uptake of hydrophilic preservatives such as PHMB. In this graph we compare preservative uptake rate, as indicated on the y-axis, for low water, nonionic lens -- the red bars -- and high water and ionic lens materials -- green, yellow, and blue bars. The names of the lens materials are indicated on the x-axis. The shaded bars represent conventional hydrogel lenses, and the unshaded bars represent silicone hydrogel lenses.

Regardless of whether the lens material is a conventional hydrogel or silicone hydrogel lens, materials with the high water content or that are ionic are associated with a higher preservative uptake rate.

As we conclude in our article, the long-established conventional hydrogel grouping system, which uses only water and ionic content as parameters to group lens materials, can help predict preservative uptake for both conventional and silicone hydrogel lenses.

With the advent of silicone hydrogel lenses, the hydrophobicity of the material became an important issue. Shown on this slide is a comparison of preservative uptake for two different preservatives; one, Aldox, significantly more hydrophobic than the other, PHMB, according to the hydrophobicity rating scale devised by Jones and Powell.

In the graph on the right with the x-axis showing uptake of both PHMB and Aldox, the authors demonstrate that Aldox is absorbed more to silicone hydrogel lenses than conventional hydrogel lenses. Therefore, hydrophobicity of the lens material can also influence preservative uptake, especially for more hydrophobic preservatives.

The five proposed silicone hydrogel lens groups take into account water content, ionicity, and hydrophobicity and, as Dr. Hutter noted, will be used to facilitate preclinical and clinical testing. Since these parameters described by the grouping system are sufficient to predict preservative uptake for both conventional and silicone hydrogel lenses, we propose to use the new grouping system to screen lenses for preservative uptake effects that may compromise disinfection.

We propose to introduce a preservative uptake method similar to Section 4.2 of ISO 11986 with the following modifications:

- One conventional and five silicone hydrogel lenses (one from each Groups 5-A, 5-B, 5-C, 5-Cr, 5-Cm) should be tested.

- One lens per well should be submerged in 3 mL of test solution in a lens case (currently, there is no volume or container specified in the standard).

The proposed acceptance criterion is that preservative concentration in the lens case should remain within the manufacturer specifications after the recommended soak time.

This is the first time an acceptance criterion for preservative uptake will be introduced into the guidance. Lenses that do not pass the acceptance criterion can be listed in the labeling or subjected to additional disinfection efficacy testing with a lens, lens case, solution, and microbial load to demonstrate compatibility.

This diagram outlines the steps needed to show that lens materials are compatible with preservatives in a solution. The proposed preservative uptake incompatibility test will add an acceptance criterion to the current method used for assessing preservative uptake. The ISO 14729 criteria, which is currently used to evaluate disinfection efficacy of a solution, will be used to verify the lower limits of the preservative concentration acceptance criterion. The ISO 14729 criterion will be discussed in more detail in the following presentation.

If lenses from a specific group caused a preservative concentration to drop below the manufacturing specification, the sponsor may perform disinfection efficacy testing with the lens, solution, and

microbes to take into account the preservative uptake rate and its effect on disinfection. If the submission does not provide data from this test supporting disinfection effectiveness in the presence of the lens, then a suitable precaution would be required in the labeling. The precaution would alert users and practitioners to the issue of problematic preservative uptake for the specific lens group in.

The Panel will be asked the following question: As a modification to our care product guidance, new product solutions will be screened for lens preservative uptake incompatibilities using representative lenses per FDA's proposed contact lens grouping system. The preservative concentration of the solution in the lens case should remain within the manufacturer's specifications after the recommended lens soak time. Incompatible lenses will be listed in the labeling. Please discuss the following:

a. Should our acceptance criterion account for patient noncompliance (e.g., longer soak times than recommended, solution reuse, et cetera)?
b. How should the incompatible lenses be listed in the labeling (e.g., bold text, a unified table, et cetera)?
c. Are there any other recommendations you would make?

Our next speaker will be Mr. Jeffrey Brocious, who will outline FDA's research efforts regarding biocidal efficacy testing.

Thank you.

MR. BROCIOUS: Good morning. My name is Jeffrey Brocious. I am a microbiologist and sterility reviewer in the Division of Ophthalmic and ENT Devices. I'll be speaking to you today about variables that may impact care product disinfection efficacy from a microbiological perspective.

FDA's guidance document for contact lens care products was published in May 1997. FDA later recognized the ISO 14729 standalone test and the ISO 14729 regimen test to evaluate disinfection efficacy. Each test has its own set of performance criteria which serve as the underlying basis for marketing.

The stand-alone test challenges the solution with known concentrations of *Staph aureus, Pseudomonas aeruginosa, Serratia marcescens, Candida albicans,* and *Fusarium solani.*

The primary acceptance criteria for the stand-alone test is to prove a greater than or equal to 3 log kill for bacteria and greater than or equal to 1 log kill for fungi. If a solution passes the primary acceptance criteria of the stand-alone, it may be labeled as a disinfectant product. If the solution fails the primary acceptance criteria, it must pass both secondary criteria of the stand-alone and regimen test as criteria to be labeled as a part of a contact lens disinfecting regimen.

These ISO test methods parallel the testing outlined in our care product guidance. However, prior to testing, these tests do not take into

account the impact of the lens, soak times of the lens within a solution, or testing the solution in the presence of soil. It has been demonstrated that the presence of organic soil may have an impact on disinfection efficacy, and since there is no standardized protocol available at this time, it is recommended that soil still be included into the evaluation of solutions. In addition, ISO 14729 does not include a protocol to determine efficacy against *Acanthamoeba.*

As mentioned by Dr. Hampton, the FDA responded to the *Acanthamoeba* outbreak that occurred in 2007 by collaborating with ophthalmic and optometric organizations to address this issue.

As mentioned, currently there are no standardized methods to evaluate disinfection efficacy against *Acanthamoeba*. In 2009 a microbiology workshop convened to discuss parameters that would have an impact on evaluation. A general consensus was reached that the following parameters were important for an appropriate protocol for evaluation:

- The strain of organism
- Life cycle, to include both trophozoite and cyst stage
- Growth method
- Methods to encyst *Acanthamoeba*

As a result, in 2012 the FDA undertook an effort to further characterize these factors. The two strains of *Acanthamoeba castellanii* were cultured bacterized, meaning, grown on non-nutrient amoeba saline agar

seeded with *Enterobacter aerogenes* or axenically, meaning grown in PYG 712 liquid nutrient growth media without the presence of bacteria.

Cysts were formed using four different methods: Neff et al., Beattie et al., starvation, and leaving trophs in growth media and allowing them to encyst naturally over time. They were then exposed to four different multipurpose solutions. Counts were determined by Beattie's most probable number method, which involves diluting the inoculated solution and determining growth at each dilution.

This figure shows the log kill between both strains tested and further compared by cyst and troph stages. It shows that cysts, which are typically more resistant -- on the left side of the slide -- showed a lower log kill than trophs, as to be expected. Though differences between the two strains were seen, these differences were not statistically significant for cysts or trophs.

In this figure, the log kill of cysts for both strains were compared by growth method, either bacterized, represented by NNAS, and axenically, represented by PYG-712 medium. With respect to growth medium used, cysts for both strains of *Acanthamoeba castellanii* presented a lower log kill when grown bacterized on non-nutrient amoeba saline agar.

This figure compares the average cyst log kill for each encystment method. Results indicate that the Beattie and starvation methods yielded significantly lower log kills than Neff's and the time method.

In this figure, encystment methods are characterized by growth method. You can see that growth method was the most significant factor and affected how the strain's cysts were affected by encystment method. As shown here, all methods of encystment demonstrated lower log kills when grown bacterized versus grown in PYG medium.

As a result, our studies indicate that the most appropriate method for studying efficacy of MPS against *Acanthamoeba* would need to include at least two strains grown bacterized on non-nutrient amoeba saline agar and encysted over time by Beattie's or the starvation method. Although the two strains tested in the study did not show significant differences in log kill, it is still recommended to test more than one strain, which may include different species of *Acanthamoeba*, as well.

The combination of these factors presents the lowest log kill of the organism and would therefore provide a framework for a robust protocol to be used for efficacy evaluation.

To address the lack of a standardized protocol, the FDA is planning to hold another microbiology workshop on September 12th to compare and discuss disinfection methods with experts across the field. We are hoping to agree upon one method that will satisfy all concerns.

The FDA has also undertaken efforts to address the impact of lens material and different soak times and solution disinfection efficacy. We have tested different lens materials against different multipurpose solutions,

assayed biocide levels, and then challenged them against *Staph aureus* or *Fusarium* to see if there's a correlation between preservative uptake and biocidal activity.

As mentioned by Dr. Hutter, different materials present with different chemical properties, to include water content and ionicity, which may play a role in biocidal efficacy.

This figure shows the concentration of polyhexamethylene biguanide in the solution -- on the y-axis -- after it was exposed to different lens materials at different soak times, which is plotted on the x-axis. It clearly shows significant decreased levels of biocide when exposed to etafilcon A -- which is boxed in red -- even at only six hours of incubation. As mentioned by Dr. Hutter, ionic lenses with high water content uptake more PHMB, as evidenced here with etafilcon. Decreased levels were also associated with galyfilcon A, comfilcon A, balafilcon A, and polymacon.

This figure compares different lens materials over different soaking times -- which is shown on the x-axis -- with respect to log kill of *Staph aureus*, plotted on the y-axis. Although many lens materials had lower log kills in their associated controls due to the high variability, results were not significant. However, it is evident that levels of decreased PHMB correlated with decreased biocidal efficacy over the seven-day soak period for etafilcon A, noted by the purple triangles. These data demonstrate certain lens materials' ability to uptake biocide well over a six-hour soak time,

as seen with etafilcon A.

In addition to *Staph aureus*, lens materials were incubated in test solution containing PHMB for various time periods and challenged with *Fusarium solani*. This table shows the log kill of *Fusarium* at 6, 12, 24, 72, and 168 hours. As you can see, with the exception of comfilcon A, all other lens-depleted solutions failed to consistently meet the one log acceptance criteria recommended by the standalone test versus the lens case and bottle controls.

In addition, boxed in red and indicated by negative values, you can see that at seven days of soaking the lens, cultures of solution that contained etafilcon A, polymacon, balafilcon A, and lotrafilcon B yielded a higher concentration of *Fusarium* than was inoculated. This implies that disinfection became nonexistent. As a result, it is important to recognize this impact since this may mimic a real-world scenario with respect to patient noncompliance.

This slide shows the log kill of *Staph aureus* versus the concentration of polyquaternium-1 immersed in myristamidopropyl dimethylamine, noted by the optical density reading after six hours. There appeared to be no correlation between concentration of this preservative and log kill of *Staph aureus*. In addition, results showed that there was an actual increase in biocide effectiveness of all lens materials compared to the controls, suggesting that the lens material produces a synergistic effect with

the solution.

It appears that some lens materials may potentially increase the biocide efficacy of preservative in the presence of other active ingredients within the solution. The main take-home message from the study is that there is a relationship between efficacy and lens material.

In light of results seen, the Panel will be asked to discuss the following question: Current microbiological test methods (e.g., ISO 14729) do not take into account "real-world" solution testing parameters in which the lens stored in a case is considered. Please discuss whether you believe the following factors should be incorporated into current preclinical testing:

a. Soil
b. Longer soak times
c. Lens uptake
d. Any other factors

Thank you. Dr. Robboy will now present to you the impact of tap water on rigid gas permeable lens care regimens.

DR. ROBBOY: My name is Marc Robboy. I am an optometrist and a clinical reviewer in the Division of Ophthalmic and ENT Devices. Today I'll be speaking to you about the impact of using tap water as a rinsing agent in the care of rigid gas permeable contact lenses.

From a historical perspective, tap water rinse, including a lens case, has been included in the care of rigid contact lenses dating back to the

1950s.

During the lens cleaning process, the mechanical action from rinsing breaks up debris and removes deposits prior to chemical disinfection with conditioner solution.

As noted earlier today, there is no standardized preclinical methodology to assess the effectiveness of RGP care products against *Acanthamoeba*. Therefore, we do not permit labeling claims regarding RGP lens care regimens and effectiveness against *Acanthamoeba*.

Although the first reported cases of ocular *Acanthamoeba* keratitis occurred in 1973, there was a large increase in reported cases that became apparent in the mid-1980s. And it was at this time that an association was first recognized with soft contact lenses. However, shortly thereafter, reports were presented which involved rigid lenses.

In this 1987 publication by Dr. Moore and colleagues, of 11 contact lens-wearing patients who presented with *Acanthamoeba* keratitis, six wore daily wear soft contact lenses, two wore extended-wear soft lenses, one wore a poly(methyl methacrylate) hard contact lens, one wore an RGP lens, and one wore a Saturn lens, a combined hard and soft lens to which we refer to today as a hybrid lens. Contributing factors for the rigid lens wearers included a tap water rinse.

As mentioned previously, the national outbreak of *Acanthamoeba* keratitis associated with the use of a contact lens solution

occurred in 2007. It had been determined that cases had been increasing since 2004. The CDC investigation showed that case patients had significantly greater odds of having used a particular multipurpose solution, one that was voluntarily recalled.

Following the *Acanthamoeba* keratitis outbreak in 2007, the Ophthalmic Advisory Panel convened in June 2008 and conveyed certain recommendations relating to improving contact lens product testing and advocating universal lens care guidelines in order to improve contact lens safety. This message was echoed at the Panel meeting by the various professional ophthalmic organizations, specifically with regard to use of water.

In a joint statement from these organizations, the key care guidelines indicated to minimize contact with water while wearing lenses, contact lenses should not be rinsed or stored in water, and rinse the lens case with fresh solution, not with water.

Subsequently, the FDA consumer website was updated, and FDA published an addendum to our contact lens care labeling guidance in August 2010.

The FDA Consumer Updates website was subsequently revised to repeat the messages conveyed by the Ophthalmic Advisory Panel and the professional organizations. Specifically with regard to water use, in the do's and don'ts section for contact lens wearers, the third bullet indicates to not

expose contact lenses to any water, never use non-sterile water, and that exposure to water has been associated with *Acanthamoeba* keratitis.

In August 2010, FDA published an addendum to the 510(k) contact lens care labeling guidance, focusing solely on those changes which pertain to the use of water. Suggested content, which included new warnings and instructions for use, explicitly underscore the need to eliminate all exposure to water. In addition, it is important to note that the guidance, as per the addendum, explicitly states that the scope of the contact lens care products labeling pertains to both RGP as well as to hydrophilic contact lenses.

In a 2013 publication, Dr. Legarreta and colleagues reviewed the labeling of the available contact lens cleaning solutions for soft and for rigid contact lenses. Although tap water rinsing was not recommended for the soft lenses, this was not the case for the RGP lenses.

Of the 18 RGP cleaners and solutions that were reviewed, 15 or 83% recommended the use of non-sterile water to rinse surfactant off of contact lenses and/or the lens storage case. It's important to note that all of the labeling was cleared prior to the 2008 Ophthalmic Devices Panel meeting.

Regarding incidence, compared to *Pseudomonas*, *Acanthamoeba* is an even rarer cause of microbic keratitis among contact lens wearers. Clearly, the normal corneal defenses are highly effective in preventing *Acanthamoeba* keratitis in most patients.

According to Dr. Radford and colleagues, in the United Kingdom, *Acanthamoeba* keratitis occurs at an estimated yearly rate of 1.2 per million adults and 0.2 per 10,000 in contact lens wearers. In addition, consider also that RGP wearers comprise only a small percentage of the total of contact lens wearers in the United States.

Later today the CDC will present their updated findings regarding *Acanthamoeba* keratitis.

So in spite of the low incidence of *Acanthamoeba* keratitis as well as the relatively low numbers of RGP wearers compared to soft lens wearers, the published literature nonetheless reports on cases in which those normal corneal defenses did, in fact, break down.

For example, in 2005 Drs. Watt and Swarbrick reported that an alarmingly high frequency, 30% of the first 50 reported cases of microbial keratitis in overnight orthokeratology with RGP lenses was attributed to *Acanthamoeba* keratitis. It was considered that this was mostly likely due to the contact lenses being rinsed with tap water as part of the lens care regimen.

In 2007 Dr. Robertson and colleagues reported a case of *Acanthamoeba* keratitis following overnight ortho-K, in which an 11-year-old boy had cleaned his RGP lenses as instructed, but followed with a tap water rinse and tap water storage. This case resulted in vision loss, which unfortunately ultimately deteriorated to light perception.

In 2010 Dr. Lorenzo-Morales and colleagues reported on a case involving a 59-year-old Spanish patient who presented with severe ocular pain and was subsequently diagnosed with *Acanthamoeba* keratitis. She admitted to having used tap water to wash her lenses.

In addition, the authors note that this is the first case of severe keratitis due to *Acanthamoeba* genotype T11 in Spain. Most of the isolated strains with a pathological potential belonged to the T3 and T4 genotypes. Therefore, the prevalence of *Acanthamoeba* keratitis due to T11 is rare worldwide, and the authors indicate that additional data are needed to clarify whether T11 is an emergent genotype in clinical cases due to *Acanthamoeba*.

And in 2013, Dr. Legarreta and colleagues reported a case in which a long-time RGP wearer used tap water to clean her lenses and was subsequently diagnosed with *Acanthamoeba* keratitis. Her vision ultimately deteriorated to counting fingers following a penetrating keratoplasty.

Therefore, because of the continued risk of undesirable outcomes that can result, we must consider alternatives to the use of water in conjunction with the care of RGP lenses. Potential alternatives include preserved saline rinse and unpreserved saline rinse.

Therefore, the Panel will be asked: Some RGP lens regimens still recommend the use of water. What alternatives would you recommend to replace water?

This concludes the FDA presentation. Dr. Jennifer Cope from

the CDC will now present her research on *Acanthamoeba* keratitis.

DR. HIGGINBOTHAM: Do you need a break before --

DR. COPE: Yes, please.

DR. HIGGINBOTHAM: Okay. So we will have a 10-minute break to resolve any technical difficulties we have.

Thank you.

DR. COPE: Thank you.

(Off the record.)

(On the record.)

DR. HIGGINBOTHAM: We can begin. Thank you.

DR. COPE: All right. Good morning, and thank you for your patience as we located my slides.

Good morning. My name is Jennifer Cope, and I am a medical epidemiologist with the Waterborne Disease Prevention Branch at CDC, which is the lead coordination and response unit in the National Center for Emerging and Zoonotic Infectious Diseases for responding to and preventing domestic water-related disease, which includes infections caused by *Acanthamoeba*.

I'd like to give you an overview of CDC's *Acanthamoeba* keratitis investigations, beginning back in 1985 through the most recent and largest investigation in 2011. I would also like to share some of the details of our new Healthy Contact Lens communication initiative.

The free-living amoebae *Acanthamoeba* are ubiquitous in water, including public drinking water sources, as well as soil, and exist in both trophozoite and cyst forms. In the cyst form, *Acanthamoeba* are resistant to many pharmacologic agents, including most contact lens disinfecting solutions.

Acanthamoeba keratitis, commonly referred to as AK, is a rare, potentially blinding eye disease caused by *Acanthamoeba*. Although the first case was described in 1973 in a Texas rancher following ocular trauma, since that time, in the United States, AK primarily affects otherwise healthy contact lens wearers. While the incidence of AK is poorly understood, annual incidence in developed countries is estimated to between 1 and 33 cases per million contact lens wearers.

Beginning in 1985, CDC received an increasing number of AK case reports among soft contact lens wearers; therefore, in 1986 we conducted a case-control study of AK in soft contact lens wearers. Significant risk factors found in the study published in 1987 included using homemade saline solution, wearing contact lenses while swimming, and disinfecting lenses less frequently than recommended by lens manufacturers. Additionally, *Acanthamoeba* was isolated from homemade saline solution during this investigation.

In 2006 an outbreak of AK was detected in Illinois when the Department of Ophthalmology at the University of Illinois at Chicago noted a

considerable increase in the number of AK cases they saw between June 1st, 2003 and November 30th, 2005. Subsequent investigation revealed it to be a nationwide outbreak.

Therefore, in 2007 a multi-state investigation of AK cases involving the collaboration of multiple federal agencies, state and local health departments, academic institutions, and reference laboratories was conducted. This investigation showed that cases apparently began increasing across the United States in 2003 through 2004, and the multipurpose solution, Advanced Medical Optics Complete MoisturePlus, was shown to be the main risk factor for the outbreak. This ultimately led to the voluntary recall of this solution.

In addition to using the specific brand of multipurpose solution, other factors associated with case status were topping off or reusing old solution in your lens case and wearing contact lenses for five years or less. A concomitant laboratory investigation concluded that the implicated multipurpose solution was not contaminated but that it's anti-amoeba efficacy was insufficient. Additional laboratory studies of 11 different contact lens solutions showed that only two contact lens solutions containing hydrogen peroxide showed any anti-amoeba disinfecting activity.

Because of the conclusion that multipurpose solution lacked anti-amoeba activity, FDA and CDC's free-living amoeba laboratory entered into a research collaboration agreement to evaluate a test protocol for

measuring the effectiveness of contact lens multipurpose solution against *Acanthamoeba* species. This project was designed to evaluate the FDA published protocol for testing multipurpose solution disinfection efficacy against *Acanthamoeba*. This testing was designed to support potential multipurpose solution manufacturer testing requirements. The project tested off-the-shelf contact lens solutions against trophozoites and cysts of two different T4 genotype *Acanthamoeba* strains isolated from AK patients. This project is still ongoing.

Following the product recall, CDC partnered with the same network of ophthalmology referral centers and commercial laboratories, hereafter referred to as the Sentinel Network, to conduct surveillance for AK infections.

Our Sentinel Network was comprised of 15 large ophthalmology referral centers and labs, as well as three states who performed additional case finding within their jurisdictions. As demonstrated here, our reporting partners had a wide geographic dispersion and a large catchment area throughout the United States. Therefore, these partners likely captured a large proportion of AK cases diagnosed annually.

From the annual Sentinel Network data presented here, we saw that the number of cases diagnosed annually after the 2007 recall did not return to levels observed before the outbreak. This graph shows the year on the x-axis with the number of cases on the y-axis. The outbreak period is

denoted from 2003 to 2007, as well as the product recall in 2007. You can clearly see that the number of cases in 2008 and 2009 did not return to pre-2004 levels. The reason for the persistently higher level of annual cases was unclear.

In the latter half of 2010, the Waterborne Disease Prevention Branch of CDC was contacted by the state health departments in New York and Georgia regarding two unusual clusters of AK cases at local ophthalmology centers, one in each state.

As a result of these two unusual clusters and the failure of case counts to return to pre-2004 levels after the 2007 product recall, the New York State Department of Health requested a multi-state Epi-Aid investigation on March 11th, 2011, to understand what might be contributing to the persistence of cases.

There were several general areas we were determined to explore as potential explanations for the persistence of AK, including the role of surveillance. For example, was there improved provider awareness of AK after the product recall, leading them to diagnose more AK? We also wanted to investigate the role of contact lenses and lens materials, contact lens solutions, hygiene behavior surrounding contact lens use, and the role of recreational and tap water exposures. All of these questions led our branch to launch the largest case-control study to date of AK.

We conducted a case-control investigation to identify

modifiable risk factors contributing to the persistently elevated incidence of AK throughout the country. Case patients were defined as U.S. residents with clinically compatible signs and symptoms of AK and laboratory confirmed diagnoses on or after January 1st, 2008.

Case patients were recruited through Sentinel Network sites and additional case finding efforts by collaborating health departments and CDC. FDA and EPA also participated in this investigation.

Case patients were interviewed to collect information on demographics, clinical history, and potential risk factors during the month prior to symptom onset, hereafter referred to as the exposure period. Forty-nine of the first 50 case patients interviewed were contact lens wearers during their exposure period. Thus, we further limited our case definition to include only contact lens wearers.

Controls were recruited from the clientele of eye care providers randomly selected from registries of ophthalmologists and optometrists. Eligible controls were contact lens wearers with no history of AK and at least 12 years of age.

Controls were matched to case patients by state of residence, type of eye care provider, and contact lens use during reported exposure period. In all, 110 matched case-control groups were formed, comprised of cases matched with one, two, or three controls. Unmatched cases and controls were excluded from subsequent analyses in this investigation.

Our cases and controls did not differ significantly by age. Cases had a median age of 36 years, compared to a median age of 40 years among our controls.

Although the median age did not differ, further analysis of the age distribution using exact conditional logistic regression revealed that cases were more likely than controls to be younger than 26 or older than 55. Additionally, cases had statistically significant higher odds of being male and rigid contact lens users.

After adjusting for age, sex, and contact lens type using exact conditional logistic regression, and only considering those exposures reported by at least 15% of cases or controls as potential risk factors, a number of exposures emerged as significant risk factors for infection.

Twenty-five to sixty-eight percent of case patients reported one or more of the five hygiene-related behaviors listed here. These include topping off, which is adding new solution to an existing volume of used solution; wearing contact lenses for five or fewer years; storing lenses in water; handling lenses with wet hands; and rinsing the lens case before storing lenses.

Notice that three of these hygiene risk factors involve exposure of contact lenses to tap water. Because of the association between these three tap water exposures and infection, we sought to determine whether any exposure to tap water posed a significant risk.

When we analyze by any reported lens exposure to tap water, whether by way of personal hygiene or lens care, we noted no difference between cases and controls. In other words, nearly everyone exposes their lenses to tap water at some point. Cases were also no more likely than controls to report a higher number of such exposures.

Finally, the following factors remain significant in the multivariate model:

- Any topping off of solution;
- Wearing lenses for less than 12 hours per day;
- Being younger than 26 years or being older than 55 years; and
- Storing lenses in water.

To address the question of whether water source and water disinfection plays any role in AK infections, we examined case and control water sources and method of disinfection of that water source. We found no evidence to support the hypothesis that the nationwide AK outbreak was associated with a corresponding nationwide change in water treatment that could have led to a widespread increase in tap water contamination by *Acanthamoeba*. Our study failed to find an association between the development of AK and various water treatment practices, including the use of chloramines.

