solution to do anything to the corneal surface when worn in conjunction with a contact lens. The goal should be to put the lens on the surface and have the cornea never know it was there, even though it has been slept in 30 nights at a time. And the goal should also be that the solution will do the same thing. It would not alter the corneal epithelium in any way that would encourage binding of pathogens.

We have not looked at fungi. We have not looked at acanthamoeba. And oh, by the way, exfoliation decreases substantially, that is all contact lens wear, regardless of solution and all lens types decrease the surface exfoliation by shutting off apotheosis. So the cornea cannot shed and in fact its cell, which is one of the losses and it's a defense mechanism that leads to microbial keratitis.

Next slide, please. In conclusion, what you have here now is lens type, wearing modality, lens oxygen. Lens oxygen has been

shown unequivocally to regulate at least pseudomonas binding. And if you -- the studies would have predicted with silicone hydrogels that the rates of MK would come down in daily and extended wear.

Well, they didn't. But they didn't go up either. And the prediction that the length of wear would not determine a future risk held up. And the prediction unexpectedly that under six months wearers would have a higher risk has stood up. So I think that the solutions are going to have to be fit into this matrix.

Now, the last point. Winston Churchill has a wonderful aphorism "Those who allow the past to continually reopen a coral to the present, lose the future." You have heard about the problems. But where do you go next?

Well, in 1986, we had the same problem six or seven medical boards want to shut down the industry, there was no data on

risk or incidence prevalence, risk safety values. The Agency was having hearings like this. Everybody was wringing their hands and everyone knew there was a major problem that had to be solved.

Don Ahearn and I and a colleague, who is since deceased, drove in a blinding rain storm down to Hilton Head Island where for three days there was a very acrimonious, but very profitable conference held attended by representatives from the ophthalmic community, the optometric community, the National Health Care Statistics group, the National Eye Institute, the FDA and all of the members of CLI and nominated representatives.

Out of that meeting came a solicitation for four schools who presented proposition proposals of which Harvard got the bid and then the famous papers in the New England Journal, Juan Poggio and Olliver Schein came out to define risk incidents. Disposable lenses rapidly followed and the

Agency was able to institute a six night wearing schedule that seemed to solve the problems.

Now, I suggest and there may be other ways to do this, but I'm sitting here thinking that the same thing is going to have to occur here. A task force like this needs to meet this summer and needs to include representatives from the ISO committees. I have great faith in my personality of my colleagues, but the ISO committee took 17.5 years to agree on the wording of a definition for infiltrates and microbial keratitis in the cornea.

So I submit to you that their time table may not be the same as those of us who have patient safety at our heart of our concern. Neither do we want to get it wrong, so they should be part of the answer.

Now, you have looked at the answer already. Simon Kilvington stood here and showed you that list of testing every solution

on the planet and what was the only one that killed all the cysts and all the tropes in four hours? Hydrogen peroxide. So why isn't that the gold standard and all the MPS solutions have to meet that standard?

The PEG, the question needs to be looked at. There are ways of doing this, but this Panel, unless it thinks it can do it on its own, and if so, God bless you, needs -- this Agency needs a white paper probably 50 or 100 pages long which if there is a subgroup that thinks that the science is not right, that the group got it wrong, they can have a minority report.

And then the Agency has a framework, a basis upon which to make some rational decisions about some of the issues that have been raised. As far as I can see, all of the problems and issues are out here on the table. I have yet to have heard a concrete time table and mechanism, however, by which they will be solved. And I make this

suggestion in good faith to the Panel, to the Agency and I think the professions would -- all of the groups would support it.

As far as funding is concerned, since the public may not know that the Agency cannot fund these kind of things correctly, and probably shouldn't, I think either the CLI and/or the professional communities or a private C3501 charitable exempt foundation could be found. In fact, I know of one --

DR. BRESSLER: Thank you very much.

DR. CAVANAGH: -- that would fund such a study. Thank you.

DR. BRESSLER: Thank you again. Thank you, Dr. Cavanagh. Our last public speaker scheduled will be Sheila Kinsey, perhaps. Yes, thank you.

MS. KINSEY: Hello. You surprised me. I'm Sheila Kinsey and I'm here to present my paper about my struggle having acanthamoeba itself for seven years. As a member of Prevent Blindness America PBA, a private

foundation devoted to saving the vision of Americans since 1908, I'm honored today to represent acanthamoeba keratitis victims everywhere.

My hope is that the FDA will move quickly to protect the 35 million Americans who wear contacts and clean them with solutions that amazingly provide no protection whatsoever, none at all against an incredibly cruel parasite present in all of our water supplies.

Through our PBA forum, MAAD, Mothers Against Acanthamoeba Disease, we've welcomed victim after victim after victim to our forum. We have answered questions ranging from where to find an AK specialist to how to sleep upright with a bag of frozen peas propped on a throbbing eye.

We have done our best to help the people who have written to us in desperation and fear, because we know that panic and pain personally. Our founder, Mary Beth

Stillmaker, was so determined to prevent her teenage daughter's four year battle with AK from happening to others, that she started our MAAD group in 2006 with the backing of PBA.

She has taught a small army of us now, all AK damaged foot soldiers, with her patient example to ease, educate and guide AK victims toward the medical help they need. Our own experiences with AK are what inspire us to keep fighting for safety in the contact industry.

I speak for Paige Reichart who lost her eye to it, for Anne Sears, whose patient -- whose sister, T.C., is still blinded by it in both eyes after a year and a half, for Julie Satler and her bright beautiful daughter, Sarah, who lost a year of her life before returning to college this fall, for Martha and Terry and Richard and David and for the scores of others who have posted their painful struggles with this beast.

My own history with acanthamoeba is

so long and so difficult that I would gladly forget it, but I'm still living it and I'm here to tell you what really happened. I woke up in California one morning in September of 2001 with my eye infection -- with an eye infection that would level my life. I was an ordinary person then living with my two extraordinary children, one a freshman in high school and one a sophomore in college.

I was a newly single mother who had worn soft contact lenses for about two years. They were a late birthday gift from my brother in Iowa on a summer visit during my rough divorce. He said something like hop in the car, sis, you look like an old foggie in those glasses, so let's spiff you up.

After a trip to his optometrist at the mall and several shopping bags of new clothes, I passed his inspection and I flew back home to my life. I wore my lenses carefully. I had always been referred to by my children as a germophobe, in fact, and I

laughed at their jibes knowing that at least we were healthy.

I never swam in my lenses, always washed my hands before I touched them and generally lived up to my reputation as a mostly healthy germophobe.

My eye infection began with mild swelling in September of 2001, but within two weeks, I was cringing with pain. Tears poured from my eye and I went outside only when I absolutely had to, huddled over and wearing a doubled pair of dark glasses.

My doctors didn't know what they could do to help me. But by Thanksgiving, the white of my eye was an oozing dark red that my horrified, but frank, hostess described as looking like port wine had been poured into it. I had taken a leave from my teaching job by then and I left my darkened bedroom only for eye appointments and extreme emergencies.

After a difficult beyond belief Christmas, trying to -- trying and failing to

get even a tree up for my children, much less shopping for gifts, I asked for a referral to the USC Doheny Eye Center, a 30 minute drive in light traffic and a two hour drive in heavy traffic.

My son, a USC sophomore with a full-time job at Fox Sports as a cameraman, drove me when he could and my friends with packed schedules of their own drove me when he couldn't. My 14 year-old daughter was my rock, but she was also a child who badly needed her mother.

2002 was a blur of excruciating pain and extreme fear. My Doheny ophthalmologist finally performed a deep tissue biopsy in July that confirmed our worst fear of all, my eye was swarming with acanthamoeba with only tiny specs of healthy cells in the photo taken during the biopsy.

When the infection got worse and worse despite treatment, I was advised to move to Iowa to be treated by one of the country's

top AK specialists, Dr. John Sutphin. The hardest thing I have ever done in my life was when I left my children that October. I wish I could say that we have recovered, but we haven't.

I missed my daughter's entire high school years, her dances, parties, holidays, her prom. My son was driven, successful and completely on his own. Instead of taking care of the most important people in my life, I was taken away from them in a series of wheelchairs through airports and out of their lives and into the University of Iowa's Iowa Clinic where I met John Sutphin, the man who would save my life.

I spent the first of countless hospitalizations that day. Since then, I have had seven corneal transplants, dozens of procedures and medications and thousands of drops. My biggest breakthrough was an experimentally off-label use of IV pentamidine in early 2004 for about three weeks. We

turned to it in desperation after I had had unresponsive active acanthamoeba for three and a half years.

After years of high doses of prednisone to save the structure of my eye, I developed bleeding stomach ulcers in July of 2003 and spent five days in an ICU receiving emergency blood transfusions. So the need for something new to attack the amoeba was clear.

Six months later, there was no sign of active acanthamoeba. We had done it. So since then, slowly, but steadily we have been doing damage control. My new AK brainiac Dr. Kenneth Goins performed my latest surgery this January, in a blizzard, linking layers of two corneas and implanting a plastic drainage device to control a prednisone-induced high eye pressure in my eye.

DR. BRESSLER: Ms. Kinsey, thank you very much.

MS. KINSEY: Okay.

DR. BRESSLER: We really

appreciated it.

MS. KINSEY: Okay.

DR. BRESSLER: Thank you.

MS. KINSEY: Time?

DR. BRESSLER: Yes, but thank you again.

MS. KINSEY: Okay.

DR. BRESSLER: I want to thank all the public speakers for allowing us the chance to give everyone an opportunity throughout the morning to get the 10 minutes in.

I would just ask is there anyone in the audience, by raising their hand, that had wanted to also address the Panel? Okay. Thank you.

I would like to ask the Panel then if they have any questions for the speakers before we break for lunch and if the speaker is still here, I would ask them to come up to the podium to respond, if there are any questions for the public speakers. Dr. Matoba?

DR. MATOBA: I have a question for Dr. Cavanagh and it's regarding that test you did where you applied topically four types of contact lens solutions to patients and all of them had corneal staining. There is some information in literature to suggest that properly used hydrogen peroxide systems do not cause corneal staining. And I wondered if you had done any testing of the hydrogen peroxide systems?

DR. CAVANAGH: Alice, we did not do that in that study, but that was the whole purpose really is to use the preserved solutions and, of course, the hydrogen peroxide solution, as you know, goes to water, so it's non-preserved. And so it couldn't possibly have that type of toxicity, but I agree with you it would be good to do that.

DR. MATOBA: Yes.

DR. CAVANAGH: To look and see if the residue of hydrogen peroxide solution in a lens case caused increases in binding. I

suspect it would not, but that's a control that could be done.

DR. MATOBA: Well, but it's just in practice sometimes they do have patients who come in who have not properly neutralized the hydrogen peroxide.

DR. CAVANAGH: Right.

DR. MATOBA: So, you know, properly used it may be safe.

DR. CAVANAGH: Right.

DR. MATOBA: But then you have to take into account that maybe sometimes they don't use it.

DR. CAVANAGH: Alice, you are absolutely right. I once had a lady who didn't neutralize it and went blind in the waiting -- AOL elevator leaving the office. Her corneas turned completely white. Fortunately, the epithelium, as you know, recovers from that and she never did it again. And most patients who use hydrogen peroxide at least, they are only going to have their

eye sting once, at least, hopefully.

DR. BRESSLER: Thank you. Dr. Szczotka-Flynn and then Dr. Mathers.

DR. SZCZOTKA-FLYNN: My question is for Professor Mark Willcox. Mark, in your -- I have two questions for you. On your IER Standing Study, when you see the patients at three months --

DR. WILLCOX: Yes.

DR. SZCZOTKA-FLYNN: -- what time of day do you see them? How long after insertion?

DR. WILLCOX: We tend to see them in the morning or after work, so 4:00 to 6:00, something like that. And so it could be a long time after insertion admittedly, yes. It could be a short time.

DR. SZCZOTKA-FLYNN: And in your-- the data that you presented looking at the rubbing and rinsing with the -- I think you used OPTI-FREE and ReNu, what was your assay for binding the bacteria to the contact lens

to begin with?

DR. WILLCOX: It was 10 minutes.

DR. BRESSLER: Okay. Thank you. Dr. Mathers?

DR. MATHERS: Yes, I had a question also for Dr. Cavanagh. In your remarks about that study, you said something about randomizing to two groups, daily wear and extended wear, but you didn't comment on the extended wear.

DR. CAVANAGH: Well, the previous studies had begun extended wear after a wash-in of -- all studies ever published in this protocol over the last 15 years have a wash-out period of a month, no lens wear. The original studies all patients entered extended wear through a month of daily wear. In this study, they entered extended wear day novo, day one. They were randomized on the first lens fitting wearing visit to either sleeping in that lens for 30 -- the next 30 nights or to go on daily wear protocol for a year.

So the only difference in the two groups is the daily wear people took their lenses in and out and used a non-preserved care system of hydrogen peroxide and the extended wear people did the same, except that they did it every 30 days.

DR. MATHERS: So the extended wear pseudomonas binding was similar to the daily wear?

DR. CAVANAGH: It was identical. And in the previous studies using the MPS solutions, identical protocol, identical entry dropping criteria, identical outcome measures, identical visit numbers, it was over -- these studies were overlapping. So the only thing I can conclude is that we lost the advantage of the high oxygen in the silicone hydrogels by continuing to use them with the preserved care solutions and we should gain them back.

The wonderful thing about hypothesis and data is it predicts things. The next prediction, like I told Fiona, look

at the first six months wearers and I predict a difference. And I looked at her and she is already doing this, hopefully we will have the results in a year or two, in that wonderful Australian registry, which she has assembled, which is a wonderful tool.

You need to look at patients in silicone hydrogels on non-preserved wear and in preserved wear and ask if the incidents of inflammatory events and/or MK is different in the two groups. And the data I showed you predicts there will be.

DR. BRESSLER: Thank you.

DR. CAVANAGH: And the hydrogen peroxide kills all the cysts and trophozoites in four hours.

DR. BRESSLER: Very good. The last comment, I think, Dr. McMahon.

DR. McMAHON: Well, this is for Dr. Hansen. Much of your talk was on establishing a compliance program for the professions and for patients and it sounds good. Do you have

any evidence that it's going to make any difference?

DR. HANSEN: Well, I can see that other behaviors have been changed, so it's speculation that behaviors of seatbelts, flossing of teeth in Australia and I guess it's the profession as charged to see if we can change this behavior.

DR. BRESSLER: Very good. I want to thank again all the public speakers for preparing and sharing their remarks and the FDA personnel as well and the Panel for the morning, but we are going to take a break now until 12:45, because we have a busy and challenging afternoon.

So we will reconvene in this room and start right at 12:45. Please, take any personal belongings that you want with you at this time. The ballroom is going to be secured by the FDA staff during the lunch break and you will not be allowed back into this room until we reconvene at 12:45 or a few

minutes before. Thank you everybody. Thank you.

(Whereupon, the meeting was recessed at 12:01 p.m. to reconvene at 12:48 p.m. this same day.)

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

12:48 p.m.

CHAIRMAN BRESSLER: Okay. Thank you. It's just past 12:45 and I want to call our meeting to order for the afternoon session.

And we now will hear the FDA and CDC presentation. At the conclusion of these presentations, there will be time for questions from the panel members and then we'll move into the questions from the FDA for the panel.

At this time, we'll start with our first FDA speaker, Dr. James Saviola.

DR. SAVIOLA: Thank you, Dr. Bressler.

Good afternoon, everybody, and welcome back.

Today you will hear several presentations concerning contact lens care products and their interactions with contact lenses. As we already heard this morning

through the excellent presentations from the public and the industry, this was the source of the reason for having the meeting today, these two outbreaks which occurred over the last two years. And both cases there was one particular care product associated with these; it was a different product each time, as we know.

We have a very ambitious agenda. You will hear updates today on the two outbreaks, *Fusarium* keratitis presented by Dr. Gene Hilmantel of the FDA and on *Acanthamoeba* keratitis by Dr. Jennifer Verani, our colleague at CDC. You'll also hear several presentations from our staff. The agenda is listed in the hand out that you picked up on the way in today.

There are several topics; both labeling pre-clinical, as well as clinical areas to discuss. And during the presentation, we'll be interlacing the questions which you'll then have later on to

discuss individually.

So these keratitis outbreaks with the rare pathogens caused the FDA staff to reassess our current guidance recommendations for multi-purpose contact lens care products. Currently, we are in a transition period. Today there are new concerns brought upon by the introduction of new lens materials and different product formulations, as well, different patterns of use that were not existent at the time the current guidances were developed in the late '90s.

We are taking the post-market experience that we've learned in the last couple of years and trying to feed it back into the pre-market review process. We've been involved in a variety of different activities such as laboratory studies, standards development, etcetera as listed on this slide.

The review group does not feel that we have the luxury of conducting business as

usual while new standards and guidance are under development. Industry continues to dialogue with the review group as new products are formulated and testing strategies need to be developed. We need your help in formulating a regulatory strategy and gathering the best thoughts during this transition period.