Given that there will be some discussion today around the issue

of rigid lens care and the use of water, I wanted to share some preliminary analyses we've done specifically on rigid lens users from both the 2007 and 2011 case-control studies.

In total, there were 54 rigid lens wearers in the 2007 and 2011 studies, 37 of which were cases and 17 were controls. Some interesting preliminary findings were that about half of the cases sometimes, usually, or always used tap water to store their lenses, whereas almost all controls never used tap water to store lenses. Twelve of thirty-seven cases slept with their lenses in, and these included four orthokeratology patients, while only 1 of 15 controls slept with their lenses in, and none were orthokeratology patients. Smoking also seems to be associated with case status, with more cases being former or current smokers than controls.

In summary, getting back to the overall 2011 case-control study, a number of hygiene behaviors were significantly associated with infection.

Topping off with solution was highly associated with AK. Topping off promotes formation of biofilms, a food source for *Acanthamoeba*, and dilutes the overall disinfection activity of the total volume of solution.

Exposing contacts to water by handling them with wet hands, storing them in water, and rinsing cases with water were also significant risk factors. Water contamination of lenses and lens products increases exposure to *Acanthamoeba*. However, the frequency of water exposure was similar

among cases and controls and not associated with risk of infection, suggesting that water exposure must be accompanied by other specific behaviors to increase AK risk.

Finally, having worn contact lenses for five or fewer years was also found to be associated with infection. New users might have poor contact lens care practices, choosing comfort and convenience over efficacy and care.

Unlike the outbreak investigation in 2007 that resulted in a voluntary recall of a single brand of multipurpose contact lens solution, the findings of this study highlighted the increased risk of AK associated with poor hygiene practices.

Nevertheless, several recommendations can be made. We must encourage proper hygiene practices among contact lens wearers. Regular cleaning of contact lenses and avoidance of lens contamination with water can reduce the risk of AK. Additional messaging should focus on effective use of disinfecting solutions. Misuse of solutions, such as topping off, can promote growth of *Acanthamoeba.*

Additionally, we must educate the contact lens wearers and eye care providers about the risks of AK, to improve adherence to these recommended hygiene practices.

Although no solutions were implicated in this investigation, CDC and FDA should work to establish standards for contact lens disinfection

efficacy against *Acanthamoeba*, so that more effective solutions can be made available.

Finally, CDC and our many partners should continue to monitor AK incidence to improve our understanding of the effectiveness of recommended interventions. However, monitoring AK incidence is one of the challenges in prevention and control of this infection. There is no ongoing systematic collection of AK cases, partly due to the fact that it is a not a reportable condition in any state. Lack of surveillance for AK makes it difficult to assess impacts of interventions to control and prevent AK.

Also, one of the unifying findings of the AK investigations is the association of poor contact lens hygiene practices with infection. These risk factors are behaviors, and behaviors can be difficult to modify, as our colleagues working in chronic disease prevention already know well, as they work to promote behavior modifications in diet, exercise, and tobacco use.

However, at CDC we've not been discouraged by the challenge of modifying contact lens wearer behaviors and have launched a communications initiative to directly reach contact lens wearers with engaging messages regarding healthy contact lens wear and care. With generous funding from the Contact Lens Institute, we have established the Healthy Contact Lens program at CDC.

One of our first tasks was to convene an external workgroup with members who are experts in eye health and infectious disease in the

contact lens industry. Many of you probably recognize these names as prominent experts in the field.

With these experts on our external workgroup and their affiliations with the various professional organizations, we have been able to establish partnerships with the listed organizations to bolster our efforts.

One of our first goals was to establish and expand the contact lens-related web content at CDC. Key content on this website includes:

- Expert-honed recommendations;
- Benefits of contact lens wear;
- Risks relating to contact lens wear;
- Collaboration with CLI and partners;
- Basic facts about contact lens wear;
- Health promotion materials; and
- Data and publications.

We're also excited that this is the first website in our branch to be created in responsive design format, which means it can be easily viewed on mobile devices such as tablets and smartphones.

One of our main goals for the website was to develop contact lens wear and care messages, with input from experts and stakeholders, that are evidence-based to the extent possible. The key message categories are:

- Your Habits, addressing hygiene and contact lens wearing practices such as not sleeping in contact lenses

and keeping water away from lenses;

- Your Supplies, which addresses proper care and replacement of contact lenses and lens cases and solution recommendations, such as not topping off; and finally
- Your Eye Doctor, advising contact lens wearers on when to visit their eye doctor and to ask questions of their eye doctor.

Armed with these messages and keeping our younger contact lens wearers in mind, we developed infographics and posters for display or circulation on social media. We've already had one Atlanta area high school print this infograph in their school newspaper.

Now that we've been generously funded for a second year, our next goal will be to conduct a contact lens health campaign to proactively reach our target audiences, which will be young adult contact lens wearers 18 to 22 years old and eye care providers. It will be a five-day campaign to be held in November, after both the American Academy of Ophthalmology and American Academy of Optometry meetings have wrapped up, with the intent of drumming up support and media interest during those meetings.

We plan to do broad outreach and dissemination of our information and materials and will do this by engaging with the media, social media, and both CDC and partner communication channels and networks.

We also plan to publish a morbidity and mortality weekly report describing the burden of microbial keratitis in the United States, using insurance claims data. We are excited about these efforts and hope that we can work closely with FDA in our efforts to encourage healthy contact lens use.

Many thanks to the organizations listed here and the collaborating individuals within these organizations.

Thank you.

DR. HIGGINBOTHAM: Thank you.

We now would like to welcome Dr. Stephen McLeod. Dr. McLeod, would you like to introduce yourself to the Panel as well as our audience?

DR. McLEOD: Hello. Yes, I'm Stephen McLeod. I'm the Chair of the Department of Ophthalmology at the University of California, San Francisco, and also on the faculty of the Proctor Foundation for Infectious and Inflammatory Diseases of the Eye. And that is indeed one of my areas of expertise, corneal external disease and ocular infection.

DR. HIGGINBOTHAM: Thank you.

I'd like to thank the FDA and the CDC for their presentation.

And now, Panel, we have a chance to ask clarifying questions to the FDA and the CDC. Please remember that the Panel may also ask questions during our deliberations later on today. So any questions?

And, Dr. McLeod, I know, it's been a difficult journey, but we'll catch you up.

Yes, Dr. Sugar.

DR. SUGAR: Just one brief question. Nowhere in the materials that we got previously or in Dr. Brocious' presentation do they define soil. Could you define, in your testing circumstances, how you quantify or use soil, Dr. Brocious?

DR. EYDELMAN: Dr. Hampton.

DR. HAMPTON: So yes, you're right, that information is not in there. I think soil, in general, is somewhat difficult to define, which is why we're talking about it today. In the ISO 14729 standard, it's described as heat-killed yeast. I think what we're looking at here in terms of representation of real-world conditions may be more of a milieu of microbes plus, maybe, components of tear film that would mimic tear film that can be used. We're thinking more of a real-world scenario, maybe, as compared to heat-killed yeast when we think about soil.

DR. HIGGINBOTHAM: Any other questions?

Yes, Dr. Leguire.

DR. LEGUIRE: I'm curious about the program that Dr. Cope related to, the CDC emphasis on contact lens wearers less than 22 years of age, which would constitute approximately 20% of the contact lens population.

Why is this whole program geared to such young children when I don't see any stats here saying they're particularly prone to contact lens misuse? I'm just curious why the emphasis on children, other than it sounds good to have children emphasized.

DR. HIGGINBOTHAM: Dr. Lepri, do you want to -- and Dr. Lepri, as you're approaching the podium -- this is Dr. Higginbotham -- I have a somewhat related question.

I know that we're targeting the known contact lens wearers, but certainly there's a whole other demographic that's getting contact lenses in a different path, and the socioeconomic status I know that we're focusing on is a much higher group. But I think there's a different socioeconomic status that is accessing contact lenses in a much less formal way, not going to physicians, et cetera. How are we addressing that, the total universe? I know we can't really put our hands around it, but the reality is there are people out there that are getting contact lenses on the Internet.

DR. LEPRI: Yes. Well, the way we're particularly addressing that is through our publications and outreach programs for providing education, is the first part. FDA has a separate entity as a working group dealing with decorative contact lenses and online purchases. That involves multiple agencies of the government, the Office of Criminal Investigations, the Office of Compliance, FDA. The demographics that I presented were not with the purpose of saying that our emphasis is on that larger group of

socioeconomic characteristics.

I believe that the interest in children in particular is that they are the upcoming contact lens wearers, and also that those of us who have had teenagers, we know that hygiene is typically not their forte and there's a certain degree of carelessness that comes with adolescence and pubescence. So we need to emphasis that group for their potential impact on their contact lens wear in the future.

Does that address your question? I mean, because we don't have any statistics that there is misuse in them or whatever doesn't mean that we shouldn't address them. Typically when there are problems, those are the ones that make the media, are the children who have been impacted by this. So because they're not representative of the entire contact lens-wearing population is not a reason for us to not also provide some special emphasis for children, because it involves also their parents being providers for them.

DR. HIGGINBOTHAM: Dr. Bergmanson.

DR. BERGMANSON: Yes, Jan Bergmanson here.

I was a little alarmed here that the gas permeable lenses can be, with FDA approval, cleaned or you can have association with tap water. And I just want to make a point here that now we have -- the most rapidly increasing gas permeable lens market is the scleral contact lens, which is a much bigger lens with a greater potential for soaking up some *Acanthamoeba*

from the tap water. And also before or as you insert the lens, you fill the shell with fluid, and that potentially could be tap water, which would be absolutely against what we recommend to patients.

My question to the presenter here, Dr. Robboy, is did you consider scleral lens issues when you bring up this matter about tap water and the cleaning of gas permeable lenses?

DR. HIGGINBOTHAM: Dr. Eydelman, do you have a comment?

DR. EYDELMAN: Perhaps we can go back. I believe our CDC colleague was trying to address the previous question.

DR. HIGGINBOTHAM: Okay.

DR. EYDELMAN: Sorry to interject.

DR. HIGGINBOTHAM: Okay, I was going to come back to Dr. Cope, but perhaps if we could have Dr. Bergmanson's question asked and then we'll go back.

Thank you.

DR. ROBBOY: Dr. Bergmanson, what we discussed applies to all diameters of all lenses, big, small, in the middle. So whether they're scleral or they are 8 mm to 9 mm in diameter, our message is still to avoid the use of water.

DR. BERGMANSON: But you agree that the scleral lens, being much bigger, is a greater potential problem?

DR. ROBBOY: Yes. Go on.

(Laughter.)

DR. BERGMANSON: Well, scleral lenses are very popular in Texas, where we like everything big.

(Laughter.)

DR. ROBBOY: A good point.

DR. HIGGINBOTHAM: I'll have to remember that one, Dr. Bergmanson.

Okay, Dr. Cope, would you like to do a follow-up on the epidemiology question?

DR. COPE: Sure. I just wanted to -- so the Healthy Contact Lens communication initiative at CDC, when I mentioned that 18 to 22 years, that's kind of who we are targeting for our first kind of commemorative week that we're planning for November. So that's mainly a communications target. It's not to say that we aren't -- this program, overall, is geared at all contact lens wearers. But for this first commemorative week that we're planning, we've chosen to target this particular age group for a number of the reasons that have already been mentioned here. But we are hoping, with continued funding, that we can continue this program and potentially target other groups in the future.

DR. HIGGINBOTHAM: This is Dr. Higginbotham.

So the week of focus is in November. Is there something that's focused on Halloween, where many of these kids will actually get these lenses

that we referred to earlier?

DR. COPE: We know that FDA does have an initiative around the decorative lenses at Halloween time, and so we've chosen not to step on that, and we'd like to keep our program aimed at the more general contact lens wearing population.

DR. HIGGINBOTHAM: Yes, Dr. Flynn.

DR. SZCZOTKA-FLYNN: I have two questions. One is on that advertising campaign. Does that include some mass direct-to-consumer advertising like TV ads and magazine ads? I would think that that has the greatest impact.

DR. COPE: No. As of yet we don't have plans for TV. We're going at it from more of a social media. We have at CDC begun entering into that arena and have seen a lot of success in reaching potentially millions via that way of communication.

DR. HIGGINBOTHAM: A follow-up question?

UNIDENTIFIED SPEAKER: No, I have my own question.

DR. HIGGINBOTHAM: Okay, okay. Yes, thank you.

DR. SZCZOTKA-FLYNN: My second question was actually for Dr. Green. You had mentioned that -- so I want to step back. I had a few questions about the incompatibility with the preservative uptake, because the lens that potentially has the greatest preservative uptake is probably the largest lens in the world, the etafilcon A material, which has been around for

over 20 years and does not have any epidemiological or clinical incompatibilities that we know of. So you mentioned something about plans for further testing if this potential incompatibility is identified. Could you expand upon that?

So I guess my concern is how will you identify lenses that in your testing are incompatible, but epidemiologically we know that they seemingly are compatible, as they have been for many years. What further testing would be allowed, and how would that impact the labeling?

DR. GREEN: Okay. Well --

DR. HIGGINBOTHAM: Please state your name.

DR. GREEN: I'm sorry. Thank you. Angelo Green, chemistry reviewer, FDA.

So the testing is based on microbiological test methods, ISO 14729. So the incompatibility testing will be grounded or validated by the criteria set by 14729. For incompatibility or even for disinfection efficacy testing, we've never used epidemiological studies as a measure.

So the actual testing. The initial criteria will be to assess the preservative, how much the lens diminishes the preservative concentration past the manufacturer specification range. The manufacturer will still be able to -- if the lens has not passed the testing, they can do a modified standalone test using a lens plus a solution plus microbe. If that doesn't work, then they can still use the regimen test to assess compatibility. So we give a

manufacturer several options to show compatibility.

Does that answer your question? So we've never used epidemiological measures. It's a micro test.

DR. SZCZOTKA-FLYNN: Okay. So I guess just as a follow-up to that, do you believe that your microbiological test -- does it mimic real-world scenarios if, epidemiologically, we're not seeing problems with some of these lens/solution combinations?

DR. GREEN: Well, that's a good question. We're here to discuss that. So if you have any comments on that, that would be great.

DR. HIGGINBOTHAM: Okay. I believe Dr. Ahearn has a follow-up to this line of questioning.

DR. AHEARN: I was curious as to the point that the inhibitory activity of a contact lens solution and its preservative effect is based on the total formulation. And so the individual components, like PHMB that was mentioned and poly -- that sublethal concentrations really for the organisms that were major points of discussion here. So this is how you would be able to determine an incompatible lens there, because again this would correlate with the epidemiologic data.

So how would you be able to select the preservative level that would be harmful, particularly since testing against some of these organisms, the solution itself would be one of the major components that would be affected? You couldn't just do it with a decrease in a level of one component.

DR. GREEN: So when the submissions come in to the FDA for a specific solution, the manufacturer identifies the active ingredient for each function, and for disinfection they usually identify the preservative as the active ingredient. The 2008 Ophthalmic Panel recommended that the manufacturer test the preservative at the lower limits of the specifications they provide. So they validate that again using the microbiological test method and criteria described in ISO 14729. So there have never been any epi tests performed to test disinfection efficacy.

Did that answer your question?

DR. AHEARN: Well, it's what those are. That's really not real world. I see what you're basing it on, yes, on what's labeled as the active component; it is a preservative. As to whether or not it provides the inhibitory capacity to the solution would be probably not true.

DR. GREEN: So I completely agree that the solution formulation in general --and not only the preservative is involved in disinfection, but the whole solution is tested in a micro test, not just the preservative.

DR. AHEARN: As mentioned earlier, with the one solution with the complete -- it was a total formulation which was ineffective at that time. So the formulation is a critical factor there.

DR. GREEN: I agree, I agree. But in the method the formulation is tested, the manufacturer specifies the active ingredient in the formulation.

DR. HIGGINBOTHAM: Great. Thank you, Dr. Angelo Green, for

your response.

Dr. Tarver has a comment on a previous line of questioning. And, Dr. Tarver, if you could just restate the question and then express your comment, that would be helpful.

DR. TARVER: Sure. I'm Michelle Tarver. I am an ophthalmologist and epidemiologist in the Division of Ophthalmic and ENT Devices.

You had asked a question about the demographic variability in contact lens use, and I think you were alluding to decorative contact lens wear, which tends to be more common in lower socioeconomic groups as well as ethnic minorities. And we have spent a considerable effort at the FDA working on outreach materials to target those groups as well as children. I think you had alluded to it as well, children and teenagers, who tend to be the most frequent users of these devices. We've also done some regulatory efforts to try to get a better handle on it.

But the underlying issue is that decorative contact lenses are contact lenses and medical devices and are regulated under the same guidance and recommendations that all contact lenses are.

DR. HIGGINBOTHAM: Thank you, Dr. Tarver. That was very helpful.

So I guess one general question is, why not align these efforts? Because it appears, if you could actually come up with a health promotion

message for the lower socioeconomic groups that are using these lenses, it helps everyone. So it seems like they're in parallel. That's mainly just a rhetorical question.

We have a few ahead of you guys. Dr. Owsley and then Dr. Lecca and then Dr. Leguire and Dr. Jacob, okay? And then Dr. Bressler.

DR. OWSLEY: Cynthia Owsley.

I'm not sure if this is directed to FDA or maybe the CDC representative who is here, but I'm wondering, in your Healthy Contact Lens education program -- I'm not sure exactly what it's called -- do you have any evidence that your communication strategies in this campaign are effective? What work did you do in the process evaluation as well as in the final evaluation of materials before they're sort of unleashed on the public?

DR. COPE: This is Dr. Cope.

So this is still very new. We are not even at a year yet. And actually we're working on the baseline evaluation at this point. So I would say this hasn't been officially launched yet. So we're really still in the development phase, working on baseline evaluation right now, and then we'll plan to go forward. But we are very -- we are keeping in mind that we'd like to demonstrate the effectiveness of this, realizing that it's going to take a long time to change behavior.

DR. HIGGINBOTHAM: Dr. Tarver, do you have a follow-up comment?

DR. TARVER: Sorry, we were playing musical chairs. This is Michelle Tarver again.

I'm one of the FDA's liaisons to the Healthy Contact Lens campaign, and they did do focus groups in the development of the messages, looking at the images and things of that sort. So they've just developed all of this material, and so they will be planning to do some evaluation of the effectiveness of the message.

DR. EYDELMAN: And, Michelle, before you leave, perhaps you can also add about other campaigns for decorative contact lenses.

DR. TARVER: Okay. We've worked extensively with a number of different professional organizations, including the American Academy of Ophthalmology, the American Optometric Association, and the American Academy of Pediatrics, all to address the issue of misuse of decorative contact lenses.

And we've done a lot of outreach materials in terms of educating providers about how to report adverse events with these devices to the FDA so that we can initiate a regulatory effort to try to control it.

We've also worked with messaging with the different professional organizations. We are in the process of developing a public service announcement, which I think just completed, with the American Optometric Association and the Entertainment Industries Council. We've worked with the American Academy of Pediatrics and their ophthalmic

section to develop a survey to assess eye care providers and measure what the incidence, as best as we can estimate, of this problem is in the population, because it is a very difficult issue to measure. But we do see very bad outcomes with these particular lenses.

So those are some of the outreach efforts that we've done. And Dr. Lepri has already mentioned some of the educational materials that we've done with MedScape and some other efforts.

DR. EYDELMAN: Thank you.

DR. HIGGINBOTHAM: This is Dr. Higginbotham.

So, Dr. Tarver, I would imagine that all of that hard work that you've been doing with focus groups, et cetera, is informing the CDC campaign, and I'm sure you're also working with the National Eye Institute and their Eye Health Education Program as well.

DR. TARVER: We haven't formally worked with the National Eye Institute's eye campaign.

DR. HIGGINBOTHAM: Okay, thank you.

Let's go to Dr. Ahearn. Did you have any other comments, Dr. Ahearn? No?

DR. AHEARN: You're asking an old professor if he has comments.

(Laughter.)

DR. AHEARN: My thoughts went back to the solutions

themselves. And if the active component is picked up by the lens, is it possible that that lens would be less likely to be transporting an infectious agent to the eye? And so in some instances, perhaps depending upon the nature of the components that were picked up, that the lens itself would be more protective. But I was just wondering if that was looked at.

DR. HIGGINBOTHAM: Is there anyone from FDA that could -- so essentially, since the lens itself is picking up the preservative, perhaps it could be a repository for some additional protection for the eye.

So, Dr. Angelo, would you like to answer that?

DR. GREEN: Sure. That's an interesting point, but we don't have any data to show that that's what's happening. The preservative works because there's a positive charge, and I'm sure you know that the positive charge disrupts the membrane. So if the positive charge is trapped or secured by the material, it's not free to interact with the bacteria. Now, it's probably going to be variable depending on the lens material and the nature of interaction with the different lens material, but we expect that the active preservative will work best if it's floating in solution.

Does that make sense?

DR. AHEARN: Again, dependent upon what type of lens that you were working with, that would be possible. And then it would be varied in with the water content also, I would presume, right? As to just how tightly it might be bound, it might actually go into the lens or it would be just bound

to the surface.

DR. GREEN: Well, it's small enough to go into the bulk material or be bound to the surface.

DR. AHEARN: Well, I would suspect that would be true for some, but not all, if the poloxamers actually have complexed with it and the poloxamers potentially would maintain it on the surface of the lens. So I'm still looking at a complex formula and how this would affect uptake of individual components. But, again, there's a lack of information in these areas.

And then I was thinking also in relationship -- not so much the *Acanthamoeba* on that, but looking at the actual penetration of the hydrogel by the *Fusarium*. And then the question -- I have the same question as to what would happen there. We probably don't have a lot of information.

DR. GREEN: There's just not enough data to know.

DR. HIGGINBOTHAM: Thank you, Dr. Angelo Green.

Dr. Lecca, I know you have a burning question, but Dr. Jacob, do you have a follow-up on the same topic? And, Dr. Lecca, is it okay if Dr. Jacob asks her question? Thank you.

Dr. Jacob.

DR. JACOB: Yes, I do. Jean Jacob.

There actually is -- you know, we know real-world scenarios where contact lenses -- you know, that's back in the '80s where the ones that

are negatively charged picked up lysozyme. Lysozyme bound to the surface. Lysozyme was the natural antibacterial substance in the tears. Those contact lenses were extremely protective and had significantly less instance of any kind of infection or problems. So to say that by taking up something that is anti-whatever is going to be detrimental, I think, is a problem.

DR. GREEN: I didn't say it would be detrimental. Of course, lysozyme is a protein, so it's a lot more complex if it's absorbed onto the material. We don't know what's going to happen with the small preservatives. If you know --

DR. JACOB: Well, it's an extremely small protein, and there are other things that are much bigger. But I still think that when it does get into the lens, it doesn't always dimerize.

But I just want to follow up on Dr. Ahearn, in saying that I feel that it is somewhat dangerous to pick one thing and say if you absorb so much of this, you're bad, when these lenses -- these solutions are extremely complex and everything is working together. And taking that one thing up may not be bad and most probably isn't bad.

DR. GREEN: It's possible. That's just how the solutions are evaluated, and the research papers evaluate the disinfection efficacy by looking at what's left in the solution. And most of the solutions are also cleared using the standalone test. So that's just how it's evaluated.

DR. JACOB: Okay.

DR. HIGGINBOTHAM: And we assume that you're happy with that evaluation. No, you don't have to answer, Doctor.

(Laughter.)

DR. HIGGINBOTHAM: Thank you, Dr. Angelo Green.

So, Dr. Lecca, your question, please.

DR. LECCA: Thank you very much, Madam Chair.

Really I have a general comment, then a question. First of all, I want to thank the presenters this morning for giving this wonderful update. In fact, I have a question about one of the updates, but I really appreciate all of the information that the FDA is doing in this important area. But let me focus on this noncompliance.

I was really struck, in some of my research and in my readings, that we really haven't -- when I see that 80% or 70% of people are not complying with what the physician has indicated or what the ophthalmologist has asked them to do and that there was still this terrible disease, I'm just struck that we haven't done enough.

So my question really goes to -- I don't know if it was Ms. Hampton who presented this noncompliance area -- where is the effect? Is it more financial? Is it because of the research? Is it the questions of the research? Is it the health professionals that are making the presentation to the patients? Where is the problem that there's such a terrible lack of noncompliance in this area? I really can't put my finger on it. You haven't

told me that, but I'm sure you're working on it, so I wish you would maybe let us know here. So that's really my question.

DR. LEPRI: Okay. This is Dr. Bernard Lepri. I was the one who did the presentation on noncompliance.

DR. LECCA: Oh.

DR. LEPRI: All of the information I presented today was garnered from review of literature on noncompliance in contact lens wear. It's a multifaceted problem. We have no information on how every ophthalmologist and every optometrist who prescribes contact lenses provides their care directions. Some of the information provided by surveys conducted on patients who admitted noncompliance, they claim that they weren't given enough proper instructions or they didn't understand them.

FDA, in general, knows that labeling is not very well read by most patients and it's a matter of, probably, familiarity -- I'm projecting here now as a former practitioner -- that you do something every day and people -- it's a natural human factor that people tend to take shortcuts. And so this is where it comes in.

They listed other factors, many of which were the cost of solutions. So you if use less or you use it less often, it costs you less to be a contact lens wearer.

So I can't tell you exactly where the ultimate source of the problem is. We do know it's multifaceted. We have tried to address it

through outreach and stuff, but there is only so much that FDA can do. We need to encourage practitioners, in our publications, to reiterate the directions every time as a follow-up visit for contact lens patients. We are providing presentations through the American Association of Regulatory Boards in Optometry. They are trying to address this with their licensees in each state, so we've provided information to them also about continuing this message.

DR. LECCA: Can I follow up?

DR. HIGGINBOTHAM: Yes, please, Dr. Lecca.

DR. LECCA: Well, maybe what I hear from you, then maybe is it labeling? Maybe we need to do a better way of labeling this information to the patients. If it's the practitioner, maybe they need to be partnered with some other profession, maybe like with pharmacists. I've read that maybe they are key professionals that work very closely with patients, and maybe partnering with them, maybe that will help in terms of bringing this around. I don't know what it is. I don't have the answer, but you've done a good job. But there's so much more to be done. And this is such a deadly disease. I mean, it has to be eradicated.