Today's meeting provides the public, industry and panel members with the opportunity to participate with FDA staff in creating a future pathway for both new products under development, as well as current products on the market. As knowledgeable experts, you members of the panel are here to help us understand these issues a little bit more in detail. We have medical device expertise on how these products are used in the marketplace. We are seeking your input on several important topics to better understand the implications of these devices.

So as advisory panel members, your

objective will be to listen to these presentations; I apologize, more listening is involved, discuss the questions presented to you and provide your opinion so that the review staff will have additional information to use in developing necessary guidance. We all thank you in advance for your willingness to take on this challenge with us and for your thoughtful consideration of the issues to be presented.

Our first speaker will be Dr. Gene Hilmantel who will talk about the *Fusarium* keratitis.

DR. HILMANTEL: Good afternoon. My name is Gene Hilmantel. I'm an optometrist and a statistician for the Division of Ophthalmic and ENT Devices.

In our presentations today, we'll be discussing some possible changes in our guidance document for contact lens products. These issues are also related to some of our work with the relevant standards

organizations. These changes in our thinking were motivated by the recent outbreaks of *Fusarium* keratitis and later *Acanthamoeba* keratitis in the last few years.

Today I will very briefly recap what happened in the *Fusarium* keratitis outbreak of 2005 to 2006, and later a CDC epidemiologist will discuss the *Acanthamoeba* keratitis outbreak.

Before the outbreak fungal keratitis had been relatively rare in contact lens wearers constituting less than five percent of cases of contact lens-related microbial keratitis. In February 2006, there were reports of significant numbers of cases of *Fusarium* keratitis in Hong Kong and Singapore. The Singapore cases were reported to be related to use of Bausch & Lomb contact lens solutions. In March 2006, the Centers for Disease Control began receiving reports of *Fusarium* cases in the U.S. These reports prompted the ensuing CDC and FDA

investigation.

The CDC conducted a case control study to try to elucidate the factors related to these fungal infections. Cases were collected through active and passive means. Controls were neighborhood-matched adult soft contact lens wearers. Confirmed cases were defined as those which had positive corneal cultures for *Fusarium*. Patients with *Fusarium* keratitis, control patients and treating ophthalmologists were interviewed.

Passive surveillance ultimately identified 180 confirmed *Fusarium* cases between June 1, 2005 and September 30, 2006. These cases came from 36 states and territories. Univariant analysis of the case control study data identified the following risk factors: Use of Bausch & Lomb ReNu MoistureLoc solution with an odds ratio of 13.3 and reuse of solutions in the case, also known as "topping off." This had an odds ratio of 3.2. In the multi-variant analysis

use of MoistureLoc remained highly significant.

The Centers for Disease Control investigated the care products used by patients with the keratitis. *Fusarium* organisms were found on external tips of a few of the opened multipurpose solution bottles, but were not recovered from any unopened product. Genetic typing of the cultured *Fusarium* strains found a high genetic diversity in the isolated strains. This suggested that it is unlikely that there was a common source of contamination.

The FDA, CDC and Bausch & Lomb cooperated in an investigation of the possibility of contamination at the manufacturing facility in Greenville, South Carolina. No evidence for contamination was found. *Fusarium* was not recovered from retained lots of care products or water samples, including municipal water, deionized water and distilled water.

This figure shows the number of *Fusarium* as a function of time. It also shows the market share of the Bausch & Lomb MoistureLoc. There appears to be something of a relationship between the two here. The *Fusarium* cases shows a high degree of morbidity. About 30 percent of cases in the U.S. needed corneal transplants.

FDA, after considering the epidemiologic evidence and the seriousness of this fungal infection, believed that further actions were warranted. As a result of FDA discussions with Bausch & Lomb, Bausch & Lomb decided to cease sale of the product. U.S. product sales of ReNu MoistureLoc stopped on April 13, 2006. There was a worldwide recall of the product on May 15, 2006. The number of contact lens-related *Fusarium* cases in the U.S. dropped rapidly after the recall. The fact that the outbreak ended within two months of the product recall provided evidence of the success of the action.

The FDA and Bausch & Lomb immediately started looking for answers as to why this outbreak had occurred. The MoistureLoc formula contained two ingredients not found in other multipurpose solutions; alexadine, a disinfectant and polyquartium 10, a moisture-retaining polysaccharide. MoistureLoc also had a high content of poloxamer 407, a surfactant. Pre-market testing had shown MoistureLoc to have a high level of efficacy against *Fusarium*. The *Fusarium* outbreak was unexpected and was a significant public health problem. The FDA started thinking about how some of our pre-market testing procedures might be changed to minimize the possibility of future such outbreaks.

The other speakers today will discuss some of our thinking with regard to what we might change in order to improve the safety of contact lens products.

Our next speaker will be Jennifer

Verani, a CDC epidemiologist, who will provide an update concerning last year's *Acanthamoeba* keratitis outbreak.

DR. VERANI: Good afternoon. *Acanthamoeba* keratitis, or AK, is a rare, potentially blinding infection of the cornea caused by a free-living amoeba that is ubiquitous in the environment. AK primarily affects otherwise healthy contact lens users. Known risk factors among contact lens users include poor contact lens hygiene practices such as improper storage or disinfection of lenses and contact with non-sterile water while using lenses such as swimming or showering with lenses. The estimated incidence in the United States is one to two cases per million contact lens users per year.

In May 2006, the Illinois Department of Public Health notified CDC of a possible increase in AK cases in the Chicago area. An ophthalmology group at the University of Illinois at Chicago was

conducting a case control study to identify possible risk factors.

In October 2006, CDC informally contacted several ophthalmologists across the country to try to ascertain whether cases were on the rise in other areas as well, however, the results were inconclusive.

So in January 2007, we conducted a retrospective survey of 22 ophthalmologist centers nationwide requesting the numbers of AK cases seen per year for the past eight years. The survey results showed an increase in culture confirmed cases starting in 2004, as shown in this graph with number of cases on the Y axis and the year on the X axis.

So on March 16, a multistate outbreak investigation was launched. The objectives were to quantify and characterize the increase in AK cases, to identify any risk factors contributing to the increase and to recommend measures to prevent future cases.

We began with a case series. Cases

were identified as persons diagnosed with AK by an ophthalmologist with symptom onset on or after January 1, 2005 that had a positive culture for *Acanthamoeba* from a corneal specimen such as a scraping or biopsy. Case finding was conducted through Epi-X, ophthalmology and optometry associations and queries of microbiology labs and ophthalmology centers. We collected data through standardized telephone interviews with case patients, their treating ophthalmologist, and for contact lens users, their primary eye care providers.

While we planned a formal case control study, we also conducted a preliminary analysis comparing the AK case patients to the controls from the 2006 *Fusarium* keratitis outbreak investigation. The *Fusarium* controls are a group of 126 healthy adult contact lens users who were geographically matched to *Fusarium* cases. Because our case patient questionnaire was similar to the one used in

that investigation, we could conduct a preliminary analysis comparing the AK case patients to the *Fusarium* controls with regards to contact lens-related products and certain hygiene practices and behaviors.

By May 23rd, 46 AK case patients had been interviewed. A preliminary analysis conducted at that time using the *Fusarium* controls found a significant association of AK with use of Advanced Medical Optics, Complete MoisturePlus Multipurpose Contact Lens Solution. On May 24th those results were communicated to your colleagues at FDA. On May 25th they were communicated to our collaborators in state and local health departments and to the AMO company. On May 26th an MMWR dispatch was released and the company undertook a voluntary recall of AMO Complete MoisturePlus.

Following the preliminary analysis and the recall, we conducted a matched case control study. The case patients were

obtained from the case series. Controls were at least 12 years old with no history of AK. They were matched to cases by contact lens use, either soft contact lenses, rigid contact lenses or no use. They were also matched geographically and reverse address directory was used to phone numbers for potential controls. We used standardized telephone interviews and asked controls about their behaviors and product use during the one month prior to symptom onset of the corresponding case patient.

A total of 221 cases were reported from 37 states and Puerto Rico. One-hundred-fifty-eight of those cases were reported to be culture-confirmed. One-hundred-five of those case patients were interviewed and included in the case series. The EPI curve with the number of case patients on the Y axis by their month of symptom onset on the X axis does not reveal any obvious trends over time, nor does it suggest a single time period of peak

exposure. The case patients were widely distributed geographically throughout 30 states, as seen on this map.

The case patients were 36 percent male with a median age of 29 years and a range of 12 to 77 years. Eighty-nine percent were contact lens users and of those, 88 percent used soft contact lenses. Presenting symptoms most frequently included pain, redness, sensitivity to light and foreign body sensation. The median time from onset of symptoms to initiation of anti-*Acanthamoeba* treatment was 49 days with a range from four to 197 days. Information on clinical outcomes was available for 85 case patients. Of those, 28 percent had either undergone or were waiting corneal transplant. Data on current vision was available for 70 case patients. Forty-one percent had a visual acuity of 20 over 200 or worse with best correction in the affected eye.

We attempted to enroll match

controls for all 105 cases. After more than 11,000 phone calls, interviews were conducted with 184 controls who were matched to 91 case patients. The cases without matched controls were excluded from subsequent analysis. Separate analyses were conducted for soft contact lens users, rigid contact lens users and non-contact lens users because of differences in potential exposures. However, the numbers of rigid in non-users were small and no significant risk factors were identified. The following results are derived from the 72 case patients and 140 controls who were soft contact lens users.

On matched univaried analysis case patients were more likely to be male, under age 25 and Hispanic. Ocular trauma was uncommon among both groups, but was more frequently reported among cases than among controls. Cases were more likely to have used contact lens for less than or equal to five years. Swimming in a lake or river with

contact lens in was a significant risk factor, while washing the face with contact lens in was surprisingly protective. The use of AMO Complete MoisturePlus was a major risk factor as we had found in the preliminary analysis. Ever topping-off solution, which refers to the addition of new solution to old solution in the contact lens case was also an important risk factor. Always capping the solution bottle after using it was associated with disease. Cleaning lenses at the bathroom sink as compared to in the bathroom but not at the sink and always washing hands before inserting lenses were both protective. An unexpected finding was that less frequent replacement of old contact lens with new ones also appeared to be protective.

Only three of these variables remain statistically significant on multi-varied analysis. After adjusting for age and gender, case patients were almost 17 times more likely than controls to have used AMO

Complete MoisturePlus. They were 2.8 times more likely to report ever topping off solution and 2.8 times more likely to have used contact lens for less than five years.

There were several negative findings of interest. No association was found between AK and any other contact lens solution type or specific product. Contact lens characteristics such as FDA lens group, whether the material is a silicone hydrogel and whether the lens is surface treated were not associated with disease. Aspects of contact lens use such as daily versus extended wear, the hours used per day or days used per week and ever sleeping with lenses in did not seem to influence risk for AK. Habits related to contact lens hygiene and disinfection, such as rubbing or rinsing lenses during the disinfection process, hand washing before cleaning lenses, handling lenses with wet hands or hours storing lenses in the case were also not significant. Finally, water exposure

variables such as showering, bathing or swimming in a pool while wearing lenses were not associated with AK. Many of these variables have either been hypothesized to be possible risk factors for AK or have been found to be risk factors for the disease in other studies.

AMO Complete MoisturePlus is a multipurpose contact lens solution used for disinfecting, rinsing, cleaning and storing lenses. The product was launched in 2003, just preceding the nationwide increase in AK cases. We found no evidence to suggest that the strong association between AMO Complete MoisturePlus and AK was a result of contamination. Lot numbers were available for 21 bottles of AMO Complete MoisturePlus used by case patients; no single lot number was repeated. The wide geographic and temporal distribution of cases also argued against contamination as the cause for the outbreak. We suspect that insufficient anti-*Acanthamoeba*

activity of the solution may be to blame. A concurrent case control study of AK in the Chicago area which included 55 cases that were not included in our outbreak investigation also found that AMO Complete MoisturePlus was the primary risk factor.

There are several parallels between this AK outbreak and the *Fusarium* keratitis outbreak of 2006. Both outbreaks of serious corneal infections occurred primarily among soft contact lens users. The three to four year duration of the AK outbreaks spanned the 2006 time frame of the *Fusarium* keratitis. In both outbreaks the primary risk factor was a particular multipurpose solution. For *Fusarium* keratitis it was Bausch & Lomb ReNu with MoistureLoc was recalled in April 2006. Both investigations found no evidence of contamination. Instead, the solutions were thought to have insufficient antimicrobial efficacy. In both outbreaks the practice of topping off solution in the case also emerged

as an important risk factor. Following the *Fusarium* outbreak, ReNu with MoistureLoc was tested under circumstances that simulated reported practices of the case patients, including topping off solution, and it was found that this practice reduced the antimicrobial efficacy of the solution. Together these outbreaks have raised concern about the safety of multipurpose contact lens solutions.

The AMO product was recalled in May 2007 following the preliminary analysis conducted as part of this outbreak investigation. Although we stopped enrolling cases in July 2007, we have continued to receive anecdotal reports of cases of AK occurring in patients who continued to use AMO Complete MoisturePlus long after the recall, even as late as March of this year. We included a question about awareness of the recall in our control questionnaire and found that less than half of respondents had heard

about a solution recall in May 2007. Of those less than a quarter could name AMO Complete MoisturePlus as the recalled product. This highlights some of the challenges in recalling a product with a long shelf life. While it quickly comes off the pharmacy or grocery store shelf, it may remain on the bathroom shelf in consumers' homes for quite some time.

In order to assess the impact of the AMO Complete MoisturePlus recall, we recontacted the ophthalmology centers and microbiology laboratories that had provided us with the data that initially detected a nationwide outbreak and we asked them to share the numbers of AK cases diagnosed during 2007. It is important to note that these are not incidence rates, since the denominator is unknown. This graph depicts numbers of cases reported by a convenient sample of referral medical centers and laboratories on the Y axis and year of diagnosis on the X axis. This data is not yet complete, however, the

responses from 10 medical centers and labs show that large numbers of AK cases were diagnosed in 2007.

Yet if we look more closely at the data from 2007, we realize that this finding is not entirely surprising. AMO Complete MoisturePlus was on the market for the first five months of the year. And we know that some consumers continued to use the product for much longer. There is often a diagnostic delay since AK can mimic other types of keratitis. We found that patients were typically started on *Acanthamoeba*-specific treatment nearly two months after symptom onset. There also may have been diagnostic artifacts with peaks in cases diagnosed soon after the recall and following a series of media reports on the outbreak in late July and early August.

In looking at the monthly numbers of cases, we see neither a clear rise nor a clear decline in cases during the seven months

following the recall of AMO Complete MoisturePlus. In order to accurately assess the impact of the recall, we must continue to follow this trend into 2008.

This outbreak investigation had several limitations. There may have been limited recollection of which products were used one to two years prior to the interview. Reporting bias was also possible following the recall of AMO Complete MoisturePlus. We were unable to assess the role of water treatment type on the risk for AK, a concern that has been raised by some researchers. Because we used geographically-matched controls, which essentially matched on water supply system, our investigation was not well-suited to assess the role of water treatment type.

Finally, because their numbers were small, we were unable to detect any statistically significant risk factors among non-contact lens users and rigid contact lens

users. Nonetheless, we found that among soft contact lens users case patients were almost 17 times more likely than matched controls to report having AMO Complete MoisturePlus, a finding which validated the results of our preliminary analysis comparing AK cases to *Fusarium* controls. The use of this existing comparison data which was shared by our colleagues in the Mycotics Diseases Branch at CDC enabled rapid public health action months before our case control study was completed. There was no evidence of contamination of AMO Complete MoisturePlus and we suspect that insufficient anti-*Acanthamoeba* activity of the solution may be the underlying cause of the outbreak. Other risk factors included topping-off solution and contact lens use for less than or equal to five years.

Further research is needed to evaluate the anti-*Acanthamoeba* activity of AMO Complete MoisturePlus and other solutions. We are completing our follow-up survey of

ophthalmology centers and laboratories for AK cases diagnosed in 2007 and are planning another survey for the first half of 2008 in order to assess the impact of the recall.

Our data highlight the importance of promoting healthy habits among contact lens users, particularly avoiding the practice of topping-off. Special emphasis should be placed on new contact lens users as they appear to be at greater risk for developing AK.

I apologize for the small font here, but this investigation would not have been possible without the efforts of our many collaborators in state and local health departments, FDA, EPA, our academic consultants and throughout CDC. Thank you.

CHAIRMAN BRESSLER: Thank you very much. And we're just going to wait a few seconds to switch the microphones. You got through that challenge, but we appreciated the excellent presentation.

So, why don't you introduce and then we'll start.

DR. LEPRI: Mr. Chairperson, panel members and FDA colleagues--and guests, this afternoon I'm going to speak to you about what we know about contact lens wearers.

Doctors Hilmantel and Verani have just provided you with a recap of the *Fusarium* and AK outbreaks. One action in the rapid and multifactorial response performed by FDA was to immediately inform the public. For both outbreaks, FDA issued a public health notification to care providers and an advisement notice to contact lens wearers.

In these public documents, FDA has strengthened our recommendations regarding the key behaviors that need to be stressed and implemented by contact lens wearers. Our recommendations are based on the fact that contact lens wearers are unique.