DR. HIGGINBOTHAM: Yes, Dr. Eydelman.

DR. EYDELMAN: If I may add. Thank you for your comments. As presented in our earlier -- as presented this morning, we have made quite a number of changes to both patient and physician labeling, and we would

love to hear from you any specific recommendations that you think would enhance messaging. And also by being so passionate about the issue, we hope that you carry this message outside this room.

DR. HIGGINBOTHAM: Any other clarifying questions?

Dr. Leguire, did you have another -- because I had you on my list.

DR. LEGUIRE: Yes, thank you.

It seemed like the previous guidelines for testing contact lenses is based on water content and ionicity -- if that's a word. It sort of was suddenly insufficient with the introduction of silicone hydrogel lenses, and now we're proposing a fifth group and numerous subgroups for testing silicone hydrogel lenses. I was just curious; these guidelines are obviously reactionary to what's happened in the past 10 years or so. I'm just curious about being proactive.

And is there anything in the literature -- and this is not a field of particular interest of mine, but are there any new materials, for example, or processes, what have you, regarding contact lenses that would not neatly fit into these guidelines? And then what a manufacturer is supposed to do? And thinking proactive versus reactive, how can these guidelines be further improved to look at the future?

DR. HIGGINBOTHAM: Yes. Yes, Dr. Eydelman.

DR. EYDELMAN: So before Dr. Hutter answers, I'm just going to

make a general statement.

You're absolutely right; we don't want to continuously play a catch-up game. And that was part of the initiative behind our multi-year research where we tried to come up with a new grouping that will address things that are in the pipeline, while continuing to be least burdensome to the manufacturers. As you will hear I believe later today, there are several other proposals which do require more actually than our current proposal.

And with that, I think I'll turn it to Joe.

DR. HUTTER: This is Joe Hutter.

Yes, I agree that it may be possible that there are lenses that we're not aware of that won't fit in these groups. But at this point we took our best shot at getting groups so we can predict interactions with care products. So that's the best we can do at this moment. But we're certainly aware that it's possible, but they may have their limitations in the future.

DR. HIGGINBOTHAM: Yes, Dr. Flynn.

DR. SZCZOTKA-FLYNN: So just a follow-up to that. Are you concerned at all that in your current five subcategories of silicone hydrogels, there's only one, for example, in the ionic group, I think, and only one in the high water, nonionic group? So how are you able to predict whether others will behave similarly if there's really only one in those groupings currently?

DR. HUTTER: Well, there are two high water. But the ionic lenses, the big issue is the negative charge with the methacrylic acid or some

similar chemicals that attract positively charged entities. And it looks like the technology is evolving the balafilcon A lens. People have moved on to a new generation of silicone hydrogels, and that's an old technology. I think more likely you'll see -- it's possible that you could see more ionic lenses in silicone hydrogels. But people have overcome -- gotten higher water contents with different technologies.

DR. SZCZOTKA-FLYNN: So actually you're just -- you don't believe that there will be any more in that group?

DR. HUTTER: I don't know if there will be any more in that group. We haven't seen one since that very first one.

DR. SZCZOTKA-FLYNN: And how are water-gradient technology lenses categorized in this five-category system?

DR. HUTTER: We use the overall water content to put them into a certain category.

DR. HIGGINBOTHAM: Do you have a follow-up, Dr. Flynn?

DR. SZCZOTKA-FLYNN: No.

DR. HIGGINBOTHAM: Okay. Dr. Huang has -- excuse me? Okay, Dr. Eydelman.

DR. EYDELMAN: So just to summarize what Joe was saying. Essentially, we believe that the proposal's proposed groupings do cover everything that we are aware of on the market or in the development; however, we can't predict 10 or 20 years down the line.

DR. HIGGINBOTHAM: Thank you.

Dr. Huang and then Dr. Bergmanson.

Dr. Huang.

DR. HUANG: I think in general, you know, in search of a good guideline for generalized coverage for all the material is good. But my bottom-line question is that we know there's an increased prevalence of the *Acanthamoeba* keratitis over the years, and we also know there is an increased use of contact lens use over the years.

But is there any literature evidence suggesting that the reasoned increase of the *Acanthamoeba* keratitis is really due to the silicone hydrogel use, increase of the silicone hydrogel use versus the conventional hydrogel contact lenses? Because all the literature has not indicated -- maybe Dr. Cope or maybe Dr. Hutter -- because, from the literature that I reviewed, there was no strong indication saying silicone hydrogel is particularly -- I mean, the user of the silicone hydrogel contact lens is particularly most susceptible than the conventional contact lens, other than their habits, the noncompliance issue.

DR. EYDELMAN: Dr. Cope.

DR. COPE: Yes, our studies have not shown any higher risk with a specific material of contact lenses.

DR. HUANG: So I'm sorry, I'm playing a little bit contrarian. So if there is no strong indication of suggesting silicone hydrogel lens is

increasing the risk of this unusual *Fusarium* or *Acanthamoeba* keratitis, do we really need an extra set of guidance?

DR. EYDELMAN: Okay.

DR. HIGGINBOTHAM: Dr. Eydelman.

DR. EYDELMAN: Now I think I understand your question. Sorry. So what we were trying to summarize as separate issues, one had to do with any kind of incompatibilities and one had to do with microbial. So we're trying to address both the chemistry and micro. And I think that's where your question was. So the silicone hydrogel grouping does not deal -- is not intended to deal with --

DR. HUANG: Microbial.

DR. EYDELMAN: -- microbial. Is that what your question was?

DR. HUANG: Yes.

DR. EYDELMAN: Okay.

DR. HIGGINBOTHAM: Okay, great. So Dr. Bressler. Thank you.

DR. BRESSLER: Thank you. I had two clarification questions for Dr. Cope. And thank you; it was an excellent presentation. And I appreciated all of the presentations.

The first was Dr. Robboy had mentioned that tap water rinsing is used typically in cleaning rigid gas permeable lenses. And my question is, did you look at that specifically, independently? I know that you had water stored in the lenses, for example, but I didn't see tap water rinsing per se.

Was that looked at independently as a univariate question?

DR. COPE: Yes, I believe it was, and the only thing that was significant was storing.

DR. BRESSLER: Okay. So that's helpful. And then my second clarification is just on the multivariate model. You have a lot of analyses there. Did you control for the multiple testing that was used? I see that everything is a 95% confidence interval. And was there any Bonferroni correction or anything else done for the multiple testings that were done for the reports, or just the multivariate model itself?

DR. COPE: Sorry, I'm not as intimately familiar with the analysis to be able to answer that.

DR. BRESSLER: Not a problem. I'm just trying to get a feel for the ones that were close to 1 in the lower bounds in their interval, and it's fine to get it later on or in the future.

Thank you very much.

DR. HIGGINBOTHAM: Is there anyone else from FDA who could respond to that, Dr. Eydelman?

DR. EYDELMAN: No, since it's a CDC analysis.

DR. HIGGINBOTHAM: All right, all right. Thank you.

Dr. Jacob and then Dr. Zabransky.

DR. JACOB: Jean Jacob. Thank you.

My question goes back to -- I have two of them and one goes --

both of them are actually for Joe Hutter, and it was on the contact lens groups and how daily disposables will fit into those groups, or are you going to have an extra category for daily disposables?

DR. HUTTER: This is Joe Hutter.

For daily disposables, we're usually not concerned with solution compatibility because you're not supposed to use solutions. But they do fit into -- we do put those lenses into those groups.

DR. JACOB: Okay.

DR. HUTTER: For example, etafilcon A is the daily disposable version, and one version you can --

DR. JACOB: Well, given the fact that we know how much people misuse their lenses, is there any proof that people that wear daily disposable lenses will not reuse them?

DR. HUTTER: I defer that to one of my colleagues.

DR. JACOB: You know, you're putting together these groupings and it's new and you want to go for like --

DR. HUTTER: Right.

DR. JACOB: -- 10 to 15 years, right?

DR. HUTTER: Right.

DR. JACOB: And so we already know people misuse their lenses all the time. They're already wearing lenses that are daily wear lenses for a week. We've already seen all of that presented this morning. So why would

we put on our rose-colored glasses for daily disposables and say that, all of a sudden, people are going to use those exactly the way they're supposed to?

DR. HUTTER: I'll have to defer to one of my colleagues to answer that.

DR. HAMPTON: This is Denise Hampton.

What I think about when I hear your question is that, regardless of daily wear or extended wear, contact lenses are medical devices, okay, first of all.

Second, what Dr. Hutter was saying was based on the material composition of that lens. Regardless of daily wear to extended wear, it would be categorized into one of these groups.

DR. JACOB: Okay.

DR. HAMPTON: Testing for the groups that he's describing, as he said in his presentation, would be for solution incompatibility and that sort of thing. And I think what you're tying in is what Dr. Lepri talked about in terms of patient noncompliance, which though related based on what you described, I don't think that's what we were getting at in terms of the grouping system itself. It's a categorization to determine interactions, but not necessarily to determine wear of patients over time.

DR. JACOB: Well, I guess my concern, as a material scientist, is that they use daily wear lenses. A lot of them are inter-penetrating networks. A lot of them do have variable water contents. I think that you will find that

once they reuse them and hit them with some of these contact lens solutions, they're going to have a lot of problems because the things that they'll be taking up from the contact lens solution are extremely irritating in other ways and won't have to do directly with infection. But then they will be killing epithelial cells and therefore ultimately having more infections.

So if you're going to go through and make a new classification system, shouldn't we potentially take into account that those things are going to be coming up the pipeline? Because I don't have my crystal ball, but having been in the industry for over 25 years, I can tell you that a problem is coming.

DR. HIGGINBOTHAM: Dr. Eydelman.

DR. EYDELMAN: So thank you very much for your comment. I just want to point out that we need to always balance being least burdensome for the sponsors -- for the manufacturers and at the same time providing as much protection to the end user as possible.

So while we want to introduce and maximize the resultant safety or the preclinical testing, there has got to be some assumptions based on the IFU. So if it's a daily disposable that's not supposed to interact with multipurpose solutions, a scheme for excessive testing for a scenario that is not on label is not our usual practice.

DR. JACOB: Okay.

DR. HIGGINBOTHAM: Okay, great.

DR. JACOB: Could I ask my second question, then?

DR. HIGGINBOTHAM: Yes. And then Dr. Zabransky.

Dr. Jacob.

DR. JACOB: This is Dr. Jacob.

And this is back for Joe. I'm sorry that you sat down so quickly.

(Laughter.)

DR. JACOB: And it's about the grouping and the testing and you said one lens tested per group. Did you mean one lens type or you actually meant one lens?

DR. HUTTER: Oh, no, no. No, one lens material.

DR. JACOB: One lens material.

DR. HUTTER: Yes. Yes, typically 20 lenses --

DR. JACOB: Okay.

DR. HUTTER: -- or some number like that. Say it's one Group 4 lenses, conventional etafilcon, and you just take that and take 20 of them.

DR. JACOB: Okay. I wasn't clear.

DR. HUTTER: Right. Right.

DR. JACOB: Thank you.

DR. HUTTER: Okay.

DR. HIGGINBOTHAM: Great. Now Dr. Zabransky.

DR. ZABRANSKY: My question is either for the FDA or perhaps even for the industry in general. In real life these lenses are stored, I think, in

plastic containers. Has anybody addressed the nonreactive nature of these plastic cases, with regard to their ability either to inhibit or to absorb the preservative that's in the solutions? We've talked about the lenses and the solutions themselves, but what about the cases, because that's where they are in real life.

DR. EYDELMAN: Dr. Hampton.

DR. HAMPTON: That's an excellent question, and it's one that I think not only we have thought about, but industry as well. I think you will hear a little bit about that later today.

In one of our publications by Dr. Megan Shoff, we do assess the interaction as part of that study, and those results in that publication noted that, in that particular scenario, the materials of the case didn't contribute. And like I said earlier, I believe you will hear something similar today from published research.

DR. HIGGINBOTHAM: Yes, any other questions?

Yes, Dr. Flynn.

DR. SZCZOTKA-FLYNN: This is Loretta Szczotka-Flynn.

On Slides 34 through 36, I think there were -- you were alluding to the fact that you are similar to these new FDA guidelines or that they interface with some ISO standards. And so I think there's a lot of confusion amongst the public, or even us in the professional field, of how the FDA is aligned with ANSI and ISO, and there were several slides that alluded to your

new guidelines being in alignment with ANSI or ISO recommendations.

So could you outline for us what some of the differences may be, and then how you decide which way you want to go and whether or not the FDA feels they need to be in alignment with these other international organizations or going their separate ways and how that all interfaces with what we'll decide today?

DR. HIGGINBOTHAM: Dr. Eydelman.

DR. EYDELMAN: That's an excellent question. So members of my staff are active members of both ANSI and ISO working groups for contact lenses and contact lens care products. What that means is they're part of the committee that develop and write standards.

Having said that, that does not automatically mean that once the standard is finalized, that we accept all of the recommendations. After the standards are finalized, there is an official recognition process for the FDA because, as you can imagine, there are many votes before the standard. So the final product does not necessarily mean that the FDA representatives of the committee opinions were the prevailing ones.

Once the standard is finalized, FDA goes through the formal recognition. And at that point, if we do recognize it, it gets published on the website, and therefore industry and manufacturers, et cetera, have ability to know if we do or do not agree with all of the recommendations in a particular standard. In addition, there are FDA-owned guidance, FDA-written guidances

that are solely FDA documents.

Did that answer your question?

DR. SZCZOTKA-FLYNN: Yes, it does answer my question. I have a follow-up, though. How do you find that being potentially problematic if standards in the United States are different than those of our neighboring countries, and the same products may be found to be compatible just across the border but we say they're not compatible here? Is there a potential issue with that in your mind?

DR. EYDELMAN: It's Malvina Eydelman again.

This is not unique to contact lenses. This is an issue across all of the medical products. As I said, we recognize both ANSI and ISO standards, and FDA has its own set of regulations that govern safety and effectiveness levels that are adequate for the U.S. public. And once we recognize ANSI or ISO, it's clear what our recommendations are, and therefore the products that meet those recommendations may get to the U.S. market.

DR. HIGGINBOTHAM: Great. Any other follow-up questions, Dr. Flynn?

DR. SZCZOTKA-FLYNN: No.

DR. HIGGINBOTHAM: Okay. Dr. Sugar.

DR. SUGAR: Joel Sugar.

This may be a naive question, but at some point in the past, I presume you went through the discussion of all of this testing happening with

lenses that had never been worn. And except for Day 1, all of these lenses are stored in solutions, having been worn. I assume you're the one to answer this, Malvina. Can you just tell us how the decision was made to test only fresh or virgin lenses, however you describe them?

DR. EYDELMAN: Actually, I'll defer to my micro colleagues.

DR. HAMPTON: Again, I need one second.

DR. EYDELMAN: While they're thinking, part of it obviously is the logistics of obtaining the lenses for experiments, and the experiments were conducted at the FDA and were purchased over the counter. I don't know of legitimate ways that we could have obtained lenses at different stages of being worn. So that was part of it.

DR. HAMPTON: I apologize for that. This is Denise Hampton. I should have deferred to Dr. Lepri. That was such an excellent explanation he just gave.

So if I'm understanding the question that you're asking correctly, as to why we made the decision to choose fresh -- I'll say fresh lenses rather than worn -- what we were discussing is that we use preclinical and clinical testing hand in hand. So the clinical tests that we recommend are for patients who have worn lenses, and our recommendations are made with a combination of that, plus the preclinical testing, for clearance of these lenses.

DR. EYDELMAN: Also let me add that our preclinical testing is

performed on "virgin" lenses. So we needed to have -- what we were trying to develop is enhanced testing for preclinical assessments of these lenses that would parallel the scenarios. Basically, our experiments were parallel to what would be performed by the manufacturer.

DR. SUGAR: I don't think the question was answered, but I don't know that you can.

Thank you.

DR. HIGGINBOTHAM: This is Dr. Higginbotham. I have a question for the CDC, Dr. Cope, just a clarifying question.

So one of the challenges that I think some patients have with these gas permeable lenses, particularly if they have dry eyes, is that they constantly have to moisturize their eyes throughout the day. So in the course of the study, did you actually ask, as part of the clinical history, whether or not people had dry eyes as well as whether or not they used tap water or saline during the day? Was that perhaps another opportunity where tap water could have been introduced?

DR. COPE: And you're asking specifically about the rigid lens user or just across the board?

DR. HIGGINBOTHAM: Across the board. I mean, with rigid lenses you don't have that problem. It's really the soft lenses, the soft contact lenses, that you find patients will -- and I'm looking to my cornea colleagues for reinforcement here. But as a glaucoma specialist, I know that a

lot of my contact lens wearers will certainly want to splash water in their eyes during the day.

DR. COPE: Yes, I don't believe we specifically asked about dry eyes or needing to use rewetting solutions or anything. You know, there may have been an open-ended question where they were allowed to say any of their comorbidities or any complicating factors, but I don't believe we specifically looked at that.

DR. HIGGINBOTHAM: Dr. Owsley.

DR. OWSLEY: Cynthia Owsley.

There's been a lot of discussion on kind of the educational importance, the importance of education of the patient, and we've kind of alluded to it a little bit. But I would also encourage as much emphasis on education of the eye care provider. The eye care provider certainly knows that they need to provide information to their patients. But there's a lot of research on adherence to medical treatments and it focuses on the dyad in the communication.

And so I would encourage as much emphasis on education of the patient as to strategies -- imparting strategies -- to finding mechanisms to impart strategies to ophthalmologists and optometrists on the most efficient and effective ways to communicate appropriate contact lens care to patients. And that would also include clinic staff because, when you actually get down to it, if you've ever been a contact lens patient, you spend probably as much

time, if not more time, with the allied clinic staff that works with the optometrist or the ophthalmologist, especially when you're first learning to use contact lenses.

So I guess my comment is just in the spirit of it's really a dyad here. It's not just all about educating the patient. It's also educating the provider who has -- who, of course, already recognizes that they have a responsibility, but also in learning strategies that are most efficient and effective.

DR. HIGGINBOTHAM: Yes, Dr. Jacob.

DR. JACOB: Jean Jacob.

I had a follow-up question from a previous one, and that is on the preclinical testing where you do the cycling of preservative uptake and disinfection and you cycle between your disinfection solution and then you put it for 14 hours in saline.

Why is not an artificial tear solution used? Is it not rocked in artificial tear solution for 14 hours? Because, I mean, that's standard academic practice for the last 20 years. And so why would we worry about what's going to happen when it's just in saline when it's never going to be off the eye? I mean, by the time you're going to slide through it with the MPS, it will have already been exposed to all of that.

And no one wants to answer me.

DR. EYDELMAN: They're coming up.

DR. HIGGINBOTHAM: Not all at once. Dr. Hutter approaches the podium.

DR. HUTTER: Joe Hutter.

You have to look at this way. A lot of the lenses that come in to us are first-time new materials, first time coming in, and the preclinical tests are screened to make sure, before we do a clinical study, that they're okay. That's kind of our philosophy. So, preclinically, we just do the clinical study. Before the people who do the clinical study, we like to make sure that the lens does everything it's supposed to do preclinically.

DR. JACOB: And so why wouldn't you do an in vitro preclinical test? That is like half a step towards the clinical, so it would be more of a bridge between what would happen only in a premarket environment versus then taking it from this never been in anybody -- a virgin type of device that once it's used is never going to be virgin. So do you see what I'm saying?

DR. HUTTER: Yeah, okay.

DR. JACOB: Why isn't it the first step?

DR. HUTTER: Okay, I can answer that partially. For the cleaning studies, for example, we do have critical mycelia concentration. When people have certain claims, we do have them evaluate protein removal from tear fluid, artificial tear fluid, things like that.

Is that answering your question? I mean, we do that kind of testing, depending on what the product is going to be doing.

DR. JACOB: Right.

DR. HUTTER: Okay.

DR. JACOB: But I guess it goes back to the previous question that says, why aren't you using worn lenses, lenses that have been exposed to tear film, blinking, all of that type of thing, to look at your disinfection? But there is a way of getting halfway there. Obviously, because it's difficult to get worn lenses, you can buy your lenses and then just do an in vitro wear situation and then test this type of disinfection.

DR. HUTTER: Could I defer that to the microbiologists?

DR. JACOB: Sure.

DR. HAMPTON: This is Denise Hampton, a microbiologist.

So I think I want to get back to your original question. And I do not purport to be a chemist -- let me put that out there. I am not a materials person.

But in getting back to your question about why saline, I think the use of saline in that particular method for the 30-cycle test is outlined in the guidance and in the standard as kind of a standard solution. I don't know if that's supposed to be more of a physiological representation, but that's my input as to why saline and not other solutions be tested.

With respect to the other question about worn lenses, and going back to Dr. Sugar's question, actually that's one of the questions that we have for discussion later today, not to defer it necessarily, but just to

say --

DR. JACOB: Okay.

DR. HAMPTON: -- real-world conditions, uptake, any other factors, that's part of the reason that we're here today. So if you have that sort feedback that you want to discuss, then please, by all means.

DR. JACOB: Okay, thanks.

DR. HIGGINBOTHAM: Any other -- yes, Dr. Flynn.

DR. SZCZOTKA-FLYNN: Loretta Szczotka-Flynn.

How will peroxide systems be tested with regards to the preservative uptake testing regimens that you suggest?

DR. EYDELMAN: Dr. Green.

DR. GREEN: Most peroxides don't contain preservative in the solution, so they won't be tested with respect to preservative uptake and release. They will be assessed for solution compatibility, but that's it. But not preservative uptake and release.

DR. HIGGINBOTHAM: Don't leave, Doctor, please.

(Laughter.)

DR. HIGGINBOTHAM: This is Dr. Higginbotham.

And I think this was in your presentation, but I'm still haunted by Dr. Huang's question earlier, given that silicone hydrogels have increased eight times since 2003 -- I think that was in Dr. Lepri's presentation -- and then looking at Slide 45, where you very nicely talked us through this

preservative uptake and release for silicone hydrogel lenses.

So I guess my question is, can this be duplicated with other classes of lenses? Or materials, I should say. Do other materials break down similarly where you might have more release of -- more uptake of preservative versus release? Because I think this is a dynamic that we're focusing on. Is this something that's typical of just silicone hydrogel lenses, and when you duplicate it with others, you see something similar or not similar? Can you help me with this?

DR. GREEN: So that's a good question. So that's one of the goals of the research that we did, and we compared conventional hydrogels to silicone hydrogel lenses. And for hydrophilic preservatives, the behavior is similar between conventional and silicone hydrogel lenses. But silicone hydrogel lenses are more hydrophobic, so they act differently with respect to uptake of hydrophobic preservatives or some tear-film components. And that's why we needed to subcategorize them and add another group for the purposes of testing.

Does that answer your question?

DR. HIGGINBOTHAM: No.

DR. GREEN: So some aspects are similar and some are not, and that's why we have different groups.

DR. HIGGINBOTHAM: It just seems like there -- this is Dr. Higginbotham again -- might be a tipping point where you have too much

of one of these components that might actually drive the most significant factor related to whether or not you have such a huge uptake of preservative and you don't have enough preservative in the solution. And if you isolate the components -- I guess that would be my question.

DR. GREEN: It's a complicated question because each formulation is different. And depending on a formulation, the preservative uptake and release can be different, so each solution is evaluated using different lenses. For that reason, we just don't know without seeing the testing. We have to do the testing first. And the grouping system we have, we think, adequately characterizes the properties for current materials, so we think we'll be able to catch any incompatibilities based on the grouping system.

I didn't answer your question?

DR. HIGGINBOTHAM: Well, it's just that I'm just recalling one of the papers that we were asked to read, where there was an uptake of preservative and then you saw an increase in the growth of -- and Dr. Hampton is shaking her head, so she recalls that, too, so it's not my imagination. So it seems like the uptake of preservative is a critically important factor.

So is there a tipping point? Is there something that we should be really focusing on, or are we just really focusing on everything? Can we prioritize the dimensions of these materials that are the most important to

focus on as it relates to the safety that we're concerned about?

DR. GREEN: So I think we did that and I think -- I mean, the grouping proposal is based on a risk assessment of the properties that we think will affect preservative uptake, and I think the grouping system adequately predicts or characterizes the properties that are important for preservative uptake.

Thank you.

DR. HIGGINBOTHAM: Any other questions?

(No response.)

DR. HIGGINBOTHAM: Well, we have time for Panel deliberations. The anchor in our day is the public hearing at one o'clock, so we cannot change that time, but we certainly can have some flexibility on other parts of our schedule today. But certainly we can go into our own Panel deliberations at this point, if you guys are finished with your clarifying questions to the FDA.

Any comments about what we're being asked to do? You've all had a chance to review the Panel questions. We have lots of expertise sitting around this table, in microbiology, materials science, cornea specialists, optometrists. There's even representation from retina and glaucoma. But Neil and I are the objective people here, as it relates to this topic, I think.

Yes, Dr. Zabransky.

DR. ZABRANSKY: This doesn't address anything specific, but

water -- the question was asked about soil. How do you define soil? Well, water is not water, either. I live in a rural community, and I have my own well. You know, there are various water systems throughout the country. People have these filters that they put on their faucets. People will filter their water in containers and then the water sits on a counter. To my thinking, water should be just completely eliminated for any way that can be done with these lenses. Stick with sterile water or sterile preservative solutions. I don't know if that can be done in any of the labeling for any of these things or not, but just get rid of the water. At least the tap water issue.

DR. HIGGINBOTHAM: And saliva too, I would think.

(Laughter.)

DR. HIGGINBOTHAM: Dr. Bressler and then Dr. Flynn.

DR. BRESSLER: I just wanted to clarify. I had a guest speaker presentation. Is that off the agenda here?

DR. HIGGINBOTHAM: The CDC was considered the guest.

DR. BRESSLER: Oh, they were the guest. Thank you.

DR. HIGGINBOTHAM: Yes.

DR. BRESSLER: Okay.