According to the data collected by the American Optometric Association in 2003,

there are 30 million plus contact lens wearers in the United States. Seventy percent of them are female; they are predominantly myopic and half of all of them range in age from 25 to 44 years old. Eighty percent of this 30 million wear daily contact wear lenses and 15 percent wear extended wear soft contact lenses. More than 50 percent wear one-to-two-week disposables. The products and regimens of care for contact lenses are just as numerous and diverse. In fact, the care of contact lenses has continued to evolve and become ever more complicated prior to becoming simplified.

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, and most importantly, they have to monitor their own wearing time and replacement schedules of both lenses and

solutions.

Considering the millions who wear contact lenses and they responsibility they have in the maintenance and care of their lenses, it is a wonder that there are so relatively few complications with respect to the number of wearers. However, these complications can sometime be sight-threatening. What are the sources of these complications? Well, 80 percent are the result of non-compliance with wear and care regimens according to Ky et al. in their 1999 study. The most interesting finding in the study was that the consumers' perception of their own compliance behavior is fundamental to minimizing and/or preventing these complications. Various other studies regarding contact lens care compliance have verified this finding.

In 2004, DeMatteo published a study analyzing general medical compliance. His study revealed that in 2000 there were

approximately 759.3 million physician visits recorded. 188.3 million of these visits resulted from patients not following their physician's orders. This translates to a non-compliance rate of 24.8 percent for general medical care. 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.

Just last year Dohshik et al. identified the complexity of treatment, frequency of duration and the cost of the regiment are the major factors that affect contact lens compliance. And, medical literature has repeatedly emphasized that there is a higher incidence of non-compliance in conditions that are asymptomatic, prophylactic or suppressive in nature. The factors necessary for contact lens safety are indeed exactly those that contribute to non-compliance. In Olivera's self evaluation of contact lens care in college students and

health care workers, it was found that 54.2 percent considered themselves poor wearers. Of these, 44.3 percent claim that they were poor wearers because of their inadequate cleaning of lenses or the lens case. Another 15 percent admitted to general medical non-compliance.

Regarding contact lens procedures, 79.1 percent responded that they failed to implement contact lens care procedures and another 30 percent claim that their non-compliance is due to lack of knowledge or being poorly prepared to care for their lenses. Collins found the non-compliance rate of 74 percent in adult wearers who had worn lenses for an average of 2.6 years. This study also found that components of non-compliance to be lack of understanding, improper usage of lens care products and poor hand hygiene. This study population had many symptoms and complaints, yet they did not perceive themselves as non-compliant.

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

The previous slides, coupled with what we have learned from the analysis of the *Fusarium* and *Acanthamoeba* outbreaks emphasizes the role of human factors and the safe use of contact lenses and care products. These outbreaks are what calls for better patient and doctor education and improved design and testing for contact lens care solutions. These human factors apply both to the consumer and the manufacturer; the blame does not lie entirely with the consumer. The goal of human factors engineering is to make products efficient, safe and easy to learn and use by understanding how the consumer actually uses the device in the real world. Although errors

are natural, the Center works with industry to prevent and/or reduce use error as well as the consequences of it.

Unfortunately, the term originally employed was "user error" implying that there was fault or liability on the part of the device user. The new term, "use error," correctly spreads the errors to include design and labeling as well as consumer use. This recognizes that simply labeling a device with dos and don'ts usually is not enough to obviate preventable adverse events.

Human factors engineering aims to reduce use error, however, it is challenging and begins with initial pre-manufacturing design and continues through pre-clinical and clinical testing, consumer testing and labeling. Human factors is especially challenging for contact lenses and contact lens care products.

This slide provides a summary of use errors or non-compliance behaviors in lens

wearers. Irregular cleaning of lenses, which also includes skipping daily cleaning or not following recommended disinfection times and also inadequate rinse times. Poor hand hygiene or the total lack of hand washing, using tap water or saliva to wet lenses, not following lens replacement schedules such as extending the wear of lenses beyond the manufacturer's or eye care professional's recommendations, lack of regular eye exams and/or follow-up contact lens exams and irregular replacement of disinfecting solutions. Which, as you've heard numerous times today, includes topping off and reuse of solution. And, they also use solutions far beyond the expiration date.

Given what we know about use errors, we have the following recommendations. Labeling should provide written instructions along with the reasons for the various procedural steps and the consequences for not following them. Eye care professionals should

reinforce lens care regimens with their patients and utilize both the patient and practitioner guides provided with the care products. Care products should be designed and tested consistent with consumer use patterns. For example, product labeling should include a discard date for use after opening of the product due to the fact that patients often use solutions far beyond their expiration date.

The use of a discard date is recommended because patients are known to use these care products outside of the expiration date long after the effectiveness has waned. Warning the consumer to discard the product within a specific number of days after opening will add a significant layer of protection.

The panel will be asked to consider the following question in their deliberations today. Please discuss our proposal for specifying a discard date on lens care product labeling in addition to an expiration date.

At this meeting today FDA is continuing their response to the two outbreaks. FDA staff will provide for your consideration the changes in labeling, pre-clinical and clinical testing which we believe are needed. The consumer use patterns discussed in my presentation provide the necessary back drop for the next presentation on labeling. All of the issues that I identified will be addressed by our next speaker, Carol Clayton, who will discuss changes in labeling.

Ms. Clayton is from the Office of Communication, Education and Radiation Programs. Thank you for your time.

CHAIRMAN BRESSLER: Thank you very much.

MS. CLAYTON: Hi. My name is Carol Clayton. I am from the Center's Office of Communication, Education and Radiation Programs. I will be talking to you today about patient labeling.

I will discuss some general principles for developing patient labeling. Then I will briefly discuss the Center's consumer recommendations from the advice for patient notifications for the *Fusarium* and *Acanthamoeba* outbreaks. Finally, I will discuss proposed new patient labeling for the panel's consideration based on the recommendations and the advice for patient notifications.

In developing these proposed new patient labeling statements, we applied patient labeling principles from your guidance document, "Guidance on Medical Device Patient Labeling." It was issued on April 19th, 2001. This guidance addresses writing instructions for use including warning and precaution statements. It does not replace the more specific guidance for daily wear contact lenses and guidance for contact lens care products.

In the patient labeling guidance

document we describe the four elements necessary for an effective warning or precaution. The signal word is used to alert the reader that what follows is important hazard information. Bold, large type, underline or color may help this stand out from the rest of the text. The hazard avoidance directive gives clear instruction to the user on how to avoid the hazard. The clear statement of the nature of the hazard characterizes the severity of the hazard and the likelihood. And finally, the consequences specify the serious adverse events, potential safety hazards and limitations in device use that may result if users do not follow instructions.

Its purpose is to give a clear idea of the risk which is likely to increase compliance. Hazard alert research has shown that this element has a significant effect on readers. If the consequences are not included, the alert is less effective.

Based on these principles just discussed and applying them to recent contact lens infection outbreaks, we developed proposed new patient labeling instructions for use and warning statements. The proposed new patient labeling is based on recommendations in these two advice for patient documents. Briefly, some of these recommendations included avoiding reuse or topping-off solution, considering rub and rinse cleaning method, using proper lens case care and removing lenses before any water activity. In both of these cases a team of experts from the Center, FDA and CDC was assembled to investigate the outbreaks and develop these recommendations.

Now I will discuss the proposed new patient labeling for the panel's consideration based on the recommendations while applying the patient labeling principles.

From the *Acanthamoeba* outbreak, the misuse of reusing multipurpose solution in the

lens case became a concern. We want to be sure that the contact lens users are aware of this potential problem and how it can be avoided. In addition to the current instruction for use, we propose this new labeling using the principles that was just described earlier. The signal word "warning" in bold, the hazard avoidance directive, "Do not reuse or top-off old solution left in your lens case," the clear statement of nature of hazard, "Solution reuse reduces effective lens disinfection," and the consequence, "Reuse of old solution could lead to serious eye infection." This is most important because it gives the user a clear idea of the risk and hopefully lead to increased compliance.

Question for the panel. Please discuss whether our proposed warning on reuse and topping off is warranted. If yes, please identify any other message that should be conveyed in this warning.

Our next proposed label. Consumers

need to also be aware that reduced rubbing or rinsing times may not be adequately cleaning their lenses. Again, our proposed new labeling includes a signal word, hazard avoidance directive, nature of the hazard, and the consequence.

Question for the panel would be, please discuss whether our proposed warning on rub and rinsing time is warranted. If yes, please identify any other message that should be conveyed in this warning.

For our next new proposed label, users should also be made aware of rinsing their lens case with the appropriate sterile solution and replacing it at least once every three months. And the importance of proper care of their lens case because of the potential bacterial growth.