DR. HIGGINBOTHAM: Okay. All right, that's good. You know, keep me honest. Great, thank you.

Dr. Flynn.

DR. SZCZOTKA-FLYNN: Loretta Szczotka-Flynn.

So while I agree that we should get rid of water, especially with rigid lenses, we don't have a great substitute, unfortunately, to tell our patients to copiously rinse their lenses. Jan alluded to scleral lenses becoming much more popular, which they are. We don't even have a good non-preserved saline to tell these patients to use. The one non-preserved saline on the market is not cleared to be used for rinsing. It's not cleared to be used for anything but heat disinfection, which is obsolete. So we don't have good saline on the market.

I agree that preserved saline would be fine to use, in my opinion, for rinsing these rigid lenses, but we don't even have good copious rinses. We don't have the aerosol salines anymore that would be able to copiously rinse these lenses. So we might tell our patients to stop using water, and as a practicing clinician, I don't have a great answer for them what to substitute it with.

So I would like to see something along more availability of good preserved salines or non-preserved salines on the market that can help us copiously rinse our lenses, because oftentimes with rigid lenses we're using some very, very harsh products. I'm not talking about daily cleaners. Those need to be rinsed very well. But there are some enzymatic-type, very strong cleaners that need to be copiously rinsed, because if those get in the eye, they're very dangerous. We just don't have a great solution for them to rinse their lenses, solution used both as an answer as well as a literal solution.

DR. BRESSLER: Could I ask a follow-up to that?

DR. HIGGINBOTHAM: Yes.

DR. BRESSLER: Neil Bressler.

That comment about a substitute for rinsing water is exactly why I asked Dr. Cope if they looked at that as one of their risk factors, and they did have that as a potential risk factor and it did not come out, as she reported in her preliminary information, as a risk factor in the rigid gas permeable lenses, so far.

Therefore, I would just question, is there evidence that we've been presented that rinsing, per se, with tap water is a risk factor? Because that's separate from storing in water, topping off with solutions, et cetera, because that would help guide us as to whether we need to even suggest at this time, based on available data, do we have to replace the rinsing part? That's what I'm concentrating on.

DR. HIGGINBOTHAM: Yes.

DR. ROBBOY: Marc Robboy from FDA.

Dr. Bressler, in my presentation, I report on some cases in the literature. I think they were Slides 92, 4, and 5. So three of the four cases that I cited, the patient histories indicated that the patient had specifically used tap water rinsing of their lenses. And in Slide Number 93, the subject used both tap water rinsing and tap water storage. So those three examples from the literature right now. I can provide additional examples if you'd like.

DR. BRESSLER: So my question to that -- thank you. Neil Bressler again. Were those independent factors, so that those people didn't have any of the other risk factors such as topping off their solution or the others that we were presented? So that was found, like in a multivariate model, to be an independent factor? Or did that just go along with lots of people, as I've just been told, rinse with tap water, so that when you look at the four cases of *Acanthamoeba* keratitis you find, ah, and they rinsed with tap water? So were those controlled, and do they fall out in a multivariate model and are still a risk factor?

DR. ROBBOY: Well, of course, my cases that I cited were just case histories, so it was uncontrolled to any other variables.

DR. BRESSLER: Okay. So Neil Bressler again.

So that's important to me because it suggests -- it's almost ubiquitous that RGP people were using tap water to rinse. It doesn't mean that the fact that they give it in a case history, that it's related unless it falls out in a model where you ask that and other factors that seem to hold true. And that's why it was very important to me that Dr. Cope did include that in at least their design.

And so we need, in my mind, these case histories. As you point out, that gives us clues as to what to explore in multivariate models of questions. But I need in my mind some good data in that regard, to know whether you should be recommending getting rid of the tap water rinse yet,

because what are the downsides of that? You know, are they going to cause other harm that you mentioned, or not rinse off other deposits that need to be done, et cetera?

DR. HIGGINBOTHAM: Dr. Sugar and then Dr. Bergmanson.

DR. EYDELMAN: I'm sorry.

DR. HIGGINBOTHAM: Dr. Eydelman.

DR. EYDELMAN: I believe Dr. Cope wanted to make a comment.

DR. COPE: Yes, I just wanted to -- this is Jennifer Cope. You know, the data that I presented about the rigid lens wearers is, first of all, very preliminary as well. You know, this is retrospective, so taking into consideration that patients were recalling habits they might have practiced potentially months to years prior. So I just wanted to add that in as a precaution.

DR. BRESSLER: Neil Bressler. Thank you.

DR. HIGGINBOTHAM: Okay, we have Dr. Sugar and then Dr. Bergmanson.

Dr. Bergmanson.

DR. BERGMANSON: Jan Bergmanson here.

I just want to make the point that we mentioned here rinsing of gas permeable lenses. But I think what is happening, too, is the gas permeable lens is also wetted with tap water, and that is important.

And, for instance, the first cases reported in Norway were people who for 10 years wetted their GPs, and that tells you that the actual wetting of lenses is another risk factor. And it takes a long time for the *Acanthamoeba* to grab the chance. That was eliminated by this paper in *Acta Pharmalogica* by the first two Norwegian *Acanthamoeba* patients.

Scleral lenses is another opportunity to use tap water. Like Dr. Szczotka-Flynn mentioned, we don't have easily accessible saline for scleral lens patients. So the temptation would be, oh, I can use tap water here; it will save me a lot of money and a lot of trouble.

And that opens up another question or concern about scleral lenses. We don't have any solutions dedicated to scleral lenses. And my own clinical experience is that, because the scleral lens is a much bigger bulk, more lens, some gas permeable lens solutions are too strong. Because these lenses are porous, they will take up some, and in the case of scleral lenses, they're just taking up more than the corneal lenses, more than that. So maybe one should even consider corneal gas permeable and scleral gas permeable as two separate entities. There is definitely a clinical difference, but I don't have a publication to back that up.

DR. HIGGINBOTHAM: Dr. Ahearn had a comment.

DR. AHEARN: Well, to the point, Neil, that you brought up, I think the incidence with the gas permeable lenses is quite low compared to with the silicone lenses or HEMA lenses. So I'm wondering -- and we probably

don't have enough information on that right now, but that would probably be a very low incidence that you would have with a typical gas permeable lens. And you are able to use a rather harsh cleaner with that. And it is necessary. And, again, if you don't thoroughly rinse that with water, then you'll get a reaction.

And, of course, there is a difference then between the sizes of the lenses and how long they're worn. So wearing the rigid gas permeable overnight is not that frequent. And with a scleral lens, potentially you can get more irritation, but it may be used overnight. So the separation of the two might be a good point. And probably we don't have a good alternative right now for tap water.

And then the other point that was brought up. Several of the keratitis cases that I've seen have been with tap water or with well water. We've isolated the amoeba from the pipes from the well, and we don't see that as a case contaminant that often with storage in the solutions.

DR. HIGGINBOTHAM: Any other comments? Questions to other Panel members? We have great expertise sitting around the table.

Dr. Jacob.

DR. JACOB: Jean Jacob.

I was going to go back to the comment you made about the paper that you read that said about the uptake, about the infections were related to that. What actually came out of that -- and I don't remember

seeing it in that paper that you referenced -- was that while those lenses did take up the preservative more and make it decrease in there, the reason why one of the major concomitant factors that they actually had an infection was that the polymer, the lubricating polymer used in the MPS solution was food, was actually a carbon, an extremely wonderful carbon source for the amoeba and for the other bacteria present. And so if you hadn't had that food source there, you probably could have still had that uptake and you wouldn't have had infection. So it's more than just one thing.

DR. HIGGINBOTHAM: Well, thanks for that clarification. So thank you.

Any other questions? Comments?

(No response.)

DR. HIGGINBOTHAM: Okay. Well, we'll have additional time this afternoon for Panel deliberations. So I think at this point we can start our lunch period. This is a site that doesn't have its own restaurant, so we wanted to give everyone the opportunity to go off site and come back at one o'clock.

So for the Panel, there is a buffet lunch that's available. Where is that? Magnolia Room. And which is obviously on this site, somewhere, but there will be signs. But for everyone, we'll be back here at one o'clock for our public hearing. And thank you for a rich discussion.

(Whereupon, at 11:13 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

DR. HIGGINBOTHAM: It is now one o'clock, and I would like to resume this Panel meeting.

We will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Ms. Facey will now read the Open Public Hearing Disclosure Process Statement.

Ms. Facey.

MS. FACEY: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement,

to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. HIGGINBOTHAM: For the record, all Panel members have been provided written comments received prior to this meeting. We have received one document from a Ms. Karin Gastineau, who is Senior Director of Global Regulatory Affairs for CooperVision. I have been asked to read her document for the record. So if you bear with me, I will be reading for the next five minutes or so. I'll try and make it interesting.

So this is dated May 6th, 2014. And, again, this is from Ms. Karin Gastineau, who is Senior Director of Global Regulatory Affairs at CooperVision.

"We write to provide comment for the FDA Ophthalmic Devices Panel on May 13, 2014. The Panel discussion will include topics such as microbiological and chemical preclinical testing, revision of preclinical test requirements to address patient noncompliance, modification of rigid gas permeable lens care regimens, and labeling for these devices. In line with these topics, we request that the Panel address the need for improved access to product labeling through electronic means.

"Background:

"Contact lenses and contact lens care products are used by more than 40 million consumers in the United States. As summarized in the

pre-meeting material, various studies regarding contact lens care compliance have shown that noncompliance is widespread despite the ease of use of multipurpose disinfection solutions. Adult wearers claim their noncompliance is due to lack of knowledge or being poorly prepared to care for their lenses.

"To assure compliance with lens wear and care regimens, and thus mitigate potential risks associated with bacterial contamination and resultant infection, the content, clarity, and availability of patient-directed labeling are important. Equally important is the timely availability of new Information regarding contact lens care which can be achieved through electronic means.

"Recommendation:

"We ask the Panel to consider the proposal that current product labeling for contact lenses may be made available electronically on the manufacturer's website, with abbreviated patient-directed labeling included with the product itself. By simplifying the information that is provided at the consumer level, a higher compliance level and improved patient safety may be achieved.

"It is proposed that the abbreviated patient-directed labeling be limited to brief and succinct proper lens care and handling instructions, including instructions to see an eye care practitioner if certain symptoms appear. Full product labeling would be made available electronically to the

eye care practitioner or consumer via the manufacturer's website or in paper form when requested.

"Regulatory Framework:

"Over ten years ago, Section 206 of MDUFMA amended Section 502(f) of the Federal Food, Drug, and Cosmetic Act to authorize the use of electronic labeling, rather than the traditional paper labeling, under specified circumstances. Patient-directed labeling is also recommended for devices such as contact lenses where consumers will benefit from the information pursuant to FDA's guidance document, Guidance on Medical Device Patient Labeling: Final Guidance for Industry and FDA Reviewers (2001). The guidance, however, states that the electronic labeling provision does not apply to prescription devices intended for home use (reference CDRH ODE/OIVD, Blue Book Memorandum #G03-1 dated March 31,2003).

"FDA contributed to the language appearing in Section 206 of MDUFMA and was a strong advocate for updating the statute to reflect the progress that has transpired with information technology. FDA anticipated the continuation of this technology revolution and introduced the term 'electronic labeling' rather than specifying computer discs, computer diskettes, computer hard drives, or the internet.

"Computer and internet use at the household level has changed greatly in recent years. In the 2011 US Census Bureau publication, 75.6% of households reported as having a computer. Similarly, internet usage has

increased to 71.7% of households in 2011."

It does say that, increase instead of decrease.

"Today, connectivity to the internet is likely to be even higher and can also be achieved via smartphones, mobile tablets, mobile applications, and other wireless devices. Thus, product labeling can be made available electronically using current technological advances.

"Conclusion:

"Product labeling is an important aspect of ensuring the safe and effective use of medical devices. Contact lenses are home-use devices, and patient noncompliance has been shown to be associated with lack of knowledge or being poorly prepared to care for their lenses. Thus, it is proposed that abbreviated patient-directed labeling be made available through electronic means, to ensure proper education on the care and handling of contact lenses. Full product labeling may be made available electronically to the eye care practitioner or consumer via the manufacturer's website or in paper form when requested."

"Respectfully submitted,"

Ms. Karin Gastineau, Senior Director, Global Regulatory Affairs, CooperVision.

Thank you for your attention.

For today's public hearing, we have received two requests to speak. Each scheduled speaker will be given 10 minutes to address the Panel.

We ask that you speak directly and clearly -- directly to the microphone, and clearly, to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. The Panel appreciates that each speaker remains cognizant of their speaking time. If you don't, we will.

The first speaker is Dr. Ralph Stone. Dr. Stone, please come to the podium. We welcome your remarks.

DR. STONE: Thank you, Madam Chairman. Thank you for the time to speak to the Panel.

Just to let you know, I am an independent researcher and a consultant to industry and to this field. I've been in the field for over 33 years, and I'm responsible for many of the products, especially in lens care development and this thing, for this whole area. I am an independent member of ANSI, and I am a U.S. expert on Working Group 9 for ISO and for this area.

For this presentation, I also have had additional advice from Dr. Mary Mowrey-McKee, who is also here. And if I get questions that I can't answer, I will ask her to help me out a little bit.

I am a consultant for Alcon, and I am a consultant for NovaBay Pharmaceuticals. I have no financial interest in any product or any current product. I did get a travel grant from Alcon to attend this portion, for part of my expenses. And I do not represent ANSI, the industry, or any professional group. These are my opinions.

For this presentation, I'm going to cover four areas quickly. I'll try to answer questions, if you have them, at the end.

Now, the first one I want to talk about is the status of the ISO Group 5 classification system, for which I am the chair, the project chair, at ISO. And so I will give you a little bit of that. I also want to talk to you about disinfection as it applies to the general disinfection of contact lenses, as it applies to things that we have tried to respond to at both ANSI and ISO. I want to talk a little bit about *Acanthamoeba* and some of the difficulties in dealing with *Acanthamoeba* as it applies to Questions 2 and 3. And, lastly, I'd like to talk a little bit about the chemical testing requirements as used as a marker organism.

Now, silicone hydrogels we were slow recognizing. We recognized they were different by 2002, okay, when the first publications came out of that. But we haven't done -- we have been really slow at reading them. These are very complex materials. They're biphasic, that is, they have two separate domains, the hydrophilic and hydrophobic domains, and we now to try to cover that all up with a surface treatment. So this makes this a very difficult area to deal with.

Now, I'm in agreement with the FDA, in their general classification that they have already proposed to you. There are some differences in what we have done at ISO and ANSI, and that is the fact that not just five, okay, that they're proposing; there are really nine groups. Okay,

four of them are novel groups at this point in time, as we have classified them. So we're classifying them by Hydrophilic Phase A, B, and C, and we're classifying them by Surface Modification Codes, which applies to each of the A, B, and C groups. Okay, today we do not have members in all of those groups.

But the difficulty is this: We have not addressed the silicone hydrophobic portion of the phases, and we don't have enough data today, or enough consistent data, to be able to classify them. I am the chair of that group, and I've been looking at these hydrophobic interactions with materials, especially with lipids and other materials, like some of the more lipophilic preservative systems, and there's not a clear picture of exactly how to classify those materials.

So we've come up and we have now this statement, okay, as a part of the current proposal at ISO, where we're looking at the fact that we need to now look at the hydrophobic phase. But manufacturers have got to be very cognizant of what they're doing and do a risk assessment in order to get the appropriate materials tested. And we think that needs to be included as a part of what the FDA proposal looks like.

Now, let me just go on beyond that to disinfection. In 2006 we started looking for -- in response to the problems of 2006, we came up with a method as a group. CLI was the leadership with that, and they'll probably talk more about that eventually. But that system, okay, of looking at lenses, lens

cases, in combination with care products, has been ongoing. A ring test was published for that in 2012. It's been applied to products, as was presented at ARVO. And this method is now being looked at as a draft international standard, okay, and it is up for vote at this point in time.

Now, this is an important piece because this covers a lot of the controversy that you were talking about earlier, in the fact that this is a method to look at the care products, the lenses, and the lens cases, and the efficacy of those products all at one time. So this, I think, is an important standard that the Agency needs to consider as a part of their arsenal.

Now, at the end of that and so forth, this method -- okay, Dr. McKee, at the end of her paper, talked about the fact that this method, used in combination with ISO 14729, which is the disinfection section, makes a robust way of us looking at the application of how we do disinfection for contact lenses.

In terms of *Acanthamoeba*, as a part of the FDA workshop, one of the things we talked about at that meeting -- and we had a difficulty because it's hard to get agreement on everything that we'd like to do in consensus. The only thing we got consensus on during that meeting was to look at encystment procedures. That was found to be related, okay, by the papers, that this was the only thing that separated the product that was recalled from other products with similar efficacy against *Acanthamoeba*.

They have gone through and looked at that as a standard, okay,

to see if we can now have a way of testing that. That has been through a ring test, that inter-laboratory testing, and it is now currently a part of our ISO/DIS procedures under vote.

Now, we're currently looking -- and this is what gave us the opportunity now to develop our ability to do *Acanthamoeba* testing. Not everybody can do that. That's not something that's easy to do, especially when you're dealing with cysts and trophs, two different forms of the organism, and multiple ways of making them interact with each other.

The experts in this area have been looking at that, and that is something that is the next step. They're now in the process of picking the right strain or strains and going through the disinfection process. But it's important, before we implement any procedure on how we're going to do that, to really come up with an appropriate inter-laboratory ring test to evaluate that process.

The big difficulty in dealing with *Acanthamoeba* and any of the more difficult organisms is that these disinfectants are close to their toxic levels. And we've always worked, as developers of these products, to look at the toxicology side.

In terms of my listening here today, I really think you need to also think about not only the impact on disinfection but the infection on toxicology, because one of the big things that most of us believe is you don't get infections unless you get a break in the cornea. And one of the ways to

get a break in the cornea is that.

The last area is uptake and release. The 2010 version, I worked on that. That looks at uptake, okay, and it looks at rate of uptake. Important is the rate of uptake. The second is the rate of release, because that is impacting on the system. We need to really look at these more carefully, and we need to make sure that we understand how -- we cannot look at the specification for final products in the same terminology as we look at uptake and release. Final product specification, the lower limit is when you start using that product. It's not what you do at the end. That is spent materials. And we need to think very carefully about how we could implement something that -- I caution you very strongly that we not look at that as a standard.

Just in summary, I've been a part of this process for a long time. I worked on the '84 and '87 guidance documents as a member of industry, and I would really advise, as a part of this stuff, that the Agency use ANSI and ISO and the industry and academia closely in developing a new guidance document.

Thank you very much.

DR. HIGGINBOTHAM: Thank you, Dr. Stone. And thank you for your comments.

We will now have a second comment from Mr. Peter Mathers, representing the Contact Lens Institute.

Mr. Mathers.

MR. MATHERS: Thank you. My name is Peter Mathers, and I am a counsel to the Contact Lens Institute, and I'm making this presentation on their behalf.

The Contact Lens Institute is a trade association of research-based manufacturers of contact lenses and lens care products. The members are Alcon, Bausch and Lomb, CooperVision and Vistakon, Johnson & Johnson VisionCare.

CLI is pleased to have this opportunity to comment on the questions raised by FDA for discussion at today's meeting. CLI agrees with the need to update the contact lens and care product guidance documents, and has previously provided recommendations to FDA on those documents. We hope to see those comments reflected in upcoming draft revisions.

Since these are Level 1 guidance documents, CLI also looks forward to the opportunity for CLI and other interested parties to comment on the Agency's release of specific proposed changes and updates before they are put into effect.

With regard to the specific questions that have been posed for this meeting, Question 1 asks about a proposed new grouping scheme for silicone hydrogel lenses. As elaborated in CLI's written comments, which you have copies of, the FDA proposal appears to properly categorize current silicone hydrogel lens products. However, CLI is concerned that the proposal

would group together future lenses that may perform quite differently.

For example, a hypothetical lens composed of a nonionic silicone hydrogel material with an oxygen plasma treatment would result in a group of V-Cm and low water content, nonionic, surface-treated lenses. However, this lens would contain an ionic surface that could possibly interact with some cationic preservatives. This lens would be in the same group as lotrafilcon but, due to the ionic nature of its surface, it might be expected to interact very differently with lens care solutions. To adequately capture the potential for interaction with lens care preservatives, it would be preferred that such a hypothetical lens be classified as an ionic if it contains any ionic monomers in either the bulk lens materials or as a result of surface modification.

There are other examples of hypothetical lenses that are either patented or otherwise being tested, which could result in similar confusion and which ought to be addressed, at least theoretically, in the general policies being adopted with respect to this grouping.

Question 2 raises the possibility of requiring that matched preservative concentration of a solution remain within the manufacturer specifications after use for a recommended soak time. CLI believes that it would be inappropriate to consider a solution to be incompatible with a lens unless the preservative concentration remains within the manufacturer specifications.

Disinfecting agent specifications are set by manufacturers as quality control and stability measures, applicable only to the testing of unused product. The antimicrobial efficacy of a solution is demonstrated by showing that it can achieve adequate disinfection when used according to reasonable and simple directions. Maintaining the biocidal concentration within product manufacturing specifications following use is not correlated to efficacy required to achieve disinfection.

There will be multiple problems with requiring solutions to remain effective after they have been used. Designing solutions to be effective when reused is not a proper path to achieving safer contact lens wear. Retained contamination with material from handling lenses that are not rinsed from the lens case after each cycle will introduce uncontrollable risk. Resistant fungi, biofilm, and *Acanthamoeba* will be more likely to increase with solution reuse, an issue that FDA needs to avoid rather than condone in any form.

Moreover, lens care products developed to account for the numerous forms of noncompliance could require levels of biocide substantially in excess of those in current products that would be unsafe for patient use.

Solution effectiveness should be assured through microbiological test methods that account for real-world conditions but do not assume the failure to use the solutions as directed. Even solutions that

might under some conditions be effective if reused will likely fail under different conditions and will likely fail if they're used twice or three times.

Moreover, requiring solutions to be effective beyond their intended single use, even if feasible, risks increasing complacency and concomitant increases in the risk of serial reuse, defeating any possible advantage of imposing such a requirement in the first place.

Therefore, CLI strongly recommends that the risk of user noncompliance be addressed through appropriate labeling and patient education. For this purpose, CLI and FDA have been actively involved in the planning and execution of the CDC Healthy Contact Lens program, funded by CLI, to enhance patient and practitioner awareness of the need for proper contact lens wear and care and careful compliance with product instructions.

With respect to Question 3, industry and FDA began work on new methodology for disinfection efficacy testing in 2006. These efforts resulted in the development of an internationally tested methodology for the evaluation of the antimicrobial efficacy of contact lens care solutions in simulated use conditions. These tests involved the inoculation of solutions with test organisms in a lens case with a lens and standard organic soil during minimum and longer recommended soak times. As a result, the disinfection efficacy of the lens care product, using this method, should more closely correlate with the disinfection efficacy achieved during actual use.

CLI supports the adoption of this methodology, now being

voted on at ISO as Standard 18259, as a significant enhancement of the methodology for evaluating contact lens disinfecting solutions, in conjunction with existing ISO Standard 14729.

With respect to *Acanthamoeba* testing, Dr. Stone already addressed the challenges that are represented there. In addition to what Dr. Stone said, I want to stress concern with the possibility that FDA is considering requiring a disinfection test method that would use cysts of *Acanthamoeba* produced by growth on agar seeded with bacteria. CLI is concerned that use of such an enriched growth medium would likely result in challenged organisms with such high resistance that they could not differentiate between solutions.

Also, use of bacteria-seeded plates would result in contamination of the cysts with bacteria. Studies show that contaminating bacteria may compete with *Acanthamoeba* for the biocide in a disinfecting solution, thus not giving a true kill rate for *Acanthamoeba* and confounding any study results.

Regarding the use of water in RGP lens care regimens, as previously communicated to FDA, the members of the Contact Lens Institute agree that it would be optimal to remove tap water rinse from RGP lens care regimens. The CLI member that distributes contact lens care products dedicated to RGP use is working with FDA on options for efficiently removing tap water from all lens care regimens described in the labeling for RGP lenses

and lens care products.

Finally, the FDA background document that was circulated in conjunction with this meeting notes that FDA is considering re-categorizing daily wear contact lenses as permanent contact devices. The members of CLI are unaware of an identified risk of daily wear lenses which would warrant such a change in classification. CLI is also not aware of the impact FDA may believe such a classification change may have on the testing or clearance requirements for daily wear lenses.

We note, however, that such a change would appear to contradict FDA's 1994 reclassification of daily wear lenses from Class III to Class II. That reclassification was based on a statutorily recognized lower risk of daily wear lenses compared to extended wear lenses, which remain in Class III. Daily wear lenses are, by definition, worn for only part of each day. Classifying daily wear lenses as permanent contact devices could set a precedent for similar classification of other device products which are not worn continuously, despite there being no evidence of a problem warranting such a change and no evidence that there has been any consideration of the potential significance or impact of such a change.

For these reasons, CLI looks forward to further elaboration by FDA regarding a rationale for considering the reclassification of daily wear lenses as permanent contact devices, and an assessment of whether such a change would be consistent with the least burdensome requirements of the

device statute.

CLI also looks forward to continued cooperative dialogue with FDA, and to further advances in the testing and approval of safe and effective contact lenses and lens care products.

Thank you very much.

DR. HIGGINBOTHAM: Thank you, Mr. Mathers. And thank you for your comments.

Does anyone else in our audience wish to address the Panel at this time? If so, come forward to the podium and state your name, affiliation, and indicate your financial interests. You will be given three minutes to address the Panel. Is there anyone who would like to express an opinion or a comment?

(No response.)

DR. HIGGINBOTHAM: Okay, thank you. I see no one rising from their seats. I now would like to state that the Open Public Hearing is officially closed and we will not take any additional speakers. However, the Panel does have the opportunity to ask questions of either Dr. Stone or Mr. Mathers, our two public speakers.

Any questions, on behalf of the Panel members, for our two speakers?

Yes, to whom are you expressing, Dr. Flynn?

DR. SZCZOTKA-FLYNN: Dr. Stone.

DR. HIGGINBOTHAM: Dr. Stone, would you mind coming to the podium? Thank you.

DR. SZCZOTKA-FLYNN: Hi, Dr. Stone. Could you help me understand the difference between ISO 18259 and the ring test described by Mowrey-McKee in *Eye & Contact Lens* (2012) and the proposed FDA preservative uptake tests?

DR. STONE: The first two I think are easy. The 2006 developed a base method for us to be able to look at what the impact of lens cases and lenses were on the disinfection process. That was subjected with a model compound, okay, a model solution that we developed, okay, and that was developed because we developed it to have a risk of failure, so to have low results.

We went through a ring test with that, okay, in which we had a series of laboratories, mostly in the United States, who participated in that ring test to make sure that everybody could do that test the same way. We included organic soil. Organic soil is yeast cells, okay -- and activated by heat -- combined with serum so it could reproduce something that looked a little bit like what you would see in tears in the eyes.

We went beyond that. That's now been incorporated in a draft standard. Okay, that's the next thing. It was proposed at ANSI and ISO as a draft standard. That now is the base standard, okay, based on that ring test with modifications or a few -- mostly editorial modifications for that process.

DR. HIGGINBOTHAM: Great. Dr. Szczotka-Flynn.

DR. SZCZOTKA-FLYNN: In the ISO 18259 proposed standard, would they also be using that same test disinfection solution or would you be using --

DR. STONE: That was just used as a model for us to develop a process. We're looking at the process to make sure laboratories -- one of the most important things we do in trying to deal with U.S. and international standards is to do inter-laboratory testing. We try to get as many laboratories in the United States and around the world to be doing these standards so that we get the appropriate ability, okay, to get reproducible results so when the FDA or any other regulatory agencies look at the data, they can be reasonably assured that people can get the results around the world the same way.

DR. SZCZOTKA-FLYNN: So if the test was done, it would use the actual solution in question?

DR. STONE: It's been done. In fact, the other paper that I referenced in the slides, okay, is a poster that was done a year ago at ARVO, and it looked at the uptake and it looked at the disinfection efficacy under that standard or that series of products on the market today. And that's the Gabriel reference.

DR. HIGGINBOTHAM: Dr. Joel Sugar.

DR. SUGAR: Joel Sugar.

You may not have answered this, but you said that the disinfectants are close to the toxic level and the typical PHMB level is 0.0001%. Clinically, when we treat active *Acanthamoeba* keratitis, we use 0.02%. So that's 200 times the concentration.

DR. STONE: When you're treating an active infection, okay, there's always a risk/benefit in there.

DR. SUGAR: May I finish my question, please?

DR. STONE: Yes.

DR. SUGAR: We see patients on that on an hourly -- 0.02% -- hourly for sometimes weeks to months without toxicity. And sometimes we go out to 0.04% or even 0.06% in certain situations. Can you tell me what the maximum tolerated level in a contact lens solution is clinically for PHMB?

DR. STONE: In research that I've been involved in over the years, okay, we found that if we -- in contact lens care products, if we get much above 1 to 1.5 parts per million, we start seeing a clinically meaningful event. Okay, roughly between 1 to 2 parts per million. Once we go above that, we start seeing meaningful toxic reactions with many of these products with PHMB.

DR. HIGGINBOTHAM: Any other questions for Dr. Stone, who's at the podium?

Dr. Reller.

DR. RELLER: Dr. Stone -- Barth Reller -- can you explain the

rationale for selecting, if I recall your statement, killed yeast cells and serum as a surrogate for "soil"?

DR. STONE: This has historically been done since I can remember. I don't now remember what the original -- maybe Dr. McKee can answer.

UNIDENTIFIED SPEAKER: FDA. It was the FDA who recommended it.

DR. STONE: It came out of the FDA many years ago, okay?

DR. RELLER: No, I understand that. But what I'm seeking to comprehend is --

DR. STONE: What we've tried to do with most of these systems is to now have a reproducible -- something we could make over and over again the same way.

Now, if we don't -- and the question asked before, why we use salines, okay, ISO saline is the one standard saline we most likely will use for other things. It's really designed to be a balanced saline, that it is balanced by pH at 7.4. It's balanced for osmolarity around 3.06, okay, which is what we think the tears are. And so when we try to do testing where that doesn't include the hard parts of the -- and I would say that the proteins and lipid portions of it, what we try to do is balance it by pH and osmolarity, which will affect parameters and some of the other pieces of what we look at.

DR. RELLER: So is the presumption that this mixture is going to

simulate what the preservative might encounter in actual use, so it would be a reproducible surrogate for what would be encountered in a patient's use of the preservative?

DR. STONE: It's the spoliation piece. It is the lipid protein cell debris that you'd expect to find.

DR. RELLER: I see nodding in the audience that that conceptually is what the intent was.

DR. STONE: That's the basic piece of the original intent, was to now have something to model with.

DR. RELLER: And I was not privy to how -- what I'm really getting at is what the empirical basis is for it resembling what is encountered.

DR. STONE: No.

DR. RELLER: It's very nice to have something that's reproducible, but what does it mean is what I'm getting at.

DR. STONE: All it does is to bulk proteins and lipids and ingredients that could inactivate some of these disinfecting systems. I mean, we can see some materials being decreased by components of solutions.

DR. RELLER: So I understand that this relieves anxiety that exposure to this is not affecting A, B, C, D preservative solution. But does it mean anything related to what patients actually do? I mean, there may not be an answer. I just want to know whether it's something that has been continued, but does it mean anything?

DR. STONE: All we can do is model these things, okay? I guess the idea is reasonable assurance. We can be reasonably assured that we are trying to now build a model that reasonably assures safety and disinfection.

DR. RELLER: Thank you.

DR. HIGGINBOTHAM: Any other questions from the Panel to Dr. Stone?

(No response.)

DR. HIGGINBOTHAM: Okay, thank you, Dr. Stone.

Mr. Mathers, would you mind joining us at the podium, please? And Dr. Joel Sugar has a question for you.

DR. SUGAR: You made the comment that growing *Acanthamoeba* in the test circumstance that Dr. Shoff and Malvina presented in the literature did not mimic reality, that is, that it should grow on non-axenic media with organisms. Yet, in the contact lens case, presumably there are bacterial organisms and many *Acanthamoeba* in the wild have symbionts within them, that is, they engulf live bacteria. So it doesn't seem to make sense to me to not use a bacterial-containing test system. So I disagree with your statement, I guess.

MR. MATHERS: Okay. Well, thank you. Can I ask for an opportunity for someone else to comment on that?

DR. McKEE: Can I comment?

MR. MATHERS: You would be happy to. I would be happy, too.

Mary McKee will comment on your comment much better than I will.

DR. McKEE: It's our concern, with growing the cysts --

DR. HIGGINBOTHAM: Excuse me, would you state your name and affiliation?

DR. McKEE: Oh, I'm sorry.

DR. HIGGINBOTHAM: Thank you.

DR. McKEE: I'm Mary Mowrey-McKee. I'm a consultant for Alcon. And we're concerned that growing the cysts on bacterized cultures will, one thing, create very resistant cysts so that when you're testing different contact lens solutions or when you're developing a new solution, you're not going to be able to tell the difference between whether you're killing or not, because they will be so resistant that you won't be able to differentiate between the different formulations.

I mean, this was true when we had *Aspergillus fumigatus* as the fungal mold challenge organism. You couldn't differentiate between products. So it was sort of useless as far as trying -- if you're trying to kill mold spores, you had difficulty in knowing what formulation was better because nothing would kill them. They were difficult to kill.

The other thing. We are concerned about contamination of the resulting cysts with the bacteria. It has been proven in the literature that the bacteria can compete with the *Acanthamoeba* for biocide. And so you would

decrease the rate -- possibly decrease the rate of the disinfection, the killing of the *Acanthamoeba*, not yet a true rate for killing the *Acanthamoeba*. And you also would confound the results. It would be difficult to analyze your data. If you have multiple organisms growing in a culture, it's harder to determine how many were killed of this or that.

DR. HIGGINBOTHAM: Dr. Sugar.

DR. SUGAR: Joel Sugar.

It seems, though, that this better mimics the clinical circumstance.

DR. McKEE: Yes, but if it creates a situation where it gives you meaningless results, I don't see what the point is. You know, if you were making the cysts so resistant to being killed by disinfecting solutions -- especially considering what Ralph pointed out, that if the disinfection process -- if you have to increase the concentration of your biocide or use different, more potent biocides and they get absorbed into the lens and you put that on an eye, you can compromise the epithelium and actually maybe create the situation where you actually create a microbial infection. You know, it's counterproductive, the way we are thinking about it, to create the most resistant cysts.

DR. HIGGINBOTHAM: Dr. Jacob.

DR. JACOB: I have a question regarding what you were just discussing.

DR. McKEE: Okay.

DR. JACOB: So in the wild --

DR. McKEE: Um-hum.

DR. JACOB: -- in your wild eye here, the *Acanthamoeba* and the bacteria that are present, they exist differently than if you co-cultured them together. So you're saying they're going to develop a resistance, and I think the point is, if they were co-cultured together, they're going to become resistant.

DR. McKEE: Oh, they are.

DR. JACOB: But they don't become resistant in the wild as they're growing together? That's my question.

DR. McKEE: Well, I would think there are different concentrations. I'm not really sure of that, to be honest. In your eye, if you had a trophozoite in your eye and you have some bacteria there, are the bacteria present there going to produce more resistant cysts? For one thing, the concentration of bacteria, I would think, in your eye, even most wild-type situations would not be as high as if you have bacteria growing in a high concentration on the agar.

DR. JACOB: Okay.

DR. McKEE: So you have a much higher concentration of the bacteria in this proposal --

DR. JACOB: Oh, I see.

DR. McKEE: -- to grow on agar supplemented with bacteria.

DR. JACOB: Okay, thank you.

DR. HIGGINBOTHAM: I have a question. This is Dr. Higginbotham. And I'm not sure if it should be directed to you or Mr. Mathers.

But on page 5 of 9 of the document from the Contact Lens Institute, the first bullet says, "The acceptance criteria should therefore continue to be based on disinfection efficacy of the solution and not the preservative concentration." I just would like you to expand on that a bit. Wouldn't it be reassurance if you had the same preservative concentration and not solely depend upon the disinfection efficacy?

DR. McKEE: Well, I think it's unreasonable to assume that you are going to have these biocides that are typically positively charged, because the cells that you're trying to kill are negatively charged. So you want there to be an interaction between the positively charged biocide and the cell surface that's negatively charged.

DR. HIGGINBOTHAM: This is Dr. Higginbotham.

It has to do with the preservative concentration versus solely depending on the disinfection efficacy.

DR. McKEE: It's really the disinfection efficacy that is important. It's how much is killed, not just the uptake. Because one thing, if you look at the paper, the paper that was published on the AEEMC method,

the ring test, and you look -- we did measure the chlorhexidine uptake, and the uptake is slower, uptake by the lens, the rate is typically slower than the rate of kill of the organisms. And, in fact, I can point to an example.

There was a solution on the market by CIBA Vision. AQuify was the name of it. The soaking time was five minutes. In five minutes you would see, frequently, kill of all three bacterial species and the uptake in five minutes would be miniscule. So if you left the lens in that solution, you know, how long would you leave it, 24 hours? You know, the kill time was five minutes, the soak time was five minutes, and so the uptake in five minutes would be very small.

Does that make sense?

DR. HIGGINBOTHAM: Yes. Dr. Ahearn.

DR. AHEARN: Is it possible that there would be multiple factors that would, say, affect the troph or the cyst that are present in the solution?

DR. McKEE: Oh, yeah. You mean multiple chemicals?

DR. AHEARN: Yes --

DR. McKEE: Yeah, yeah. Oh, pH. Yeah, yeah, the chelating agent EDTA is commonly used. Or you could have citrate as another part of the buffer, but that's also a chelating agent that can affect the efficacy of the solution. I mean, I think you pointed this out earlier this morning, that it's a combination of factors in these solutions. These solutions are rather complicated. When you formulate them, you're considering a number of

different ingredients that have different purposes.

But I think one perfect example is there are a number of contact lens care products containing PHMB. They're all formulated at 1 ppm; however, they have different efficacies, they have different uptake into lenses, and that's due to the other ingredients that are included in these formulations.

So it's not just the biocide. What we have identified is the active ingredient, but there are other ingredients. I mean, there is even osmolality that can affect the killing rate, pH. There are a lot of factors. Detergents, surfactants.

DR. AHEARN: You mentioned the rates. Were the rates different?

DR. McKEE: The rates?

DR. AHEARN: Yeah, the kill rates or the effects of the different components in there.

DR. McKEE: Yes, yes. When you formulate a contact lens care product, you look at different components and different concentrations of those components. You do DOEs, and it can be quite elaborate to get the best, the most efficacious solution while maintaining a low potential for irritation or toxicity.

DR. HIGGINBOTHAM: Dr. Huang, do you have a question?

DR. HUANG: Andrew Huang.

Dr. Mowrey-McKee, I have a question. When we are using any of the antimicrobial agents, we're often confronted with the in vivo and in vitro in our efficacy discrepancy between the testing. So when you are proposing using various methods, these are presumably all in vitro testing?

DR. McKEE: Um-hum.

DR. HUANG: So how does that translate into the in vitro situation? Because, especially in the *Fusarium*, we all know the antifungal agent, predominantly it's ineffective in in vitro situations. However, we do find the clinical therapeutic effect in in vivo situation. So I don't know if any of this testing will have a direct impact in terms of the disinfectant capability.

DR. McKEE: Well, I would say, when you're developing an assay for anything, microbiology, for example, you need to take representative organisms. You know, there are what, thousands, millions of different microorganisms in this world, but you can't test all of them. So you take representative organisms and use those as challenge organisms, the same way you do an in vitro method, you know, such as we did with AEEMC where we tried to simulate patient use.

So the way microbes get on the contact lens typically is by patient handling. They touch them with their fingers. And there are papers showing this.

So we had the lens put in the lens case, as you would do, inoculate the lens before you add the solution, the disinfecting solution, with

the challenge organism in organic soil and allow it to have a contact time of 3 to 10 minutes, and then you add the disinfecting solution and incubate it for various periods of time and analyze it.

DR. HUANG: No, I appreciate the empirical rigidity in terms of that. But the problem is, even in real life, we don't really know what's the colony count of any organism that is causing the infection, and we don't really even know how long the organism has been in contact with the solution or with the patient or even on the patient's skin, if it was really from the finger. So how do we standardize that, and in order to use those standards to extrapolate into most of the contact lens care products?

DR. McKEE: Well, I think that's what we have tried to do, take the best parameters that we know about. They're available to us to try to simulate what happens in vivo. And we've done studies. I mean, industry has done studies looking at what types of organisms are found in lenses if you just handle them. If you remove a lens with your fingers, if the lenses are removed from the eye aseptically, you know, which kinds of bacteria, which kinds of fungi, how many per lens? And we've done a lot of studies in that order, trying to understand sort of what does the disinfecting solution see, what is on that lens typically, and as I said, try to pick challenge organisms that represent the various categories of microorganisms that may be contaminating contact lenses and that could cause -- you know, that could be pathogenic to the eye.

DR. HUANG: In general, I agree with your assessment. I mean, we use the best model there is. But you do try to simulate as close to the gritty eye in vivo situation. You know, taking Dr. Jacob's previous comments, that using the bacteria culture with the *Acanthamoeba*, because in real life, outcomes and power has certain, you know -- no more organism in there. And then there's also some skin flora on a lid or our hands. And so why are you excluding the microorganism in your amoeba culture?

DR. McKEE: Well, does anybody else have a comment to that? I don't really have anything more to say about that than what I've said. I don't know -- I mean, we've done studies. I don't really know what else we can do to understand exactly what is happening in vivo every time a person uses a contact lens.

DR. HIGGINBOTHAM: Well, thank you.

We have two questions -- three questions. Dr. Reller, Dr. Zabransky, and then Dr. Szczotka-Flynn.

Dr. Reller.

DR. RELLER: Barth Reller.

I'm not obsessed with this word "soil," but I'd like to come back to it.

(Laughter.)

DR. RELLER: Perhaps my interest in the word, because words are important, is getting at the key ingredient. And it's also colored by the

experience that I worked my way through college, working as a soil chemist for the Soil Conservation Service, and I did many quantitative chemical analyses of soil. And we looked for magnesium and iron and aluminum and many components that were -- and I recognize, as an avid gardener, the importance of organic matter in soil. But soil is very complex.

DR. McKEE: Um-hum.

DR. RELLER: Now what I'm getting at is that -- and I appreciate the complex interaction of the preservative. And if one seeks to tease out one component or another without considering the interactions, it seems to me that that's a dangerous path, as opposed to looking at the total effect of what the preservative is in a reproducible test methodology to assess its overall effectiveness. Okay?

DR. McKEE: Yes.

DR. RELLER: So in trying to look at the big picture of the end result as being the most important in the challenge milieu, what is the most important component of the soil? Is it the mixture of inorganic components of the soil or is it -- as in a paper that was passed by my colleagues, that sort of implied that this was the genesis of using the *Candida* serum mixture as a surrogate for protein contamination. Or is it protein plus lipids? And if so, why not call it what it is? So I can appreciate that the effectiveness of a microbicide or something that's microbial static will be affected by organic material.

DR. McKEE: Yes.

DR. RELLER: That I appreciate fully.

DR. McKEE: Um-hum.

DR. RELLER: It's easier to infect individuals if certain things are present in addition to the "pathogenic organism." That's well known.

DR. McKEE: Um-hum.

DR. RELLER: There's much data on that point. So what is the component that is most critical that one is seeking to assess the effect on the total product? Is it protein? And if so, when I call it protein, if it's a protein lipid mixture, why not call it a lipid protein effect on what you are measuring as opposed to a word that is so ambiguous, at least to those who are looking at this freshly?

DR. McKEE: Well, I believe the term "soil" has been used for a number of years in doing other microbiological evaluations, like catheters -- yeah, catheters and other plastics. I think the term "soil" resulted from its use in other applications.

DR. RELLER: But does everybody use the same soil?

DR. McKEE: No. No, I have not worked in another industry to know that exactly. I just know soil is used. I don't know --

DR. HIGGINBOTHAM: I think it's good that we have this on the record, but it is an important point. So I'd like to get to our three other -- our two other questions, Dr. Zabransky. But hold that thought for the Panel

questions because it is an important comment. Dr. Zabransky and then Dr. Szczotka-Flynn.

And actually, Dr. Mowrey-McKee, would you like reinforcements at the table here, because you've been at the podium for a bit.

DR. McKEE: I don't care. This is okay. Unless you want me to go.

(Laughter.)

DR. HIGGINBOTHAM: I was going to invite your colleagues, Dr. Stone and Mr. Mathers, to sit at the table, if you'd like, just so we have a chance to have the full benefit of your wisdom.

Dr. Zabransky.

DR. ZABRANSKY: I don't really have a question. My comment here is the fact that several of us here that are laboratorians are used to the word "in vitro." And I'm most familiar, as is Dr. Reller, with antibiotic testing. And it's a prediction of what we hope will happen in a clinical setting and that's why we have a standardized test and that's what they're trying to develop here.

So whether or not -- and I agree, I don't like the term "soil." When I first read this, I was thinking of some kind of a mixture of humus from my garden that was sterilized perhaps. But these are standardized tests, and that's the purpose of the ISO and ANSI and all of the rest of it. And just like

antibiotic testing, it's just a prediction of how it's going to react in the human setting.

DR. HIGGINBOTHAM: Thank you.

Dr. Szczotka-Flynn.

DR. SZCZOTKA-FLYNN: Thank you.

I just wanted to see if I understand the CLI viewpoint. So can you correct me if I'm wrong? So CLI doesn't believe that preservative uptake tests are valid simply by looking at preservative concentration. But rather you propose a ring test because it looks at the survivors left in these contaminated solutions after a certain soak time, therefore showing us what the residual efficacy is of that solution after a certain soak time. And the FDA papers show us that preservative concentration and efficacy are highly correlated, I believe. Do I understand that correctly?

DR. STONE: Let me just take you back, okay? The test method --

DR. HIGGINBOTHAM: Dr. Stone --

DR. STONE: Yeah?

DR. HIGGINBOTHAM: -- your name again.

DR. STONE: Oh, Ralph Stone.

DR. HIGGINBOTHAM: Yes, thank you.

DR. STONE: The method that I talked about and they talked about in terms of using lenses, lens cases, okay, and organic soil -- okay, I'll at

least give you organic soil. That whole idea was, that is a better representation of the process. Okay, we tested it in a ring test to validate the procedure. Okay, that's what that was done for. It's to be applied to new products or product test mechanisms. That is the critical piece of that thing. We think it's a better representation -- combined with the efficacy of the solution itself, as being a better representation of the disinfection efficacy of a product.

The difficulty with using uptake and release is that uptake and release are not necessarily with all things. They don't come out at the same rates, okay, and they may or may not be correlated with efficacy per se, microbiological efficacy. Okay, if we're going to use that as a methodology to set lower limits, okay, and we start saying that the lower level of the manufacturer specification is the appropriate level, I have a lot of difficulty because I can sell that product in the marketplace until it hits that lower level. So I could have a product legally going to the marketplace at that concentration level. That assumes that the disinfection process takes up, in terms of its interaction with lenses, with lens cases, okay, or just air. Okay, nothing can be lost, which is not a realistic standard for anybody to be proposing. And I'm going to be honest here. I have no idea what that lower limit number ought to be. And the only way I know to try to evaluate disinfection efficacy is using microbiology.

DR. HIGGINBOTHAM: Great. Dr. Mowrey-McKee, do you have

a comment, because you were questioning about the contact lenses, the two positions.

Thank you, Dr. Stone, for your comment.

DR. McKEE: Well, I agree with what Ralph just said. I mean, that's basically it. We agree that --

DR. HIGGINBOTHAM: Could you speak into the microphone, please --

DR. McKEE: Oh, I'm sorry.

DR. HIGGINBOTHAM: -- Dr. Mowrey-McKee? Thank you.

DR. McKEE: Okay. Disinfection efficacy should be determined based on using a microbiological method, and I think it should simulate patient use. And what we're talking about is normal patient use according to the regimen, the directions. You're not putting it into a solution that's already been used. You know, we're talking about putting it into a fresh solution. And I think it makes the most sense to measure the efficacy based on a microbiological method, partly because of what I said before, that the rate of uptake of the preservative by the lens may be slower than the kill rate.

So that's really what's important. You put the lens in the solution with the bugs, and does it kill or does it not? And there might be some uptake over whatever period of time the person chooses to put it in there. But if everything is killed in the first 5 or 10 minutes or whatever, you know, what does uptake over 24 hours really mean in that situation?

DR. HIGGINBOTHAM: Okay, thank you. Dr. Joel Sugar has a question. But, Dr. Mowrey-McKee, are you representing the Contact Lens Institute officially?

MR. MATHERS: As far as I'm concerned.

DR. McKEE: Okay.

(Laughter.)

MR. MATHERS: Pete Mathers.

But I could elaborate on that answer.

DR. HIGGINBOTHAM: Okay. I just needed that clarification for the record. I've been asked to make sure that we understand your clear affiliation for the record. Is it the Contact Lens Institute?

DR. McKEE: Yes.

DR. HIGGINBOTHAM: Yes. Thank you.

And, Mr. Mathers, you have an additional comment, because in the future we can only have one of you at the table, okay?

MR. MATHERS: Okay. Well, I'll stand.

(Laughter.)

DR. HIGGINBOTHAM: Or one of you present.

MR. MATHERS: No, I just wanted to clarify that the comment that CLI made on the subject is that requiring a level of preservative or biocidal ingredient to remain in the solution after the soak time is over is establishing an artificial floor which doesn't necessarily correlate at all to the

efficacy of the solution which you've just used up. The level of preservative could be going down because it's taken up by the lens. It could be going down because you have a self-neutralizing solution arrangement that, in order to not be toxic, the level of the biocide is designed to go down. You could have a solution where the biocide is taken up by the bacteria as you're killing it and it's used up.

To require the preservative to still be there after the product has been used, the only rationale for that would be concerning that it's going to be reused. And that we object to because it's against the instructions for use, and we warn all users not to reuse or top off their solutions. So the ability to reuse the solution and expect it to work again should be irrelevant to whether you can -- whether the solution is effective. And so that's the CLI concern.

DR. HIGGINBOTHAM: Thanks for that clarification.

Dr. Sugar, do you have a question?

DR. SUGAR: Joel Sugar.

Pardon my ignorance, but what is the ring test?

DR. STONE: What is a ring test? A ring test, we use it as a general terminology for inter-laboratory testing of a method. So when everybody does a method with supplies supplied by a central unit, okay, everybody does the testing according to procedures written, and we evaluate can they get -- can all the participants get the same result out of that method

to validate the efficacy of that test.

DR. SUGAR: So you're not suggesting that it is a specific test?

DR. STONE: No, no. It is a way to now validate the test procedure. This is critical, as we're trying to now develop test methods that can be used around the world, that can be supplied to governments around the world to assure the safety and efficacy of products.

DR. HIGGINBOTHAM: Great. Any final questions for our public speakers?

Yes, Dr. Leguire.

DR. LEGUIRE: It's obviously absorption of the preservative, whatever is the major concern here, and efficacy of the solution to do its job. I was just curious about -- I have two questions, actually.

The saturation. Is there a point of saturation of the contact lenses, regarding the preservative -- or any component for that matter, I guess -- where it's no longer an issue that it is 8 hours, 12 hours, whatever?

DR. STONE: When you look at uptake --

DR. HIGGINBOTHAM: Dr. Stone, thank you for your comment.

DR. STONE: I'm sorry. I apologize.

When you start looking at uptake, these occur. When we first started looking at uptake we looked at the plateau, that is, the top end. How much could mostly go in no matter how much solution you had? Okay, we said that that was no longer really relevant to what we wanted to look at. In

2010 we wrote that standard to say let's see how fast it goes in, because that's what's most important for the time frames we're looking at. Usually it takes several days, okay, with the same conditions, that is, unlimited conditions, in order to see the maximum go into these lenses. So it goes in for a numbered period of time, okay?