Question for the panel. Please discuss whether our proposed warning on lens case care is warranted. If yes, please identify any other message that should be

conveyed in this warning.

Another concern we would like contact lens users to be aware of is the risk of eye infection while involved in water activities such as taking a shower, using a hot tub or swimming.

Last question, please discuss whether our proposed instructions for use and warning on water activities are warranted. If yes, please identify any other message that should be conveyed.

All the best labeling using all the correct labeling principles we discussed today will not completely eliminate adverse reactions. There can be issues with the user not comprehending the labeling and/or the user's lack of compliance. But if we can provide the best label possible to all who can use it as contact lens users or practitioners to help disseminate the information, the better. If this labeling for some reason does not reach the users, then all of us needs to

be sure this important information is relayed to users some way. There are other communication strategies that can accomplish this and here are a few examples. Thank you.

Our next speaker is Dr. Joseph Hutter.

DR. HUTTER: Hello. My name is Joseph C. Hutter. I'm a chemical engineer reviewer in the Division of Ophthalmic and ENT Devices. I'm going to discuss lens and care product solution compatibility. My talk will address the current regulatory lens grouping system and its limitations in dealing with new silicone hydrogel lenses and the increasing complexity of care product solutions. The proposed testing strategy based on the currently available silicone hydrogel technologies will be discussed.

The FDA regulatory groupings for contact lens materials were initially developed to categorize lens behavior when used with different care product solutions, as

well as lens interaction with proteins in the titer film. The concept of lens grouping was first presented as part of the July 1985 FDA draft guidelines for testing contact lenses and care products. The FDA guidelines subsequently resulted from collaboration between the FDA and the contact lens industry, which was facilitated by the Contact Lens Institute and the Contact Lens Manufacturers Association.

The monomers used in conventional contact lens polymers can be categorized into three classes: hydrophilic monomers to interact with water to form the basic hydrogel component; hydrophobic monomers to add mechanical strength; and cross-linking agents to form a gel, increase mechanical strength and add thermal and physical chemical stability.

For hydrogel lenses the main hydrophilic monomers, which are used alone or in combination, are: hydroxyethyl

methacrylate, abbreviated HEMA; glycidyl methacrylate, abbreviated GMA; vinyl pyrrolidone, abbreviated VP, and methacrylic acid, abbreviated MA.

The primary rationale described for the separation of lenses into groups is related to ionic content. For example, adding methacrylic acid will increase the water content and its negative charge leads to a heightened interaction with tear proteins and preservatives. The secondary mechanism is based on the lens' water content, which is related to the pore size and hydrophilic nature of the material. Low-water non-ionic contact lenses between 38 to 45 percent water typically contain HEMA, vinyl pyrrolidone or glycidl methacrylate. Water non-ionic contact lenses between 70 and 79 percent water generally contain vinyl pyrrolidone-based polymers. The differences in solution interactions depend on the relative amounts of either vinyl pyrrolidone-based monomers.

The end result is a four-group system with lenses separated into ionic and non-ionic groups, and further subdivided according to the water content. Group 1 is non-ionic hydrogels less than 50 percent water; Group 2 is non-ionic hydrogels greater than 50 percent water, Group 3 is ionic hydrogels less than 50 percent water and Group 4 is ionic hydrogels greater than 50 percent water.

In a 1994 guidance for contact lenses, 30-cycle tests with the recommended care regimen were completed. If lens care products have been approved for use with lenses of the same group by the lens care product manufacturer, compatibility testing did not have to be done since compatibility was considered established. Our current practice for lens care manufacturers is to request the category testing with Group 1 and Group 4 lenses. And if silicone hydrogels are included in the indication, representative

hydrogels are tested.

The four FDA groups worked well for conventional poly(HEMA) materials. However, the limitations of the groups became more apparent when silicone hydrogels entered the marketplace. There were two well-publicized solution compatibilities with silicone hydrogels. In both cases when care products were tested with these lenses, lenses were distorted out of ANSI dimensional tolerances. The AMO ULtraCare solution was tested and was found to be compatible with FDA Group 3 lenses. Despite this, the solution was found to be incompatible with the balifilcon A silicone hydrogel which was initially assigned to FDA Group 3. A precaution was added to the labeling for the AMO ULtraCare solution. Similarly, SoloCare tested and was found incompatible with Group 1 lenses, but was subsequently found to be incompatible with the galyfilcon lens, a silicone hydrogel assigned initially to FDA Group 1. The SoloCare

product was replaced in the market with an updated product. Causes of the incompatibilities were never determined.

Lenses have changed from simple poly(HEMA) hydrogel materials with oxygen and water transfer occurring through water-filled pores. Silicon hydrogels have some of these same features, but polymer modifications were required to form a hydrophilic phase in a material that had a hydrophobic silicone phase which was added to improve oxygen transfer. To improve hydrophilicity of the lens, modification such as surface treatments, addition of hydrophilic monomers, as well as entrapment of water soluble polymers such as poly vinyl pyrrolidone in a semi-inter-penetrating polymer network have been used.

In addition to lens changes, formulations of care product solutions have become more complex. To improve convenience compliance, solutions have been formulated to combine cleaning and disinfection in one step.

The further enhance solution performance new components have been added to improve such things as wettability, moisture retention, lubrication and comfort. For example, in ReNu MoistureLoc, a polymer was added to help retain moisture on the contact lens. This particular cationic water soluble material was also used in hair and skin care products to condition and moisten. It appeared to function due to its ability to attract water from the air and deposit a film to create mass transfer resistance to evaporation. Under the right conditions, Levy and others, found that the polymer film interfered with the disinfection of the *Fusarium* fungus.

In the case of AMO Complete MoisturePlus, propylene glycol was added for similar reasons, wetting and comfort, and was identified by AMO as one of the factors contributing to the *Acanthamoeba* outbreak.

The International Standards Organization Group Work 9 is considering

adding a fifth group for silicone hydrogels as part of ISO 18369-1. There are differences between each silicone hydrogel and how they interact with care product solutions. Therefore, it's unlikely that one group will fit all materials. I discussed the merits of sub-divisions in my editorial at siliconehydrogels.org. I anticipate that further sub-division will be likely based on the properties such as pore size, ionic content, surface properties and silicone phase considerations. Data to definitively define these subcategories has not been established. Working Group 9 also anticipates further subdivision of Group 5 when data becomes available.

Based on the current information, there are four lenses that represent current silicone hydrogel lens technologies: lotrafilcon B has a surface modification plasma polymerization and a relatively high H_2O content. Balafilcon A has plasma

oxidation surface treatment and large macropores on its surface. Galyfilcon A is not surface treated, but contains a semi-inter-penetrating network of a water soluble polymer. Comfilcon A is a material that co-polymerized with substantial vinyl pyrrolidone to improve hydrophilicity.

There are seven different silicone hydrogels currently on the market and more to come. Without an effective grouping system, the burden is on lens care manufacturers to conduct testing with essentially all the currently available silicone hydrogels. So to make it easier, we would like to provide this proposal for consideration. This list will grow as more silicone hydrogels come on the market.

The panel will be asked for the recommendations regarding clinical testing in the absence of a grouping system for silicone hydrogel lenses.

Questions for the panel. Please

discuss whether you agree with ISO's current consideration of having silicone hydrogel lenses as a separate group and FDA's plan to further stratify the silicone hydrogel lenses groups into subcategories.

The next speaker will be a microbiologist from the Division of Ophthalmic and ENT Devices, Myra Smith.

CHAIRMAN BRESSLER: Thank you.

DR. SMITH: Good afternoon. I am Myra Smith from the Division of Ophthalmics and ENT Devices. I will be discussing the microbiology issues.

In my presentation I will begin by providing you with an overview of the current microbiology test methods. I will then discuss limitations to the current test methods and studies related to the limitations. And finally, I will outline the microbiology issues for panel consideration.

I would like to begin by giving you a brief overview of FDA's current pre-market

microbiology test methods for contact lens multipurpose solutions.

FDA recognizes the ISO 14729 stand alone test and the ISO 14729 Regimen Test to evaluate disinfection efficacy. FDA recognizes the ISO 14730 anti-microbial preservative efficacy test to evaluate the anti-microbial activity for solutions packaged in multi-dose containers. Each test has its own set of performance criteria which serve as the underlying basis for marketing. These ISO test methods parallel the testing outlined in our care product guidance which predates these ISO standards.

Currently the ATCC bacterial strains used in both stand-alone and regiment testing are *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Seratia marcescens*. The yeast strain used is *Candida albicans* and the mold is *Fusarium solani.* The stand-alone test is designed to measure the rate and extent of microbial kill under ideal test

conditions. It evaluates the potency of sterile fresh solution which is taken directly from a sealed product container. No lenses are added to the test solution. For all test organisms samples are taken at predetermined time intervals up to the minimum recommended soak time. For yeast and mold an additional time point is done to establish that no growth has occurred at approximately four times the minimum disinfecting time.

FDA recommends this testing scheme for products with digital rub and rinse directions. ISO 14729 was written and adopted when cleaning instructions included separate rub and rinse steps. The stand-alone test's two-tier performance criteria eliminates evaluation of the entire care regimen for products meeting the more-stringent primary performance levels for microbial kill. Products which fail to meet the secondary performance criteria are rejected for marketing.

The development of no-rub products raised concerns that the ISO 14729 performance criteria were inadequate to assess no-rub cleaning directions. Eliminating the digital rub step during cleaning may result in more residual soil and microorganisms on the lens. In addition, the antimicrobial activity of some preservatives decreases in the presence of organic soil. Therefore, all no-rub regimens FDA recommends an additional stand-alone test in which organic soil is added to the test solution. Additionally, an evaluation of the entire care regimen's ability to kill and/or physically remove organisms is recommended using the ISO 14729 Regimen Test.

The Regimen Test is a simulated use test which is performed according to the manufacturer's proposed directions for cleaning and disinfecting lenses. The test measures both physical removal of a high inoculum due to the rub and/or rinse steps,

and microbial kill of the remaining inoculum during the soak step. It is performed by technicians using gloved hands under aseptic laboratory conditions. Since the test was initiated prior to the development of silicone hydrogel lenses, only conventional soft lenses, Group 1 and Group 4, are included.

The same Regimen Test criteria apply for both rub and no-rub products. There is an allowance in the performance criteria for recovery of a very low number of organisms due to an expected variability in performing a care regimen which relies on both physical removal and kill of microorganisms to meet the performance criteria.

The preservative efficacy test evaluates the preservative system's ability to prevent microbial contamintion in the product for up to 30 days. Testing includes an additional re-challenge inoculum on day 14. Products need to meet the performance criteria throughout labeled shelf life. Currently,

preservative effectiveness also serves as our basis for allowing up to 30-day lens storage after disinfection in an unopened lens case. However, the effects of preservative uptake by lenses are not addressed by this test method.

For preservative efficacy testing, the test organisms are: *Pseudomonas aeruginosa, Staphyloccus aureus, Eshirichia coli, Candida albicans* and *Aspergillus niger*.

I would now like to discuss why there is a need to update disinfection efficacy testing.

First, updating these test methods is essential in light of the association of two different care products with two different outbreaks of microbial keratitis, *Fusarium* and *Acanthamoeba*, that were identified by the CDC during its investigations.

Secondly, contact lenses and contact lens care products have changed significantly since the current FDA guidances were provided to manufacturers in the 1990s.

In light of these events, there is a need to improve our predictability of the real world performance for these products.

In the recent microbial keratitis outbreaks both identified care products met current FDA ISO performance criteria for cleaning and disinfection. Also, efficacy testing against *Acanthamoeba* is not currently recommended, nor had it been evaluated.

Disinfection efficacy may be affected by complex interactions between lens materials, care product formulations, microorganisms and even lens case materials. Preservative uptake by lenses and its effect on antimicrobial efficacy is not adequately addressed by the current methods. Testing with silicone hydrogel lens materials is not part of the Regimen Test protocol. And as noted earlier, disinfection efficacy tests were designed prior to a trend towards no-rub cleaning directions.

Current test methods may not

reflect real world experience with these products. For example, Regimen Tests performed with labeled cleaning directions up to 20-second rub or rinse times likely exceed typical consumer practices. Longer rinsing times also may result in very few uses per container due to the high volume of product required. Reduced microbial activity due to improper topping-off by consumers and the potential for biofilm formation on lenses and lens cases, as well as the resistance of clinical isolates may need to be addressed in the updating of pre-clinical tests in order to improve their predictability of product performance.

Disinfection and preservative efficacy testing are not always done with product at the lower end of the active ingredient specifications to simulate a worst case for product efficacy. This may unknowingly lead to reduced efficacy in marketed lots.

In a recent study, FDA and CDC examined Alexidine absorption by lenses during soaking and its effect on disinfection efficacy against *Fusarium solani*. During testing both silicone hydrogel and conventional hydrogel lenses were inoculated with *Fusarium solani* in lens cases. Instead of only assaying during the recommended minimum soak time, assays were done at multiple time points for up to seven days. Both Alexidine concentration and antimicrobial assays by the stand-alone test were performed. The study concluded that Alexidine uptake by lenses during soaking significantly reduced preservative concentration in the lens case over time and that there was a corresponding decrease in the antimicrobial efficacy against *Fusarium solani*. This study and others suggest need for further investigations with other care products and lens types.

Additional studies reported in the literature have examined a variety of lens

types and solutions formulated with different preservatives. In most cases, decreases in preservative concentration during lens storage affected disinfection efficacy. Both the ISO and ANSI standards organizations are in the process of developing a new test method to evaluate disinfection efficacy in the presence of a lens soaking in a lens case over various storage times. Silicone hydrogel, as well as conventional hydrogel lenses, are proposed in the testing. The same challenge organisms currently specified in ISO 14729 will be included. FDA plans to participate in an industry-sponsored reg test to help validate and refine the methodology.

Current test methods use planktonic challenge organisms, however, organisms forming biofilms may be more tightly attached, more difficult to physically remove and more resistant to multipurpose solutions than unattached planktonic organisms. Recent studies have investigated organism attachment

to lenses, biofilm formation and the subsequent susceptibility to lens care solutions. Findings suggest that microbial attachment may vary by lens type and by species, and/or strain of microorganism. However, the effective biofilm formation on lenses or in cases is not evaluated in current disinfection efficacy test methods.

Both rub and no-rub products have been cleared by FDA and are currently marketed. In light of the recent outbreaks, FDA is reconsidering the advisability of no-rub care regimens. The potential benefits of retaining a digital rub step may include the removal of additional microorganisms from the lens prior to disinfecting in the care solution. Shih et al found that rinsing alone 10 seconds removed three logs of bacteria. The addition of a rub step removed an additional log for a total of four logs. Rosenthal et al compared the Regimen Test performance of standardized rub and rinse,

rinse only for five seconds and no rub or rinse for soak only regimens utilizing various preservative solutions. All solutions passed with the rub and rinse regimen, some regimens failed with the rinse only and all failed with the soak only.

Rubbing may also remove additional lens deposits or other debris from the lens. Nichols et al observed lower levels of three to four-plus deposition when subjects who were heavy depositors used digital rub regimens when compared to a no-rub regimen.

We are requesting the panel's recommendations regarding the need to include separate rub and rinse directions in the care and disinfection of contact lenses to potentially provide an increased safety margin for patients including separate digital rubbing and rinsing steps prior to disinfection may reduce both the number of microorganisms and deposits on a lens thereby reducing the microbial challenge during

disinfection, having fewer residual lens deposits, less biofilm formation and decreased interference with disinfection efficacy. This may result in cleaner lenses for insertion into the eye.

Our panel question is, currently rub and no-rub care products have been cleared by the FDA for marketing in the United States. In light of all the data currently available, please discuss your recommendations for continuing to have no-rub directions in the Product labeling.

We are interested in the panel's recommendations regarding our proposed modifications to the Regimen Test in order to improve predictability of real world performance. We are interested in your recommendations regarding the inclusion of marketed silicone hydrogel lenses and for establishing realistic rub and rinse times in the Regimen Test.

FDA is currently working with

members of ISO regarding modifications to the Regimen Test.

Our question for the panel is, please discuss our proposal to revise the current Regimen Test in order to improve predictability of real world performance and include the following topics in your discussion: Testing marketed silicone hydrogels, defining worst case rub and rinse times; for example, five-second rub and five-second total rinse time.

We are interested in obtaining the panel's recommendations regarding a need for incorporation of *Acanthamoeba* into the current pre-market stand-alone and/or Regimen Testing, as well as newly proposed test methods. In light of the variability of *Acanthamoeba* test methods cited in the literature, we are also interested in panel recommendations regarding the development of new assay methods for *Acanthamoeba*.

Our question for the panel is,

please discuss your recommendations for adding *Acanthamoeba* as a challenge organism in disinfection efficacy testing.

Newer or revised methods which evaluate preservative uptake by lenses and the effects on disinfection efficacy could be used for identifying lens solution incapabilities and serve as a basis for a recommended storage time following disinfection. We are interested in the panel's recommendations on such testing.

And our question reads as follows: Please discuss our proposal to develop standardized test methods to evaluate the effects of preservative uptake by contact lenses on disinfection efficacy.