DR. LEGUIRE: Larry Leguire.

That obviates the need for my second question, then.

DR. HIGGINBOTHAM: Any final questions for either Dr. Stone or Dr. Mowrey-McKee or Mr. Mathers?

(No response.)

DR. HIGGINBOTHAM: I thank you for your comments and enriching our conversation. Thank you.

DR. McKEE: Thank you.

DR. HIGGINBOTHAM: At this point I would like to invite Dr. Hampton and Dr. Cope to the table, in case any of our Panel members would like to ask the FDA additional questions, or CDC, who is our guest today, or if either the FDA or the CDC would like to add additional comments to their previous comments.

Dr. Cope, I understand that you have a comment you'd like to add.

DR. COPE: Yes, I wanted to follow up with Dr. Bressler's question that I was not able to answer earlier. There was no Bonferroni

correction done for that multivariable logistic regression.

DR. BRESSLER: Thank you.

DR. HIGGINBOTHAM: Any other Panel members have an additional question for Dr. Cope?

Yes, Dr. Huang.

DR. HUANG: Not for Dr. Cope. Sorry.

DR. HIGGINBOTHAM: Oh, okay.

DR. HUANG: For Mr. Brocious. Jeffrey? Yeah. In your presentation, you know, you mentioned that in the previous guidelines for testing, there were some deficiencies in the soil, the various materials, the lens materials. The extended soaking time in the evaluation of amoeba was not included. But in 2009, the care product microbiology workshop had additional recommendations.

But from my reading, I wasn't quite sure if there was any additional measure taken to ensure the antifungal activities about these preservatives, because it seemed to be lopsided towards the amoeba evaluation. And we've spent a lot of time discussing the amoeba. But the antifungal aspect, I don't know what's in your future consideration or anything.

DR. HIGGINBOTHAM: Was there a particular slide that you had in mind?

DR. HUANG: Yes. This is Andrew Huang. This is slides from 67

to 69.

MR. BROCIOUS: So the question you're asking is including fungal studies --

DR. HUANG: Yes.

MR. BROCIOUS: -- in addition to *Acanthamoeba*. I mean, that's something that we could -- you know, we definitely will consider for the microbiology workshop. I don't think the workshop will be explicitly just *Acanthamoeba*, but yes, it's open for further microbiology discussion.

DR. HUANG: This is Andrew Huang again.

The previous one is already including the *Fusarium*. But I was just wondering, since we have touched upon the *Aspergillus* and other unusual -- even yeast, you know, the *Candida* infection -- and it wasn't included in the original standard five typical organisms. So I don't know if that should be a consideration or not.

MR. BROCIOUS: Jeff Brocious.

Yes, certainly. I mean, we only looked at *Fusarium*. We didn't actually look at *Candida* or any *Candida* species. But yes, that is something to be considered, absolutely.

DR. HIGGINBOTHAM: Any other questions from the Panel?

Yes, Dr. Eydelman.

DR. EYDELMAN: There are two points of clarification that I just asked my staff to make. Dr. Hampton has two points to make, and then I

believe Dr. Green has a point as well.

DR. HAMPTON: Hi, this is Denise Hampton.

So with respect to the point that was made by Mr. Mathers regarding reclassification of the contact lens, the last point that he made, I just wanted to clarify and apologize if that wasn't clear in the Executive Summary.

The statement that was made regarding that classification is for biocompatibility testing. So we don't intend to reclassify contact lens devices per se or at all, in terms of biocompatibility testing. Because of repeated wear on the eye, we want to reclassify that contact classification as a permanent mucosal-contacting device. So I just wanted to make that clarification in terms of biocompatibility testing, not reclassification of the device.

The second point. Regarding the two standards in development that have been discussed by Drs. Stone and Mowrey-McKee, neither of those standards have been published at this time. They're under development. So in terms of thinking about recognition, as Dr. Eydelman referred to earlier, it's premature at this point to talk about that topic.

Now Dr. Green.

DR. EYDELMAN: Dr. Green.

DR. GREEN: Angelo Green, FDA.

So I'd like everyone to still refer to Slide 64, and I just want to

make one quick point. So the purpose of this new test is to identify potential lens solution preservative incompatibilities, as our research and others have shown that certain lens materials can absorb too much preservative from the solution to compromise disinfection efficacy. While it's related to disinfection efficacy testing, it's not the same as a disinfection efficacy test that will still be performed.

Now, the initial criteria, which will be grounded in microbiological test criteria, ISO 14729, is that the preservative concentration should not be lowered below the concentration limit set by the manufacturer. But we do have an alternate criteria where sponsors can test the lens, the solution, and the microbes to account for differences in preservative uptake rates. Now, the outcome of that is that the lenses, the incompatible lenses, will be listed in the labeling. And, again, this is not disinfection efficacy testing. This is an incompatibility test where the lenses would be listed in the labeling.

DR. HIGGINBOTHAM: Yes, Mr. Pfleger.

MR. PFLEGER: So I think we need to understand why you're calling it incompatibility. So, obviously, I think everyone understands the incompatibility from the standpoint of, if it changes the physical dimensions, base curve, diameters, et cetera, that would be an incompatibility problem. But, theoretically, you can have a huge amount of uptake that has no impact at all on either of those physical parameters and has no impact on the ability

of the product to kill and doesn't have a toxic effect of release afterwards.

So if you get that scenario, how is that -- and why would we call that incompatibility as opposed to it's just a preservative uptake level?

DR. GREEN: You know, preservative uptake is already assessed as part of the premarket testing, but there's no acceptance criteria. But you have a good point. If the manufacturer believes that the lens is still compatible, they can do the alternate testing with the lens and the solution and the microbes. But the lens won't necessarily be listed as incompatible in the labeling. There will just be a precaution to alert consumers or practitioners that, with that lens, you may require additional disinfection because the lens can absorb too much preservative from the solution.

MR. PFLEGER: So just a follow-up.

DR. HIGGINBOTHAM: Mr. Pfleger.

MR. PFLEGER: Michael Pfleger.

This is the question: What's the problem we're trying to fix with any new criteria? And so if you've got a situation where it passes the microbiology, then why would we need to tell a patient -- what are they going to do with the information that says this lens/solution combination has a higher level of preservative uptake than some other solution/lens combination? It doesn't tell them to do anything, and that's why I'm just puzzled as to -- again, calling it an incompatibility has a very negative connotation.

DR. GREEN: Well, it alerts the practitioner that there may be some issue with compromised disinfection with that lens.

DR. HIGGINBOTHAM: Yes, Dr. Eydelman.

DR. EYDELMAN: If I can interject. I guess what would be communicated to the patient is actually one of the questions that we're asking you: What is the best way to communicate it? But the goal is, considering the number of different contact lenses and different contact lens care productions, to eliminate and minimize utilizing two that are not the best combination.

So if you're buying contact lens A and you know that contact lens care product B is incompatible with A, why not choose product C, since there are so many options on the market? That's where we were going.

DR. HIGGINBOTHAM: Yes, Mr. Pfleger.

MR. PFLEGER: Michael Pfleger, to follow up.

So that's exactly what the concern will be. Because if you can't show what that negative -- there has to be a negative to say don't use A with B; use something else. Then there needs to be a reason why there's that negative assumption of don't use A with B. And preservative uptake, in and of itself, doesn't seem to be a reason why you would say don't do that. If you were to say there was a toxic reaction because there is too much, or it decreases the microbiological efficacy of the product -- that combination -- so it wouldn't pass, those clearly would be ones that I think everybody would

agree should be labeled. But just preservative uptake and release by itself, quite frankly, that's puzzling as to why that's a negative.

DR. GREEN: I agree. But the criteria is grounded in the ISO 14729 criteria, which assesses microbiological efficacy. The lower limit of the specification would be verified by that criteria. If that's not passed, then manufacturers have the option to do the modified standalone test to show compatibility because that assesses everything else, like preservative uptake rate. So it is grounded by the ISO 14729 criteria, if you look at the flowchart.

MR. PFLEGER: Michael Pfleger.

So one more time, though. What's the negative that preservative uptake and release --

DR. GREEN: Compromised disinfection efficacy.

MR. PFLEGER: Okay. So if we are able to show that it doesn't have a negative impact -- so we're looking for a worst-case combination for preservative uptake to demonstrate that it still passes the microbe. Then I think that's an understandable way of looking at it. But just preservative uptake by itself really shouldn't be viewed as an incompatibility. So I think if we can change -- this is somewhat similar to soil. You know, it means things to different people at different levels of discomfort, and so it's something we should probably work on.

DR. GREEN: Understood. Thank you.

DR. HIGGINBOTHAM: Great. Dr. McLeod, do you have a

question?

DR. McLEOD: Stephen McLeod.

The question was actually for you. Don't try to escape.

(Laughter.)

DR. HIGGINBOTHAM: You're very popular today, Dr. Green.

DR. McLEOD: Yes. Stephen McLeod, UCSF.

And forgive me for my late arrival. So I may have missed the explanation for this earlier on. But if I think of, for example, the peroxide system where you would expect it to have very little antimicrobial activity after it is neutralized, if you do get down to a point where you've really reduced your load and you're no longer effective, then how do we know that that's actually a situation that would be difficult for patients?

DR. GREEN: I'm not sure I understand the question.

DR. McLEOD: So essentially what we're saying is that if you have an uptake issue, then you're dropping your antimicrobial activity, right? If you're in a closed system where you're not getting reinfected, why is that an issue if you assume that you've gone below a certain level? Because that's basically what happens in a self-neutralizing peroxide system, right?

DR. GREEN: Well, the solution is tested based on the assumption of a certain concentration of preservative. Now, the solutions aren't tested with lenses at all, so we're trying to give sponsors options to test the solutions with lenses, and the initial criteria would be that the lenses

do not lower the concentration of the preservative below a certain limit which has been tested. So we're essentially seeking a minimally effective concentration.

DR. McLEOD: Stephen McLeod.

I understand that, but that doesn't answer the question, because again, if you have a closed system, you start it at one level and you end at a different level. What is the relevance, at that point, of the lower level even if you have a lens in place?

DR. GREEN: It depends on the lens material. I think it really depends on the rate of uptake. I mean, you could have materials that are absorbed really quickly -- preservatives that are absorbed really quickly by the lens material and don't disinfect. Or you could have a slow preservative uptake where it doesn't matter. So you're right in that respect. But this is a quicker screening process for assessing whether there's any type of, for lack of a better word, incompatibility between the solution and the lens material.

DR. HIGGINBOTHAM: Okay. Dr. Sugar.

DR. SUGAR: Joel Sugar.

Is it fair to ask you a question, Malvina, as a representative?

DR. HIGGINBOTHAM: No, no, please don't leave.

(Laughter.)

DR. SUGAR: Dr. Mowrey-McKee and Dr. Stone both said that having a bacterized amoeba in testing makes testing not doable. And then

your paper with Dr. Shoff seemed to show the opposite. So I need to understand that disagreement -- inconsistency.

DR. EYDELMAN: So Dr. Hampton has been involved in these conversations as an ISO rep for many years. So having been the spokesperson on this topic, I'll turn it back to her.

DR. HAMPTON: Denise Hampton.

Dr. Eydelman is right, this has been a topic of conversation, actually for many years, about why there's not currently agreement on the protocol to use going forward.

You're right. In the studies that we conducted that were conducted by Dr. Shoff, we believe that using bacterized cultures represent a more real-world situation, whereas growing axenically, we believe, makes more susceptible to disinfection. That's the simplest quickest answer I can give without going into more detail.

DR. SUGAR: But you were able to demonstrate that you could test and find differences between preservative systems using that model, correct?

DR. HAMPTON: Right. I didn't know if there were more questions.

So the publication that Dr. Shoff wrote in terms of the protocol, the basic protocol that was published examined a whole host of factors that we thought should be examined when developing a protocol, and it included

strain cyst formation, bacterized cultures, as Mr. Brocious alluded to, versus axenic growth. All of those were considered as part of our research.

DR. EYDELMAN: And if I can just add. A lot of this conversation we intend to continue at the workshop that we will be holding in September --

DR. HIGGINBOTHAM: Great.

DR. EYDELMAN: -- as we will be obtaining more data by that time, which is not finalized right now.

DR. HIGGINBOTHAM: We have three panelists that have questions. First Dr. Reller, followed by Dr. Szczotka-Flynn and then Dr. Jacob.

DR. RELLER: I don't understand the importance of residual activity if the intended job of the preservative is accomplished and what seems to me is a standardized approach that is clearly delineated of what the components of the testing system are to be. And then there are only two questions.

Does the preservative, if used as directed, including whatever soak time it is, et cetera -- and how it's handled thereafter -- does the preservative on a given product -- a lens -- change the optic qualities, I mean, the physics of what the purpose of the lens is supposed to do to enhance vision? And if preservative A alters those qualities that render the lens not -- that should be delineated.

And secondly, given the preservative, if it's doing its job as

regards bacteriostasis, fungistasis, when it's developed containment of amoeba at some acceptable measure, that no matter -- if it doesn't change the optics and it enables the combination of the lens and the preservative to pass the test, that's all that's important. And what's very critical is to have a standardized test by which all of the preservatives would be assessed and the combination with the lens would be assessed.

Again, the standardization, so that anyone doing it with any preservative/lens combination would have to have the same bar, is critical. I mean, think about the efforts in the standardization of susceptibility testing. You know, they're multiple. There are E-Flex pumps and this, that, and these enzymes and those enzymes. And all that counts -- it's not a predictor of success, as more of not failing from the outset, because how it's used is going to affect what its ultimate efficacy is.

But all one can do is, if you use it the way you're supposed to and you have the preservative that's compatible with the lens, it will do what it's supposed to do and you'll get your vision improved by its use. If you stray from those parameters, we can't say how it's going to work. And to get into something that we don't know represents what you are trying to achieve, seems to me to -- it may be satisfying to measure, but it's not assessing what you're really interested in.

This is from an independent view of all of this. Just listening to all of the discussion this morning, those are my thoughts.

DR. HIGGINBOTHAM: That's very helpful. Thank you.

Next, we'll go to Dr. Szczotka-Flynn.

DR. SZCZOTKA-FLYNN: I have a question to, I guess, the FDA. Where did he go? There you are.

(Laughter.)

DR. HIGGINBOTHAM: We invited you to stay.

DR. SZCZOTKA-FLYNN: Would this testing method go backwards in time? In other words, how does this affect current products already on the market? Because again, as a clinician, I'm very concerned that lenses that we, as clinicians, feel are compatible, because they've been on the market for 20 years and have used these solutions, that in the papers look horrible, but clinically we know they work, so I'm just concerned, as a clinician, are you going backwards or are you only going forward?

And then part two is, on your slide where you say, precaution, storage beyond X hours will require further disinfection, I don't understand that comment because, especially in the *Fusarium* papers, the longer you store it, it actually grows. So I don't understand why you would put that comment or even consider that comment after the precaution statement.

DR. EYDELMAN: So this is Dr. Eydelman. I'll take the first part and then I'll give it back to Joe and Angelo.

We're considering this as part of the revision of the guidance, which means that it will be applicable for all of the products from now on, not

backwards.

DR. HIGGINBOTHAM: Dr. Angelo Green, you have a comment.

DR. GREEN: Angelo Green.

So the manufacturers recommend a certain disinfection time, and it's only up until that time, typically, that the solutions are evaluated. So storage beyond X hours would be the time recommended by the manufacturer.

DR. SZCZOTKA-FLYNN: Loretta Szczotka-Flynn.

So the manufacturer would be able to decide what they put on the label there at that point?

DR. GREEN: They decide what their recommended disinfection or soak time is. So that would be determined by their recommended soak time. That's correct.

DR. HIGGINBOTHAM: Thank you.

Dr. Jacob.

DR. JACOB: Jean Jacob.

I have three questions. And, Angelo, don't go away.

(Laughter.)

DR. JACOB: And they go one, two, and then Joe, if that's okay. So the first one is for Dr. Hampton, and that is the FDA method with the bacteria and amoeba system, has it been ring tested?

DR. HAMPTON: Denise Hampton.

No, it has not.

DR. JACOB: Okay. So that's the difference between the FDA method and the other methods that were discussed by the outside groups.

DR. HAMPTON: With respect to their AEEMC testing, it has been ring tested.

DR. JACOB: Okay. So that's one of the differences between them.

DR. HAMPTON: Right.

DR. JACOB: And the second one is for Dr. Green. The specific difference between each side of that chart is that one has a lens in place and one does not.

DR. GREEN: That's correct.

DR. JACOB: Are manufacturers required to do disinfection or kill rate with a lens in place?

DR. GREEN: Not currently.

DR. JACOB: Okay. So are you trying to get to the disinfection with the lens in place by your uptake testing?

DR. GREEN: That would be an initial criteria. If the lenses are shown to be -- if lenses compromise disinfection by lowering the concentration below the manufacturer's limits, then they can do the alternate testing of lens and solution with microbes to account for preservative uptake rate.

DR. JACOB: So I guess I'm confused as to why you would go through all of that uptake and HVLC and all of that, instead of just doing the disinfection testing with the solution alone and with a lens in place, because that way you do the same test, just two ways.

DR. GREEN: So manufacturers have that option. But with the alternate testing, it's more cumbersome because we're going to be requesting five lenses -- six lenses, one lens type from each group. For each lens, several organisms have to be tested versus a simpler test where you're just looking at the concentration lower limit to verify for each lens. So it may be slightly more difficult to pass a simpler test, but we allow the alternate option.

DR. JACOB: Okay. And you feel that they give the same -- you would get the answer that you would like?

DR. GREEN: I think so, because again the concentration lower limit is subjected to the micro test that takes into account the whole solution. And once the lens has not lowered the concentration below that limit that's been tested, then it's the same as testing the solution at the specified concentration.

Does that make sense?

DR. JACOB: Yes, I see what you're saying; I see what you're getting at. Okay.

DR. GREEN: Thank you.

DR. JACOB: And my third question actually --

DR. HAMPTON: Dr. Jacob, I'm sorry to interrupt you, but can I clarify one thing?

DR. JACOB: Sure.

DR. HAMPTON: So this is Denise Hampton.

I'm sorry, I shouldn't have been so absolute earlier in my answer to you. Though we have not gone through an official ring test for the testing that you asked about, we have been exploring ways to validate this method. I want to make sure that that's clear.

DR. JACOB: Okay.

DR. HAMPTON: That was alluded to by Dr. Cope in her presentation, that CDC is also doing internal research and exploring other collaborations with other labs, government labs, to try to achieve this purpose and validate the protocol.

DR. JACOB: Okay.

DR. HAMPTON: Thank you. And this will be one of the topics discussed at the workshop on September 12th.

Thank you, Malvina.

DR. JACOB: Okay, great. My third question. Jean Jacob again. My third question actually has to do with Slide 48 and the materials group. Do you want to finish the disinfection before I go on to something else?

DR. HIGGINBOTHAM: No, I think just ahead of us is a short

break and then the Panel questions, so let's do as much as we can now.

DR. JACOB: Okay.

DR. HIGGINBOTHAM: So the materials group can come up. Who presented? Dr. Hutter, yes. Thank you. Your question, please.

DR. JACOB: Sure. Jean Jacob again.

So one of the questions that we're supposed to answer is about the scheme for the lenses which is on Slide 48, right? Okay. And I'm a little concerned about how it addresses ionicity and nonionicity, because I know of a lens that is on the market that would be characterized as a low water content, even though its surface is a high water content and it will behave with a high water content lens. So you're going to group it with a set of lenses down over here, and it's not going to behave that way at all.

So I guess in some ways I agree with the other ones a little bit more as a chemist, that in silicone hydrogel, it's not about the water content, it's about the structure of the water that's in it. And I think taking an absolute water content, an average of these that have a range of hydrophilicities, which most of them do have, that the center of most silicone hydrogel lenses have a different water content than what you see at the surface. So most of the time you're taking an average number. But as we're getting to more advanced silicone hydrogel lenses, that average number is very far away from what the tear film and the tissues actually see. So I guess that's my question number one, how you think this addresses that.

And number two, it's about surface treatment. There's a whole thing in polymer chemistry that is being used in a lot of the lenses now, as something called surface-modifying end groups, which are not technically surface treatments. So just for the group at large, what it is is the polymer chain that is polymerized in it has these hydrophilic end groups that then associate most commonly with the surface, but they are also throughout the lens to a certain degree, but they do change and are put in there specifically to change the outer section of the lens. But they are not technically classified as surface treated, because a surface treatment is something that is done post-lens polymerization. After that, how do you put that in -- how does that go in this?

DR. HUTTER: This is Joe Hutter.

First, the lens you're talking about with the difference between the surface high water content and the inside was different. We looked at that lens when it was under review here, and it fit. But I can't really discuss -- answer your question specifically because it is proprietary information.

DR. JACOB: Okay.

DR. HUTTER: Okay. But we did see -- and it did fit in this scheme. You found a limitation with these end groups; there's a limitation. The semi-interpenetrating networks do something similar to that. I think we would have to consider that, I think we could consider that a surface-treated lens. We didn't define that. We really weren't aware of that when we were

developing this.

Regarding ionic content, specifically, a difference between this and the previous four groups were conventional.

DR. JACOB: Um-hum.

DR. HUTTER: The previous four groups had a one mole percent criteria for ionic content, and they also had a pH, I think, that was 7.4, if I'm remembering right. When we looked at the data in our own experiments, we tested some lenses with different ionic content, and I thought, at the time and the data I saw, that the one mole percent was way too high and it should have been much lower than that, maybe more like 0.1%.

But when we brought that to ANSI, ANSI said well, yes, it should be lower. But how low? We probably can even go lower. Why this arbitrary 0.1%? So we specifically wrote just being ionic at pH 6 to 8, which broadens the 7.4 criteria that was picked in the past, and we took out that one mole percent, which was arbitrary, because we did see effects of ionic content at much lower numbers than that.

So the hypothetical lens brought up by CLI, that they're talking about in the letter that they sent, I would have put that in an ionic group with this criteria, not in an nonionic group.

DR. JACOB: So only the nonionic ones would be discriminated or regulated with --

DR. HUTTER: That's correct, that's correct.

DR. JACOB: -- high water content.

DR. HUTTER: That's correct.

DR. JACOB: Okay. Okay, thank you.

DR. HUTTER: There are limitations with this grouping system, and it's possible what you're describing doesn't fit, but we have not seen that lens yet.

DR. JACOB: Okay.

DR. HUTTER: And it's possible we would have to look at that, but I don't know how it would work yet.

DR. JACOB: Okay.

DR. HIGGINBOTHAM: Do you have a follow-up question, Dr. Jacob?

DR. JACOB: No.

DR. HIGGINBOTHAM: Great, thank you.

Dr. Leguire.

DR. LEGUIRE: Larry Leguire.

In the earlier discussion, I was hoping to clarify an issue regarding preservative content after the contact lens has been bathed in it. And I think this deals with, in part, redundancies built into the system and the issue of noncompliance, since patients are notorious at topping off their cases such that if you start at a high level and then you treat a lens, it goes down to some minimum level, but acceptable level, and they reuse that. Will

that still be effective the next day is where I'm sort of going. And that would address the issue, in part anyways, of patient noncompliance of reusing the same solution.

And so I do think it is important, again, regarding creating redundancy in the system and addressing the issue -- at least one part of the issue of noncompliance. And so when you drop that solution, yeah, it has done its job of disinfecting the lens. But if the patient put it back in the next day, if it's at some acceptable but minimum level, then they do this job again. And so I can see where that would be valuable in terms of noncompliance.

DR. HIGGINBOTHAM: Thanks for that comment.

Dr. Ahearn.

DR. AHEARN: The lens solution, once it starts to evaporate down or have components removed, loses its integrity. And so you have actually osmolarity changes, you have all kinds of changes. Each of these individual changes can have an effect on a contaminating organism, and it can occur in different levels.

So we're talking about amoebae, we're talking about *Fusarium*, and the *Fusarium* itself will become resistant. But these are resistant stages. These are not what we're talking about as the classical adaptation. This is an inherent change in the organism, its capacity to differentiate.

So these organisms, these are eukaryotic. They're differentiating into a resistant stage, differentiated resistant levels, different

levels, and there is a time element. So that first killing effect is very important here, and we haven't gone too much into those areas and the fact that the bacteria in these two groups of organisms behave quite differently.

The content of those contact lens solutions with topping off is altered dramatically. That's why that has shown us the top problem, not knowing why that was happening, but that's the top problem. Personally, I always bring in evaporation and where the lens case would be. So I just wanted to clarify those points as to why the topping off has a lot of different effects.

And as the different solutions behave, the different organisms will behave. The *Fusarium* and the *Acanthamoeba* are going to behave quite differently than the bacteria. So it's a very difficult thing to work with the strains in a pure condition. It's very difficult to find *Acanthamoeba* in a pure condition.

And they carry all types of organisms internally, and they will behave differently depending on what organism is present. What's the number of organisms internally? That will affect just how it's resistant. So you worry about a number of internal organisms, what kind of symbionts are there, which ones can't we identify and which ones are present that we haven't categorized yet. So there's a lot of areas here that are still questionable.

DR. HIGGINBOTHAM: Great. I don't see any additional hands,

so thank you, FDA, for a wonderful set of presentations and all of your hard work. And thank you for all of the great literature and all of the research you've done in this area and preparing the Panel for this discussion.

Panel, we have five questions that have been posed to us. I was going to suggest that take a 15-minute break to make sure everyone is fresh and ready to go, so we can be efficient. I also want to be sure that all the Panel members received an additional paper by Schunk and Schweisfurth regarding s-o-i-l and contact lens disinfectant solutions. But I think it was a very -- we have additional copies. So we have 2:52 now.

Dr. Jacob, do you have a question?

DR. JACOB: I don't have one.

DR. HIGGINBOTHAM: Okay, we'll give you a copy. If you don't have a copy of this paper, raise your hands and we'll get you a copy.

So I have 2:52 now. Dr. Bressler is offering 3:05 to return. Hearing once. Hearing twice. Okay, go.

Thank you.

(Off the record.)

(On the record.)

DR. HIGGINBOTHAM: We are waiting for -- oh, Dr. Zabransky is here. That's great. Dr. Szczotka-Flynn is nearby, I'm sure.

And we'll get started, okay.

So we have in front of us five questions. Panel, I hope you have

found them in your folders. And just to clarify, particularly for those in our audience, I asked each Panel member if they had received an additional copy of a paper that is listed at the bottom of Slide 68. It's a reference that talks about the impact of soil on the disinfectant. So I wanted to be sure that the audience was aware that this is on Slide 68, and it's the reference by Schunk and Schweisfurth, and it is, I believe, in German.

(Laughter.)

DR. HIGGINBOTHAM: Okay. At this time, let us focus our discussion on the FDA questions. Panel members, copies of the questions are in the left pocket of your folder. I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription.

FDA, please read the first question.

DR. HAMPTON: Question 1: Do you believe that FDA's proposed grouping scheme for silicone hydrogel lenses is adequate to mitigate concerns regarding dimensional tolerance and compatibility? If not, what recommendations for modifications would you make?

DR. HIGGINBOTHAM: We had a rich discussion earlier, and I did not hear any modifications to the grouping scheme that was proposed. Is there anybody that would like to disagree?

Dr. Jacob.

DR. JACOB: Sorry, Jean Jacob.

I do think that the current scheme, which puts so much

emphasis on water content in discriminating between lenses, is really not necessarily as appropriate for silicone hydrogels as they were for conventional hydrogels, and that those limits need to be addressed more completely than they have been.

DR. HIGGINBOTHAM: Okay.

Yes, Mr. Pfleger.

MR. PFLEGER: Michael Pfleger.

So I just would recommend that FDA continue the work they've done with ANSI and ISO, where a lot of the industry does participate, and so some of the proposals that are being made there will incorporate some of the what's coming in the future that had been talked about earlier.

DR. HIGGINBOTHAM: Okay.

MR. PFLEGER: So that probably would be helpful to continue that effort.

DR. HIGGINBOTHAM: Yes, thank you.

Any other comments?

Dr. Lecca.

DR. LECCA: No, I don't really have any comments. I agree with the comments that were already made. But I don't have the fifth question. Evidently, I don't have -- I have a different draft proposal. I don't have --

MS. FACEY: You can check on the left side of your panel folder.

DR. LECCA: This right here?

MS. FACEY: Yeah.

DR. HIGGINBOTHAM: And it was also on our DVD.

MS. FACEY: That's the draft.

DR. HIGGINBOTHAM: Oh, that was the draft. Thank you.

Okay, good. We're all set.

Yes, Dr. Sugar.

DR. SUGAR: Is it appropriate to just add a category of "other," so that you can incorporate things that don't appear to fit into those categories or will that be used as an opt-out by industry to not follow --

DR. HIGGINBOTHAM: Dr. Eydelman -- oh.

Dr. Jacob, you had a comment?

DR. JACOB: I think that would be an opt-out. Yeah, I think it really needs to be --

DR. HIGGINBOTHAM: All right.

Dr. Eydelman, did you want to comment on an "other" category?

DR. EYDELMAN: No. At this point, I just want to thank you for your input.

DR. HIGGINBOTHAM: Thank you.

All right. Dr. Lecca, did you have a follow-up question?

DR. LECCA: No, no.

DR. HIGGINBOTHAM: Your light is on. Okay.

All right. So Dr. Eydelman, in response -- oh, yes.

Dr. Leguire.

DR. LEGUIRE: Larry Leguire.

One of the institute representatives, Mathers -- you know, had on their page 3 of 9, sort of an alternative way, I believe, of looking at the categorization. And I would like to take a minute or two for that discussion. I was thinking of ways to try to help me understand things, and this scheme, on page 3 of 9, again, Mathers presentation from the CTIC? CLI.

DR. HIGGINBOTHAM: Contact Lens Institute.

DR. LEGUIRE: Yes. That sort of makes more sense to me, although I'm not sure about the intricacies here. Perhaps someone a bit more experienced in this area could compare this table to the one proposed and comment on that?

DR. HIGGINBOTHAM: Well, Dr. Jacob, if you don't mind me putting you on the spot.

(Off microphone response.)

DR. HIGGINBOTHAM: Okay.

(Off microphone response.)

DR. HIGGINBOTHAM: Yes, Dr. Steinemann.

DR. STEINEMANN: Tim Steinemann.

While we're waiting, just an aside. Where would scleral lenses or hybrid lenses fit into this schematic, then?

DR. HIGGINBOTHAM: The hybrid lenses -- Dr. Eydelman, do you want to help us with that?

DR. EYDELMAN: I'm not sure what you mean by hybrid lenses.

DR. SZCZOTKA-FLYNN: This is Loretta Szczotka-Flynn.

I think what they do is that the soft skirt, the hydrophilic part, will have its own classification scheme; it does. And so, therefore, the hybrids have two materials and so -- this is only a hydrophilic lens grouping, so the rigid portion would be excluded, and then the skirt would follow these same guidelines.

DR. EYDELMAN: Yes.

DR. SZCZOTKA-FLYNN: Is that correct?

DR. EYDELMAN: Yes.

DR. HIGGINBOTHAM: Okay.

And Dr. Leguire, did you see, on -- let's see, slide -- page 3 of Dr. Stone's presentation? There was a current ANSI/ISO approach. It's not a new proposal, but it's the current -- just so we are including that.

So anyone want to respond to Dr. Leguire's question? If this diagram is something we need to consider as part of this first question.

Dr. Jacob.

DR. JACOB: Jean Jacob.

Okay, I have all three of them right here. I think the best way to explain this is the CLI is probably, in many ways, just taking a broad look

and dividing two basic polymer ways of doing it, right? So there's anything that's ionic versus anything nonionic, and it's really not worrying about the water content within it. And then it's going through and saying is it surface treated and if it's not surface treated, as having -- when you're in those two groups and going through.

Whereas the ANSI then takes that actually a step further and is looking at the specific polymer makeup within technically these two categories. So that if your monomer or oligomer is within the polymer -- as I was saying, there are oligomers now that are almost amphoteric, if you want to say, in themselves, that have these surface modifying end groups and things like that, where they would -- they would be fit in here with these three categories that two of them take into the total amount of water in the lens.

Whereas in the FDA classification, anything that's ionic -- it doesn't matter how much the water content -- goes into one basket. And then if it's not ionic, they divide those up based on the percentage of water, the average percentage of water within the lens; and then within those, whether they're surface treated or not surface treated and ionic versus nonionic. And it puts a lot of emphasis on the hydrogel portion of the silicone hydrogel lens.

So that's my explanation of the three different categories. Then there's my personal scientific opinion, and I don't know whether you

want me to give that or not.

DR. HIGGINBOTHAM: Yes.

DR. JACOB: Okay.

So my personal scientific opinion, as a polymer chemist, is that the silicone portion and those oligomers within that silicone portion are as important as the hydrogel. And to have a classification that then just ignores those differences to a certain degree, which is the current one that Joe is working on, inherently has some problems for the future, because what I'm aware of in the industry, what everyone is working on is making their silicone monomers more individualized and optimized.

Our hydrogel players are hydrogel players that have been around for conventional hydrogel lenses. They're not changing. There's the PVP, there's acrylic acid, there's -- I mean, there is a list of them, and those are our cast of characters. What's really changing and what makes these lenses different is the silicone moieties and how they're arranged in the new monomers. And a lot of patents are based on the differences in the silicone portions of these lenses. And I don't think that -- which is what I was trying to allude to in the water content of my question.

DR. HIGGINBOTHAM: Dr. Eydelman.

DR. EYDELMAN: So I think you've hit on a very important point that I just want to reiterate. One of the challenges I gave my group is to come up with a classification and testing that would be least burdensome for

the companies and that would cover everything that we have currently reviewed.

So you're right in that it does not necessarily cover lenses which might be coming down the pike. However, I do want to point out that this does cover everything that we have reviewed in the least -- and with the requirements of the least testing.

DR. JACOB: Yes. Jean Jacob, yes.

And I agree with that. It's just that your non-water specification ionic is going to be a big bucket of very different items. That group, 5-A, is going to give all kinds of different results all over the place, and it's going to be very difficult when you're asking later, down the line, to pick one lens from that group to see if it tests adequately. So that's where it's going to run into some problems. So I just think it needs to be tweaked more, polymerically, in general categories.

DR. EYDELMAN: Thank you very much.

DR. HIGGINBOTHAM: Any other comments from any of our members, particularly those who have background in polymer science or material science?

(No response.)

DR. HIGGINBOTHAM: So, Dr. Eydelman, generally, in response to Question 1, the Panel -- as you just heard so eloquently from Dr. Jacob, is that we need to consider other components of the lens beyond the water

content, particularly given the variety of elements in the silicone space, if you will. And we also would like to ensure that the FDA continues its conversations with ANSI and ISO.

And I didn't hear a full vote of support for a category of "other," but it sounds like 5-A could be that "other," at least for the moment.

But that's a summary of Question 1.

Any amendments or any revisions to that summary, Panel?

(No response.)

DR. HIGGINBOTHAM: Great. Question 2.

DR. HAMPTON: Do you believe that the proposed clinical test matrix for silicone hydrogel lenses is sufficient to address clinical performance issues? If not, what additional testing would you recommend?

DR. HIGGINBOTHAM: Well, based on our discussion, it sounds as if, you know, particularly given the concerns in Category 5-A, you can't just take one representative lens from that category as one example. So there are some challenges taking representative samples from these categories.

Any comments on Question 2?

DR. SZCZOTKA-FLYNN: Loretta Szczotka-Flynn.

I don't think this question -- I think this is a new question to us, so the Panel -- this was the fifth question you're alluding to that wasn't there earlier, so I didn't have a chance to think about this, and I felt that the two slides pertaining to this were breezed over. So I'm not exactly sure what

you're asking. Perhaps we can get more clarification.

Are you asking about just simply the groupings that you are now proposing, or are you talking about -- for example, what is the clinical parameter or outcome you are concerned about in these clinical tests? Are we talking about corneal staining, patient comfort, adverse events? This has not been clarified at all.

So I'm talking about Slides 52 and 53 in the slide deck.

DR. HIGGINBOTHAM: Microphone.

DR. ROBBOY: He had a couple questions.

DR. HIGGINBOTHAM: Yeah.

DR. ROBBOY: First question had to do with what exactly are we asking here, right? And so the slide laid out -- as compared to the matrix from the 1997 guidance, that was the 20/10 for the Groups 1 and 4 -- what we're proposing is to test the five groups of silicone hydrogel lenses and then in addition, the Group 4 etafilcon A lens in a 2:1 ratio of 3 to 15. So that's the matrix that we're asking for your endorsement. Do you agree with that proposal to test that new matrix, okay?

DR. SZCZOTKA-FLYNN: This is Loretta Szczotka-Flynn again.

You mean you want 30 patients using the test solution with each of these lenses and 15 subjects using a control solution --

DR. ROBBOY: Correct.

DR. SZCZOTKA-FLYNN: -- with representative lenses from each

of these groups?

DR. HIGGINBOTHAM: Right.

DR. ROBBOY: Right. And it comes out to a total of 270 subjects.

DR. HIGGINBOTHAM: Yes.

DR. SZCZOTKA-FLYNN: And what is the outcome of the test? Is it --

DR. ROBBOY: Well -- and that was your second question. What we're referring to there is just simply the clinical parameters, as have been described in the 1997 guidance, if you're familiar with the guidance. You know, there are objective and there are subjective findings; there are the slit lamp findings, as you alluded to; corneal staining. There are subject -- for example, like comfort, dryness. Just the standard clinical outcome that we have been addressing for years, as defined in our guidance, in our contact lens care guidance. Does that answer your question?

DR. SZCZOTKA-FLYNN: It does, but I think that second question is huge and really difficult to answer. For example -- and we haven't even talked about corneal staining.

DR. ROBBOY: Correct.

DR. SZCZOTKA-FLYNN: But there will be many instances here where the lens solution combination will cause staining after a certain amount of time and -- this is just a really big question, and I think just giving

you our endorsement on this new categorization is not possible without kind of understanding the ramifications of the outcomes of these clinical parameters.

DR. ROBBOY: So, for example, let's take corneal staining. So for a new contact lens care solution, would recommended testing be done according to the matrix that we have proposed? Typically, it's a 90-day or three-month study. We would see patients at probably Day 1 approximately one to two hours following dispensing to check for corneal toxicity type staining.

And then we would see patients at, I believe, one month, two months, and three months. And at each visit, we would check -- we would do a full slit lamp examination; we would test visual acuity; we would test for problems, symptoms, complaints. We would check the wet-ability and the depth position of the lens surface; just go through all the standard testing, again, as described in our guidance.

DR. HIGGINBOTHAM: Any follow-up there? Did you have your question answered or are you still -- we can come back to you.

Mr. Pfleger and then we'll have Dr. Reller.

MR. PFLEGER: Yes. So not discussing it, what lens groupings, but just the numbers that are being recommended for testing and control. What are we expecting to see with 30/15 instead of 20/10? What's the reason for changing those numbers?

DR. ROBBOY: I'm going to -- I hate to defer this. This is actually before I came to work at FDA.

(Laughter.)

DR. ROBBOY: I think --

I can surmise that the decision for upping the number was because it was felt at the time that silicone hydrogel lenses represent a brand new entity that hadn't previously been evaluated by us, and we just wanted to learn more about them compared to the conventional lenses that had been around for that much longer of a time.

Does that seem like a plausible response?

MR. PFLEGER: Almost, but we still have 30 versus 20, and so are we saying we expect 10 patients are going to change our perspective of the safety or efficacy of the lens?

DR. EYDELMAN: I think Dr. Lepri is going to answer this.

DR. LEPRI: Bernard Lepri.

Part of the reason for that change that occurred, many years ago, starting in I believe it was around 2005, we started recommending that as the new silicone hydrogel started to come on the market was that we see contact patients are not just noncompliant in the care of their lenses, they're also noncompliant in these studies because they're short-term.

So some of them will get into a study, get the product, and then not return, and this would account for better follow-up of patients and

also to account for a dropout. And so we increased it a little so that they would have sufficient numbers to allow for statistically valid study results.

DR. HIGGINBOTHAM: So as a follow-up -- this is Dr. Higginbotham.

Do you have enough experience now since 2005 to be able to actually estimate that at certain centers you could get 20 versus 10 patients to follow up consistently?

DR. LEPRI: I can't answer that question appropriately -- it's Bernard Lepri again -- because we haven't done any type of analysis to show that across all the products that have been submitted during that time period.

DR. HIGGINBOTHAM: Mr. Pfleger.

MR. PFLEGER: Yeah, Michael Pfleger.

So just a suggestion you could consider. Instead of changing numbers -- because the way most people, I think, in industry are going to read it, that's the minimum number that we have to have finished, so if you want 20, we can have what we've had in some of the other guidances, an expectation that you have a minimum of 20 that finish the study completely and that gives you your bottom. And then it's up to the company to get an idea of who they're using, what kind of history they may have on getting patients and keeping patients, and just so that we have the minimum number we have to have.

DR. LEPRI: Okay, thank you.

DR. HIGGINBOTHAM: Dr. Reller, you had a question?

DR. RELLER: My question, actually, was exactly the same and whether -- if there were a rationale for the number. It bothers me a bit that the numbers are different. And we say one, we're okay and it's been around a long time. Unless there's something special about these new categories of lenses, why would it change the number? And perhaps what has been suggested, the minimum number is better. I mean, it's also conceivable that the bar was too low before. But to have different criteria doesn't make any sense to me.

DR. HIGGINBOTHAM: Dr. Eydelman.

DR. EYDELMAN: I was just going to say thank you; we'll take it into consideration.

DR. HIGGINBOTHAM: Dr. Jacob, I'd like to come back to you. Considering your answer to Question 1, how would you actually frame your response to Question 2?

DR. JACOB: Jean Jacob.

Well, I think that the number of these categories is onerous in some ways in that unless -- especially certain categories are more specific that you have -- and because people have the ability to choose any lens within that category, that you will not have a truly standardized test with the current proposal.

DR. HIGGINBOTHAM: Any other comments?

Dr. Lecca and then Dr. Szczotka-Flynn.

DR. LECCA: Can I go back to this idea about the numbers? If we change from 20 to 30, is there any assurance that increasing the number will get the number that would be significantly sufficient, statistically sufficient? If you know. You say you upped it so that you can get -- because a lot of people drop out.

DR. LEPRI: Right.

DR. LECCA: Is that right?

DR. LEPRI: That's correct.

DR. LECCA: So how sure are you -- I mean, is there some experience that you had that you know that doing 30, you know you'll get your 20?

DR. LEPRI: This is Bernard Lepri again.

I want to make it clear to the Panel that this is not something that's just going to start now. We're presenting it to you now, but we've been doing this 30:15 ratio for almost nine years now, okay? We're explaining as to what was in the guidance from the '90s and now, while we're rewriting the guidance, we're going to put these numbers in because this is how we have been doing business. And we haven't had any pushback from the companies and we've gotten good results; they turn in sufficient numbers of data.

As I mentioned before, we haven't analyzed all the data from all the new products during this time period to see whether they're getting a full 30 or whether they're getting 25 or 20. We can't answer that question there. But this is not something that we're just about to start.

DR. EYDELMAN: Having said that, we obviously value your input on the subject, and we're going to take a look at this again before we put it in the final guidance.

DR. HIGGINBOTHAM: Yes. Dr. Szczotka-Flynn, you had a comment?

DR. SZCZOTKA-FLYNN: Yes. I have a question first. Have you also been doing these different subgroupings for the past nine years or just the number ratio?

DR. LEPRI: We've been doing -- for each new product that came in, but they were not labeled as these groups, okay? For example, we started out with at least two silicone hydrogel lenses. When the next new product came in, it was a different chemical formulation; we added that one on. So then the companies were then testing three groups, and eventually it became four groups and five groups. Because the numbers of types of silicone hydrogels have increased so dramatically, FDA decided to start looking at all their chemical properties and to try to put them into groups to minimize the number of subjects that would have to be tested.

So that's where the grouping concept has come from, based on

the grouping that was done from the '80s with Groups 1 through 4. And with advanced experience, then we didn't necessarily require companies to test all four groups, but just Group 1 and Group 4. And now we're moving to just Group 4 and the silicone hydrogels. And as that progresses, of course, then we can modify that to ease the burden of investigations for the sponsors.

DR. SZCZOTKA-FLYNN: Loretta Szczotka-Flynn.

One more thing.

So I don't have a problem with the numbers. I think the patients can easily be recruited across the sites, and it sounds like you've been doing that, so I don't have any problem with that. I guess my only concern is if you haven't been doing all these different subgroups of silicone hydrogels -- it sounds like you have been, though.

DR. LEPRI: Yes, but they weren't labeled as such.

DR. SZCZOTKA-FLYNN: Okay.

DR. LEPRI: Yes.

DR. SZCZOTKA-FLYNN: My only concern is, going forward, if you're going to revise that, you may have to revise some of your clinical endpoints, which -- I'm sorry, I'm not familiar with what all of the clinical endpoints were from the 1994-1997 documents, but there are certain clinical scenarios that we know we will see with some of these combinations.

And as I mentioned before, it's a whole separate discussion of whether or not those clinical scenarios are clinically important, and whether

or not these signify any adverse findings, so just to comment that you may also need to redefine some clinical endpoints.

DR. HIGGINBOTHAM: You had a comment?

DR. ROBBOY: Marc Robboy, FDA.

I wanted to add, in addition, getting back to the numbers, that the contact lens care solutions are relatively much more complex now than they were 20, 30 years ago, and that's another reason that we feel that increasing the sample size provides us with additional information. It's easier. It facilitates our better understanding of these emerging technologies in contact lens care solutions.

DR. HIGGINBOTHAM: Dr. McLeod, you had a comment earlier?

DR. McLEOD: It's been answered.

DR. HIGGINBOTHAM: It's been answered, okay.

You have me speaking with an accent now.

(Laughter.)

DR. HIGGINBOTHAM: I said ahn-swer, ahn-swered.

(Laughter.)

DR. HIGGINBOTHAM: Okay. Dr. Eydelman, in response to Question 2, the concerns that the Panel had with the precision of the categories alluded to in Question 1 carry over somewhat to Question 2. There are questions whether or not you'll be able to get a clear representative from each of these categories that reflects the dimensions of

others that you have in these categories. Does that make sense?

(No audible response.)

DR. HIGGINBOTHAM: So 1 and 2 are somewhat related. There was also some question about whether or not you actually need the numbers of patients recruited, as noted, and so is it that you've heard discussion, you'll get back to us on that or at least consider it.

And then finally, depending upon these new lenses, the clinical endpoints will need to be further refined or at least reexamined to ensure that they are capturing what you want them to capture.

DR. EYDELMAN: Thank you.

Question No. 3, please.

DR. HAMPTON: As a modification to our care product guidance, new care product solutions will be screened for lens preservative uptake incompatibilities using representative lenses per FDA's contact lens grouping system. We propose that the preservative concentration of the solution in the lens case should remain within the manufacturer's specifications after the recommended lens soak time. Incompatible lenses will be listed in the labeling. Please discuss the following:

a. Should our acceptance criterion account for patient non-compliance (e.g., longer soak times than recommended, solution reuse)?

b. How should the incompatible lenses be listed in the labeling

(e.g., bold text, a unified table)?

DR. HIGGINBOTHAM: Would you like to propose a response to this, Mr. Pfleger?

MR. PFLEGER: Yes. So starting with the question, itself. I don't think there's an issue with providing data about preservative uptake. We have procedures for doing that and that's this data. It's the specification concept that causes, I think, industry a fair amount of concern. We don't know what it means, we're not sure what products that exist on the market today would be able to pass that. If we're going to use those as predicate products, that would create a regulatory problem, going down the road, for future products. And I also think it needs to mean something.

So if we're going to call something an incompatibility, even if it can pass the disinfection efficacy, then that's something I think we would be very troubled with. So I think, to answer Question (a), we don't think patient noncompliance can be built into -- I think all of you who are in practice know patients are incredibly creative in their noncompliance. And it's not possible to have any kind of a standard that everyone in the world test their products against if you're going to try and build in different kinds of noncompliance into a regulatory system.

And so then I think incompatible lenses, if you actually have incompatibilities where you either have a question about the physical parameters, that clearly should be built in -- probably the bigger, the bolder

the text, the better -- both on the solution as well as certainly on the lens, which is probably even more important. And then if you have an issue where you're not passing your micro testing, then that also would need to be very prominently clear to patients and to physicians such as yourselves.

DR. HIGGINBOTHAM: Thank you.

Dr. Bressler.

DR. BRESSLER: I think you could build it in, but I don't recommend that you make it after the recommended soak time at this time because at least we haven't been presented any data to tell us how long that is. So if, for example, you showed confident data that said 90% of the people are using this for a week longer, a month longer, six months longer, a year longer, fine. Then go back to the industry and say, you know, no matter what we put, we are confident that everyone's going to use it for a week longer, a month longer, a year longer, and then I believe it might be fair to consider having it go beyond whatever that date is.

I still don't like the concept in general, but then I'd be more comfortable recommending it. At this time, not knowing how long "longer" is, not understanding how much "after" is, to me it seems best to put what it is and then do education to the healthcare providers, to the public, and make them recognize, look, we mean this amount of time because of these complications that may occur.

DR. HIGGINBOTHAM: Does anyone want to speak in favor of

incorporating noncompliance issues into the testing model?

Dr. Lecca.

DR. LECCA: Let me refer to No. 3. Yes, I agree with what was said so far, but I think that yes, I wouldn't disagree that maybe -- it says two weeks or a week to soak and scrub is sufficient, and we don't have really that much information about it, how effective that is, rather than to increase it. So I would say leave it at that. But I think that it's important that we contact or let the practitioner know that we mean business and that he has to or she has to let the patient know what has to be done. I don't think that that's very clear to the patient, evidently, because they're really not compliant. So I think that it has to be done.

As far as the labeling, I believe that should anything be done in terms of how it is listed as incompatible in terms of how it's listed in the labeling, I think it should be in bold and underscored. And I think it's important to do that. I mean, I have other recommendations, but I mean, in this particular case, I think it should be -- if anything -- in bold and underscored for the patient, for (b). But I would also like for the future that we might want to consider, let the manufacturer know that there are a lot of people out there and a lot of them don't -- I'd like to see that they put it in other languages. I'm thinking about the clinical work that's done in Texas where I work, 90% of those are in Spanish.

We have a major problem with inserts that they don't

understand. I have to go there, and it takes me just a lot of time to explain it to them and to interpret this. If it came from the manufacturer, it would be much easier. But that's something that doesn't -- it does have that here, but I mean I would like to let that manufacturer know that it would be important for them to do that. But as far as this is concerned, I would go along with most of it. I'm going to leave it at that.

DR. HIGGINBOTHAM: I guess one of the key questions -- I just want to make sure I understand your answer -- is that the preservative concentration, as it relates to the lens versus the solution, you would consider that as being an incompatible characteristic? Because --

DR. LECCA: No, I said -- I'm sorry. What was that again?

DR. HIGGINBOTHAM: The preservative concentration that -- the uptake of the lens, the preservative.

DR. LECCA: I would go along with that, yes.

DR. HIGGINBOTHAM: You would go along with that.

Is there anyone else who believes that that would be incompatible? Yes, Dr. Leguire.

DR. LEGUIRE: Larry Leguire.

I still don't understand the rationale. And this goes to earlier discussion about why the minimum amount should be maintained after soaking. Why? If it's not related to compliance at all, and as the gentleman here said earlier, probably has -- you know, there were other things going on

-- you know, why?

If it does its job, who cares if its zero or still some minimum amount or the maximum amount? You know, it's why? And why would we have this kind of guideline in there if it has no meaning? So what is the meaning of this? Why is that in there? I want to know that.

DR. HIGGINBOTHAM: So some of these questions can't be answered, but I think -- I'm going to make a stab at this.

Dr. Eydelman, I -- oh, yes.

Dr. Jacob.

DR. JACOB: I just had a comment, but that's --

DR. HIGGINBOTHAM: Go ahead.