Finally, we are interested in the panel's recommendations regarding efficacy testing at the lower end of product specifications, and, whether there is a need to test products against more resisting clinical isolates.

Our panel question is follows: Please discuss our proposal for modifying disinfection and preservative efficacy testing by testing at the lower end of the active ingredient specifications to simulate worst case conditions and including more resisting clinical isolates in these tests. Thank you.

I would now like to introduce our next speaker, Dr. Visvesvara from the Division of Parasitic Diseases at CDC.

DR. VISVESVARA: Thank you. Good afternoon, ladies and gentlemen. It's good to be here and such a distinguished panel; I'm very happy to be here.

My talk today is on the resistance of *Acanthamoeba* cysts to disinfection in multiple contact lens solutions. My coauthors are Stephanie Johnston, Ramir Sriram, Yvonne Qvarnstrom, Sharon Roy and myself.

I would like to tell you that *Acanthamoeba* is a very, very hardy organism. It has got two stages in life cycle, the

trophozoite and cyst stage. It's a bacteria feeder and it is ubiquitous for almost everywhere; all seven continents in the world you can find them there going from Antarctica and found everywhere. Swimming pools and power plant effluents and a lot - of number of these you have mentioned all day.

But I would like to specifically entertain your attention to the isolation of *Acanthamoeba* from toxic waste dump sites with high levels of pesticides, herbicides, pharmaceuticals, including contact lens solutions, heavy metals, PCBs, et cetera. No wonder they have become resistant to all of these different physical and chemical stimuli that exist in nature resulting from the dust in the air.

Now *Acanthamoeba*, it also causes a very chronic granulomatous type of infection called the amebic encephalitis. Goes into the brain, lasts anywhere from two weeks to two years and very gradually kills the patient.

It also causes sinus infection, mostly in immunocompetent people and also lung infection in people who have suffered transplantation, et cetera. Additionally, it also causes *Acanthamoeba* keratitis as you all very well know.

I don't want to talk a lot about *Acanthamoeba* keratitis. You are all experts in this thing. It leads to all kinds of problems. The only thing I want to mention here, *Acanthamoeba* -- I was initially involved in 1973 with the isolation of *Acanthamoeba polyphaga* from one of Dr. Dan Jones' patient in Houston, Texas. It was an *Acanthamoeba polyphaga*. Both trophozoites and cysts were forming in the corneal tissue, and we did some study on that.

Then from '73 to 1980, we used to get cases from different parts of the country to our lab to identify the invading organism, and it invariably turned to be and *Acanthamoeba*, either a *polyphaga* or a

castellanii. There are more than 20 different species of *Acanthamoeba*, but the most commonly found are the *Acanthamoeba castellanii* and *Acanthamoeba polyphaga*, *Acanthamoeba rhysodes*, and recently we are also finding an *Acanthamoeba hatchetti*.

We did this in 1983 and we wrote a report in '86, and 20 years later we are revisiting the same thing again. Dr. Verani, my colleague in CDC, they found that there is a multistate outbreak of *Acanthamoeba*. It was for all different places. It was found that some of the contact solutions were not really doing their job properly.

So we elected to take some of these 11 contact lens solutions. We just pulled it off of the market, from the shelf from the area stores, and we wanted to test whether any of these things have any activity against *Acanthamoeba* cyst stages. I thought *Acanthamoeba* trophozoite is a fairly delicate organism, so I didn't bother to test the

Acanthamoeba trophozoite. But since cyst is a very impervious structure; you got two different strains, an outer coating is a proteinaceous material and an inner cell wall which is a cellulose-based, it's very, very resistant to all kinds of physical and chemical stimuli.

So we used for this particular purpose three different species that we had isolated most recently from the *Acanthamoeba* keratitis investigation that we did at CDC in 2007. These are the *catellanii, polyphaga, hatchetti* and what we did was we used to regrow them on our agar plates. I don't believe in using an axonic strain. When you use an axonic amoeba, you are selecting the amoebas. And every time you axenize, only a small proportion of them will really going to axenic culture; the rest of them do not. So I do not believe testing that axonic strains. We always use a strain that is freshly isolated which had all the experience of being

in the environment and being able to combat the environmental pressures. So we used that one.

And secondly, we used based on the morphologic and genotypic. They all belong to the T4 genotype which is the most commonly found *Acanthamoeba* genotype in the environment. And we used only about 10 microliter containing about 100 cysts and put them on one ml of contact lens solutions and then incubate them for either four six hours, or 24 hours, based on the recommendation of the manufacturers.

Now when we are looking, after the exposure to the various time periods, we washed the organism in the contact lens solutions and then put them again on agar plate having -- because these are the bacteria feeder. *E. coli* is a very good organism and they feed very much on the *E. coli* and multiply. And when they excyst, the cyst, when they excyst, they do not fit in one place

and form a plaque. Especially the most recent ones, they do not form plaques. They are wanderers. They wander all over the place. And you can see them by looking at those track marks they produce on the agar plate. They are going right on top of the agar toward the bacteria and they leave a specific mark. If you follow the mark, you will see at the end of each mark an *Acanthamoeba*. There's a very good way of looking at the culture. We used to examine that every two hours, every four hours and some of these contact lens solution, we were able to get them to excyst between a matter of two, three hours. Even after 24 hours of exposure. Some of the contact lens solution, for example, we looked at some of these things and none of these had any activity even after 24 hours of exposure to the various solutions.

The next one, same thing. In one case Ciba Vision which has hydrogen peroxide, it killed most of the *Acanthamoebas* in all of

the plates. We were not able to recover any of the amoebas at all. But only in the case of *Acanthamoeba hatchetti*, it was very surprising to me, but some of the amoebas were present and not able to colonize the plate over a period of time. And as you have seen here, there are other also here Bausch & Lomb, only after 24 hours some were able to excyst and then produce the -- yes.

So in the research, what I would like to just summarize, that only one of the solution which had hydrogen peroxide, Ciba Vision Care demonstrated the greatest inactivation of cysts of all three species of *Acanthamoeba*. Of the 11 contact solutions tested, two of them showed some activity against *Acanthamoeba Castellanii* cyst. Ciba Vision Care was 100 percent effective at both six and 24 hours. But as Boston Simplus, or the Bausch & Lomb, had no activity at four hours, but was active, say 66 percent effective at the 24 hours. Similarly here

also, the four other solutions had some activity after 24 hours, like the Bausch & Lomb Boston Simplus and Bausch & Lomb ReNu with MoistureLoc, that was 33 percent effective at killing cysts of *Acanthamoeba polyphaga*. That means they were not able to excyst on the plate. The Ciba Vision Aquify and Kirkland Signature MPS were 66 percent effective at *Acanthamoeba polyphaga*.

In the case of *Acanthamoeba hatchetti*, only the Ciba Vision Clear had 100 percent effective at six hours, whereas it was 33 percent effective at the 24-hour contact lens. Bausch & Lomb Simplus also had some activity at the 24-hour contact time. But it's best that can be concluded that only though the Ciba Vision Care with had the three percent hydrogen peroxide was able to effectively kill off a *Acanthamoeba castellanii* cyst and *Acanthamoeba polyphaga*. But and yet both at six and 24 hours, whereas in the case of *Acanthamoeba hatchetti*, it was

only 33 percent effective after 24 hours.

Finally, with solutions without hydrogen peroxide had varying activity against *Acanthamoeba*, but none had any activity at four hours of contact time. Some of them had after 24 hours. So but you have to realize that most contact lens wearers do not soak lenses longer than eight to 12 hours, all night. So, we could not do a eight to 12 hours because of logistics problem. We had to get somebody to come at 9:00, at 10:00 and to look at those things and I do not have any post-doctors, you know, who I could ask them to come in and do that thing, so I can't do that thing. So, that's how we had picked up 24 hours. And thank you for your attention.

CHAIRMAN BRESSLER: Thank you.

Our next speaker then will be Dr. Molly Ghosh on lens solution interactions.

DR. GHOSH: Good afternoon. My name is Molly Ghosh. I'm a toxicologist with the Division of Ophthalmic and ENT Devices at

CDRH. My presentation will be on lens solution interactions from a biocompatibility perspective.

Here is the overview of my presentation. First, I'd like to give you some background as to why we are looking at interaction between lens and lens care solutions. Then I will present FDA's guidance proposal for cytotoxicity testing of multipurpose solution to address such interactions and would like to get panel's recommendations.

FDA's 1997 guidance document is currently followed by the manufacturers for preclinical testing of contact lens care products. However, as new products evolve and new issues arise, it is important to reevaluate testing recommendations. Silicone hydrogel lenses were introduced in 1999. Use of silicone hydrogel lenses for daily wear has been increasing over the years, as is the use of the multipurpose solutions. The