DR. JACOB: Are you going to summarize?

DR. HIGGINBOTHAM: I was going to try and summarize, yes.

Yes, please.

DR. JACOB: Jean Jacob.

Mine was going to 3a, which is the solution reuse and whether or not you should test for it. I mean, I just think that it should be on every contact lens case, every contact lens bottle, that solutions just should not be reused, no matter if it's a drop versus the whole lens case. And I don't think -- making someone test for it almost makes it, well, it is okay if they reuse it because it's really still going to be all right, and I don't -- I mean, I think if you go down that, that's a slippery slope to go down and that -- you know,

solution should not be reused.

You don't wash your dishes in the water you washed your dishes last night, and you don't usually bathe in the bathwater you used yesterday, so you don't wash your contact lenses in -- I mean, that just should be an absolute. And I think if you start going down, well, they can use it one more time or two more times, I don't think it makes it that more effective because if you tell them that you can use it more than once, they're going to use it 10 times or all month. So I think that's a slippery slope, and I think that it just should be out there. Solution should not be reused.

DR. HIGGINBOTHAM: Thank you.

Dr. McLeod, you had a comment?

DR McLEOD: So I think that we've talked quite a bit about the issues with the preservative uptake as a metric of something useful. But there's no question, obviously, that the topping off issue is an important one. I think that, as a general rule, it's probably not a great idea for, in my opinion, regulatory agencies to deliberately say one thing and as it were, in principle, mean another. And essentially setting one criteria on that one knows what it's supposed to mean, but then in the background, there's really another meaning I think undermines the integrity of the process.

DR. HIGGINBOTHAM: Thank you.

I will attempt to -- oh, yes.

Dr. Reller.

DR. RELLER: Barth Reller.

It seems to me that the firms bringing data to the FDA should be held accountable to the performance that they say when used in accord with the directions given, period, which it reinforces what others have said here. I mean, otherwise -- to ask a company to cover for noncompliance with product use and labeling is unreasonable, in my view.

DR. HIGGINBOTHAM: Okay. I see no additional hands raised. I will attempt to summarize. And please feel free to revise.

So, Dr. Eydelman, in response to Question 3a, the Panel generally believes that we should not ask industry to insert issues within its model for testing that may be attributed to patient noncompliance, such as longer soak times and solution reuse, that we should be testing the ideal and dimensions that are repeatable, as opposed to dimensions that we really don't have a lot of evidence for in a very reliable fashion.

Regarding No. 2: We had rich discussion about whether or not preservative uptake and the concentration of preservative that remains in solution is really a meaningful outcome to actually test or whether it's the efficacy of the mitigation of microbial growth, which would be a bit more of a valid measure for industry to follow rather than preservative concentration. So there were some questions about that.

Physical properties of the lens that may be changed in the solution, that would be compatible with incompatibility, but generally, the

Panel did not feel that the concentration of the preservative was meaningful as it relates to efficacy.

Other recommendations: Clearly, there was strong support for robust patient education, particularly education that's culturally sensitive and literately appropriate for the patients' education level, et cetera.

DR. EYDELMAN: Thank you.

Question 4.

DR. HIGGINBOTHAM: Well, did any amendments -- because that was a bit -- I felt it was a bit rambling, but I tried to capture as many of the comments that I heard around the table.

Okay, I'm seeing nods.

DR. HAMPTON: Current microbiological test methods (e.g., ISO 14729) do not take into account "real-world" solution testing parameters in which the lens stored in a case is considered. Please discuss whether you believe the following factors should be incorporated into current preclinical testing:

a. Soil

b. Longer soak times

c. Lens uptake

d. Any other factors.

DR. HIGGINBOTHAM: Okay. Any comments on this one?

Dr. Reller, did you want to comment on this question?

DR. RELLER: Fine. Barth Reller.

(Laughter.)

DR. RELLER: There are some aspects of 3 and 4 that I think are quite ambiguous. And in the scheme presented that has to do with this compatibility/incompatibility, I think those words obfuscate things. The residual concentration issue, I think we've dealt with because what we emphasize in answering that question is performance; that's what counts.

So particularly (a), the soil component, I could potentially see the relevance of the effect of protein, which was really the variable in the reference given on the efficacy of a disinfectant, if the disinfectant was what was being presented to some component of the FDA for approval as a disinfectant. But what I've heard the discussion about was by what criteria should a lens preservative solution be assessed? And I would think that a company developing a preservative would want to do due diligence about the preservation of antimicrobial activity under varying standardized conditions that may include the influence of protein on the activity of the special mix that they come up with because it's not only the microbial side, but the stabilizers and the other components that have been emphasized over and over again, that the preservative solution is a complex mixture and any one component thereof -- one can't get hung up on the component, but what the performance of the labeled product is.

So as a consequence, it escapes me why one would -- it's

something that the industry would appropriately do, but having that as a component, that is that whole right side of the algorithm that has to do with testing. The preservative itself has to pass, and if the preservative passes, then it's assumed that it will work unless there is some aspect of the lens, such as absorption, that leaves too little concentration left to be efficacious anymore.

So it would seem to me that if it's complex and there's an interaction with the lens, that all that should be assessed before clearance is the left side of the diagram for the microbiological testing with the lens as part of the component, and with the different category of lenses to the extent that they may differ. That's the categories that were -- the old categories and the new categories with the silicone hydrogel lenses.

So to me, what is important? We sort of dispensed with the longer soak times component. The lens uptake, we realize, is important; that's why you have to test the different lenses, so we sort of dealt with that. The soil, when you put the lens in, are you going to put the bacteria in the preservatives, as well, or are you going to use the mock protein soil surrogate test before you even put your lenses in? I mean, you're not going to put that in with the lens mixture, as well -- it would seem to me. That doesn't make any sense.

So what I'm interested in is develop your preservative mixture that you intend to have cleared for the purpose of keeping the lens safe and

effective within the boundaries of how your product is labeled and used -- used as directed -- and then the FDA would want to see your data, that it works with the different lenses; and if your preservative does not work with some lens, doesn't do its preservative job with some lens, that that be delineated.

So preservative solution X is cleared for use as directed with all of these lenses, do not use it with these other lenses -- and that could be in a box or in bold or -- you know, we'll get into that for the discussion. But it seems to me this all could be simplified within the end result. What we're interested in is what works with these lenses when used as directed.

DR. HIGGINBOTHAM: Okay. Any other comments?

Yes, Dr. Leguire.

DR. LEGUIRE: I do have some concern about lens uptake of any product and how this is then -- say you have really long soak times; how the preservative, if you will, is released when it is put on the eye, itself. And so I haven't seen any literature here at all, what was given to us or otherwise, documenting how much is released actually in vivo.

DR. HIGGINBOTHAM: So that is your other factors. So what about these other specific questions related to soil, longer soak times and -- well, we already addressed lens uptake.

DR. LEGUIRE: Yes. Larry Leguire again.

Again, the longer soak time, specifically, and lens uptake are

basically together. And what consequence do these have, if any, on a patient.

DR. HIGGINBOTHAM: Okay.

DR. LEGUIRE: And when it's released, I assume some of this is released when it's put back on the eye. And is that concern addressed? Or is it so low that it's not a concern at all?

DR. HIGGINBOTHAM: Okay. Because we already said that we're not incorporating in the model issues that go outside of the recommendations of the industry, as it relates to specific products. So longer soak times would be one of those noncompliant type issues. So are you suggesting that we should be testing for longer soak times here? I'm just trying to make sure that I understand.

DR. LEGUIRE: Yes. They seem to go -- Larry Leguire -- hand in hand: longer soak times and lens uptake. The longer it soaks, the more the lens will uptake the preservatives until several days, possibly later. And so I imagine -- again, I'm not a contact lens wearer, but put it in the case, it stays in there three days, and then they wear it. What's the consequence of that?

DR. HIGGINBOTHAM: Okay. But I think the lens uptake with the different classes or categories of lenses that we were interested in testing.

Okay, yes. Mr. Pfleger.

MR. PFLEGER: So industry, I think, has been pretty clear they're obviously in favor of doing more real-world testing; a lot of time and effort

has gone into it. So my recommendation would be, to FDA, is to continue to work with that group through the ISO/ANSI process. And as long as those procedures are acceptable to them, then we should go forward with those because they're the furthest, most developed testing methods.

DR. HIGGINBOTHAM: Dr. Jacob and then Dr. McLeod and then Dr. Lecca.

You had a comment?

DR. JACOB: Jean Jacob.

I understand that this whole FDA response is due to the problems in 2007 where people said, well, how could this product be on the market and why didn't the FDA do more. But I don't think that you can test for bad behavior, and you can't do a test that's repeatable for bad behavior. And that is, I think, where we're kind of coming from. I think that the FDA has done a great amount of work to try to figure out how everybody behaves badly so that we could find the parameters to test to make sure that those kinds of consequences -- and people having to have corneas replaced -- doesn't happen again. But I don't think lens uptake is the way.

I would agree with Dr. Reller in that the whole microbiology needs to be done with the lens in place, and if you don't do it with the lens in place, it's not the real world. Sure, you can test the solution against the bug, but it doesn't take into account the case and the lens, and that needs to be done that way and it needs organic soiling agents on the lens.

That was my comment.

DR. HIGGINBOTHAM: Thank you.

Dr. McLeod.

DR McLEOD: Just in brief, I'd suggest, just in terms of any other factors, but again, reiterating the concept of identifying when the end of the soak time or when the end of a defined storage time is and then looking at microbial recovery at that point in time.

Does that make sense?

DR. HIGGINBOTHAM: Yes, thank you.

Dr. Lecca and then Dr. Szczotka-Flynn.

DR. LECCA: I would just very briefly comment on this longer soak time. I think it's important that we follow that. I think-- how much time? I don't know. A week, a day, an hour or two, whatever. But my question is, I read quite a bit about some companies feel that we should not be bothered with soaking time because patients don't follow instructions anyway, so why do we have to put it down? Well, I don't go along with that. I believe that we have to do it, and we won't put the onus on the patient. So my thinking is that the longer soaking time is fine. I don't know about soil. We had our expert over here talk about that. But other than that, that's the main thing I wanted to talk about.

Thank you.

DR. HIGGINBOTHAM: Dr. Szczotka-Flynn and then we'll have

Dr. Huang.

DR. SZCZOTKA-FLYNN: Loretta Szczotka-Flynn.

Just in response to the lens uptake, I think that it is important. I think what we're all agreeing on, just to clarify, is that you trust the efficacy of the solution in the presence of a lens, and I think that will then, therefore, clarify the lens uptake question.

With regards to other factors, one thing that hasn't come up is considering potentially other isolates to be tested, some that are more modern, more relevant, other than the five strains that have been continually tested; for example, the *Fusarium* strain is weak, doesn't form biofilm. So I'm sure there are better experts than me that can tell you what are better isolates to use. But I would consider revisiting the five isolates that have been classically used.

DR. HIGGINBOTHAM: Dr. Huang.

DR. HUANG: My point is very similar to Dr. Flynn's comment, is that in laboratory or -- that this meeting is really reactionary to what has happened in the past, in 2006-2007, so therefore we are here to talk about how to provide better contact lens care products. And so, therefore, I think FDA has done a great job in their 575, and they have expanded a scope after previous -- the examination pattern, including the recommendation under amoeba testing.

But I think we should also look a little bit further, maybe a little

bit more proactive. You now, we are not just try to prevent a *Fusarium* outbreak again or amoeba outbreak again, because down the road we see antibiotics changing, you know, that we may have emerging resistance to -- so that probably the FDA should consider expanding the specific organism, such as a typical *Mycobacterium* or E. coli. I mean, inserting the public health problems.

And then the gram-negative organism where this is the main -- some of the gram-positive has become also an issue, not just the *Staph aureus;* sometimes *Staph epidermidis*, you know, is becoming an issue. So in terms of how five gold standards maybe should be expanded.

DR. HIGGINBOTHAM: Thank you.

Dr. Eydelman, in response to Question 4, the Panel would like FDA to continue to work with industry through its collaborations with ANSI and ISO. However, there were some refinements on the preclinical testing interventions listed here. Certainly, it would be helpful to know the effect of protein on a disinfectant as opposed to just soil, but I guess soil is certainly a standard, but really refining that a bit. Trying to be true to Dr. Reller here.

Longer soak times. What is the efficacy after defined storage time, you know, not just a longer soak time but a defined storage time. Certainly, all of these tests should be done with the lens and the cases to reflect real-world experiences and besides -- well, in addition to actually testing each of the categories.

And then other factors were they would like to consider, such as to ensure that we are testing emerging organisms beyond the five categories that have been classically tested thus far. In addition, the concentration of the preservative on the eye was the release in the actual eye and what impact that might have to the aqua tissue. Those are at least two additional things to consider.

Any other revisions or edits from the Panel?

(No response.)

DR. EYDELMAN: Thank you.

Question 5, please.

DR. HAMPTON: Some RGP lens regimens still recommend the use of water. What alternatives would you recommend to replace water (e.g., preserved saline, unpreserved saline, etc.)?

DR. HIGGINBOTHAM: Yes, Dr. Szczotka-Flynn.

DR. JACOB: I'll just restate what I said earlier, that I think unpreserved or preserved saline would be acceptable to me as a rinse in replacement of water, whereas sometimes in soft lenses we prefer an unpreserved approach. And rigid, I would not be as concerned, as a clinician, because the lens doesn't take up the preservative and usually cause any ocular problems.

So I would be fine with preserved saline, but I would also want better options on the market that would allow copious rinses that would be

affordable, cost effective, easily found, that wouldn't squirt out drops of saline. But I would like to see some more aerosols and that sort of thing so that we can educate our patients on what to buy.

DR. HIGGINBOTHAM: Great.

Dr. Bressler.

DR. BRESSLER: Neil Bressler.

As I said earlier, it's tough to replace the force of what comes out of a faucet, and if you do, indeed, show some confident data that that is contributing to these AK problems, for example, then I'm all for trying to find some substitute that can come out with that force -- preserved saline, unpreserved saline, whatever. But we have not yet been shown, in my opinion, data that show that that's an independent -- even in a univariate analysis, a risk from the CDC's preliminary information, while it does exist in AK series, that people said that they used running water, for example.

We also were told that almost everyone does, so you would expect that in a questionnaire to people, or that half of the people do. So, again, I would reiterate that I wouldn't recommend any alternatives right now until you have more information that that's the causative agent and you have information that something is better. I wouldn't want to get rid of this force that's getting rid of deposits and find out by not having that, you have other problems that develop, for example.

DR. HIGGINBOTHAM: So you would keep things as they are? I

just want to make sure.

DR. BRESSLER: To answer the question "what alternatives would you recommend," I would not recommend alternatives to replace water at this time for rinsing.

DR. HIGGINBOTHAM: All right.

Dr. Bergmanson.

DR. BERGMANSON: Yes. I would just like to bring up the very fact that the countries with a higher density in the tap water, like United Kingdom and Hong Kong, they have a higher incidence of *Acanthamoeba*, so I think that's evidence for that we want to avoid tap water at all costs. And I will also add to what Dr. Flynn said, that to replace the tap water -- actually, unpreserved and preserved saline -- I think preserved is probably the better choice because so often the unpreserved comes in a bigger bottle that could become contaminated through its use.

DR. HIGGINBOTHAM: So you're speaking in favor of preserved saline, no tap water? You're speaking in favor of preserved saline, no unpreserved and no tap water?

DR. BERGMANSON: Yes. And I think preserved saline and unpreserved saline are far better than tap water. But I'm saying my preference, if that was -- a good choice on the market would be to give patients the recommendation of preserved saline.

DR. HIGGINBOTHAM: Okay, thank you.

DR. BRESSLER: Just as a comment to your comment. As far as other countries are concerned, again, I would recommend the FDA look at those data, confirm that they are not contaminated by confounding variables such as they also were topping off the solutions or areas like that. It may very well exist. It wasn't, at least, within the packet of the information we were given on the *Acanthamoeba* keratitis infections.

DR. HIGGINBOTHAM: Dr. Huang and then Dr. Sugar.

DR. HUANG: I agree with that. The rest of the comment, you know, that I think there's really no strong evidence saying that tap water is really the source of the infection, and until we have further evidence, I don't think we should mix the possibility.

But on the other hand, I also agree, as a clinician, we really have a real shortage of good, high quality preserved or whatever solution you want to call it, a rinsing solution. But I'm just wondering if there's -- you know, that we have so many experts here, is it possible to use a bottled water or boiled water as a substitute until we settle the issue of all this, you know, so-called preserved water or preserved saline, those kind of situation? So this may be good steps and more pragmatic approach.

DR. HIGGINBOTHAM: Great.

Dr. Sugar.

DR. SUGAR: I disagree with Dr. Bressler's comments, with all due respect. I think there is good evidence that the water supply is a major

source of organisms, and it's been studied in Florida, Illinois, London, and other places. Regardless, I don't know that rinsing with saline solves the problem unless the saline has been kept in some aseptic environment. My question, actually, was when you say lens regimens, you mean also cleaning the cases as well as the lenses? Because I think that that's an equal issue.

DR. HIGGINBOTHAM: That's where the aerosol delivery system would come into play.

Dr. Lecca.

DR. LECCA: I just want to say that, listening to the discussion here -- and I have put down even before that -- I would recommend purified water to be used rather than tap water. The literature that I have read and people I have spoken with would recommend -- they say purified water rather than tap water, so that's what I would recommend.

DR. HIGGINBOTHAM: Before I come back to you, Dr. Bergmanson, I would like to go to Dr. Steinemann because you see cornea patients, right? So do you have a comment on this?

DR. STEINEMANN: I guess I would agree with Dr. Sugar's comments. I think that water is important, and I think, in terms of talking about labeling for product care materials, I think it's important not to have it on there.

DR. HIGGINBOTHAM: So you're speaking in favor of no tap water? No tap water.

And, Dr. Owsley, you actually spent a lot of time thinking about the quality of lives of patients, et cetera. Do you think the saline, if we recommend saline only, is that an issue? Or what are your thoughts?

DR. OWSLEY: Cynthia Owsley.

I actually agree with Dr. Bressler's analysis and comments. Listening today, I have not heard any strong evidence that we know that tap water for rinsing is the problem. So at this time, I would answer this question, "what alternatives would you recommend to replace water" for rinsing, I would not recommend any alternatives at this time. But I want to emphasize that I think more research clearly is needed on this issue, and it could very well -- down the road, the data would come out. But right now I'm just not hearing or seeing that data today.

DR. HIGGINBOTHAM: And Dr. Bergmanson.

DR. BERGMANSON: Yes, I would just like to point out that the exposure to tap water is exposing the cornea to a low tonicity environment, and that has been shown to open up the space, open up spaces between the epithelial cells. And those spaces create, by un-physiological exposure -- those spaces are big enough for the acanthapodia, the feet of the *Acanthamoeba*, to get a foothold between the cells and then later on work their way in.

So it could be that, at least in many cases, the exposure to fresh and low tonicity water is not exactly where the *Acanthamoeba* invasion

happened, but it set the scene, it opened the door. And then if you have a dirty lens case or something like that where you have plenty of amoebas, then the door is open and they can work their way in.

So I think there are two reasons, then, why exposure to low tonicity water -- tap water, fresh water, or hot tub water is not a popular way of getting it. There are two. One is that you have amoebas. The other one is that this exposure of the ocular surface create spaces that the amoeba could work their way in on.

DR. HIGGINBOTHAM: Thank you.

Dr. Ahearn, you had your hand up.

DR. AHEARN: Dr. Ahearn from Atlanta.

And back in Atlanta, we had hot tub exposures. We also had exposures from mixed well water, and that came in, in tap water. And we're well aware of the difficulties that we had with preserved saline and unpreserved saline with *Acanthamoeba,* and this was the first outbreak in the '70s. And also outbreaks in Hong Kong, and again some of the ones that were in Finland and Poland. And the difficulties rise in that if you keep the bottled water at home and if you keep the saline at home and used and it's in a container, in just a very short time it's contaminated with all types of bacteria, and that's supportive of the amoeba.

So if you were to look at the information that we've had here today and the very, very low incidence of *Acanthamoeba* keratitis associated

with a rigid gas permeable lens, and you look at the fact that it is ubiquitous in nature, then I would have to definitely agree with Dr. Bressler and also with Cynthia and the statements that they have made, that we don't have a good substitute right now.

Even back when we used the aerosols, which at first were good, but they have a limited use because of the tube getting back-contaminated, and then we had an increase of bacterial keratitis. And so if they had used them and used them flush -- but what is the noncompliance there? Well, no. You don't want to use that aerosol right up, so you don't want to use it just to flush the tube and then you don't want to take the time to keep it sterile. So dealing with the noncompliance all the way down the line is very difficult. The one need is for a better way to remove potentially more toxic types of chemicals that can be used and the chlorhexidine content.

We're removing products that actually are used in therapy, which was talked about before, both PHMB and -- will have an effect against both the *Fusarium*, as well as the *Acanthamoeba*. So I'm still thinking, in my mind right now, that the best resort we have is to use the tap water here. If the tap water is gray water and if it's from, say, Scotland areas where they're using gray water, Hong Kong where they had reservoir water on the roof, then you have difficulty. If you have untreated tap water, problem. But I think here in the States right now is what we're talking about, what our recommendation would be.

I would not want to say that you could not use hot tap water. I think the incidence of *Acanthamoeba* is relatively low under these circumstances, but the major point is that you can clean that rather thoroughly. You can clean the lens rather thoroughly; you can remove deposits and so forth. So unless I had more information that the tap water in the USA was a problem, I would go along with the previous discussions.

DR. HIGGINBOTHAM: Thank you.

Yes, Dr. Szczotka-Flynn.

DR. SZCZOTKA-FLYNN: I just wanted to clarify Dr. Bergmanson's comment about water in the eye. I was never considering at all that water would go in the eye because any of the current RGP solutions -- I'm not even familiar what they say, but I'm assuming they say rinse the cleaner before disinfection and then from disinfection it goes directly in the eye. So there really should be a clear message that water should never go in the eye. That would include the soaking over the night in water and then in the eye. Of course, that should be well known.

So I think we have to be sure we're all talking about the same thing. When we say rinsing with water, we mean rinsing off some chemical, some cleaner, some very strong enzyme solution, and then following up with proper disinfection procedures and never re-rinsing with water right before it goes in the eye. That's a very important point.

DR. HIGGINBOTHAM: I think that was a very helpful comment.

Dr. Steinemann.

DR. STEINEMANN: Just one comment on that though, Loretta. A lot of people -- again, noncompliance reigns. They don't use the product that way. They should do it basically in the evening, presumably taking their lenses out. It's easier to debris the lens, get it cleaned off, and put it in the disinfecting solution. But the reality is that they wake up late for work the next morning, they do it quickly, they want to rinse it off and they don't put it in the disinfecting soaking solution. They rinse it off with tap water and put it in their eye.

DR. HIGGINBOTHAM: Dr. Zabransky, not to put you on the spot, but you're a microbiologist and we'd like to really get your opinion.

DR. ZABRANSKY: Zabransky.

My comment earlier about, you know, don't use water at all, I keep coming back to some of my experiences in rural areas and not necessarily with *Acanthamoeba*, but with other amoebic diseases that are transmitted from well water. And I don't know how many patients in the United States live in the rural areas with well water that use contact lenses, and I didn't see any of the data in here that distinguished infections that were due to water or thought were due to water, whether it was rural water or city treated water.

And, again, cities use different types of chlorine treatment for water, as well. Remember in Milwaukee we had the big *Cryptosporidium*

outbreak from a water treatment plant. We don't know how many other amoeba were in there, as well. So the aspect of rinsing well, but perhaps -- you know. And then making sure that the lenses go back into the disinfecting or preservative solution afterwards is the answer. But, again, this is an issue of compliance, and I don't know how we can monitor that.

DR. HIGGINBOTHAM: Dr. Owsley.

DR. OWSLEY: Just from the standpoint -- earlier you asked me about patient burden, consumer burden, and it seems that if we're going to ask the consumer, we're going to ask the patient to buy a non-water type solution and they would be purchasing this -- I'm sure they're not getting it free -- that we should have strong evidence that tap water is not appropriate. So from a patient participant, patient burden perspective, I think that's something we need to take into account.

DR. HIGGINBOTHAM: Dr. Eydelman, in response to Question 5, there were mixed responses to this question. But I think, generally, many of the Panel members felt that there was insufficient evidence to mandate saline solution, but it goes back to patient compliance. And here again, zip code may be more important than anything else as it relates to sources of water, but that will have to be up to the provider to ensure that patients are appropriately educated about not putting freshly washed lenses that have been in tap water directly into their eyes, among other factors. In the future, it will be nice to have a delivery system that doesn't require a lot of work on

the patient's part, such as aerosol.

DR. EYDELMAN: Thank you. That concludes our questions for the day.

DR. HIGGINBOTHAM: Well, Dr. Eydelman, do you have final remarks?

DR. EYDELMAN: I would like to thank my team for years of work on this topic and for working very hard to try to make today's meeting as comprehensive as possible. I also would like to especially thank all the panelists. I think I, together with my team, were quite taken by the thoughtful and quite detailed discussion that transpired today, and we thank you for the time that you've committed to this endeavor.

DR. HIGGINBOTHAM: And I would like to thank you and the FDA, Dr. Eydelman, for such a wonderful presentation, on behalf of the Panel. I think we're all educated about the contact solutions and contact lenses and what's new more than any of us realize. It was information available to learn about, but I think we've all been educated, and I hope that this discussion is helpful to you.

And I also would like to thank the CDC member for being here, as well. I know she already left.

But thank you to all the Panel members, too. It was wonderful getting to meet all of you. We don't always get a nice, diverse group like this, but I think I personally have learned a lot from each of you, so thank you for

the time that you put into this effort.

The May 13, 2014 meeting of the Ophthalmic Devices Panel of the Medical Devices Advisory Committee is now adjourned.

Safe travels, everyone.

(Whereupon, at 4:33 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

OPHTHALMIC DEVICES PANEL

May 13, 2014

Germantown, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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CATHY BELKA

Official Reporter