historical basis, but suffice it to say that we have an opportunity to learn that is really unprecedented, and I think this is a very, very important moment in the history of contact lenses, and contact lens wear and care.

I think, when we look at the issues ahead of us, one of the first questions we ask, one of the first questions that we've pondered for many years is, is compliance an issue? Has it been an issue specifically with these outbreaks? Well, in truth, anyone who is involved in contact lenses, in medical care in general, realizes that patient compliance is poor, and has been poor.

I think Otto Wichterle, when he first designed the contact lens 30, 40 years ago, dealt with compliance issues almost immediately. And the issue is that we have attempted to deal with this. We have attempted to deal with this as an industry, with labeling. We have attempted to deal with

this as practitioners, and I know we have instituted numerous approaches when I was with the Contact Lens and Cornea Section.

And in truth, it has not been successful. And I think we need to make this our reality. Patients do what they do, and unless we can change those patients, and we haven't been success at doing it, we need to adjust for it, and adapt to it.

I think it's very telling to note that, prior to the introduction of no-rub contact lenses, about 50 percent of patients rubbed prior to -- or rather after the introduction of no-rub solutions, about 50 percent of patients rubbed. And even after the Fusarium outbreak, with intensive media focus on patient hygiene, 50 percent of patients rubbed. There was no difference that was discernable, regardless of what we did to change that behavior.

And when we look at the data from the CDC, and I see these outbreaks really as

microscopes that allow us to drill down and look closely in ways that we wouldn't have been able to do before, we find that there was no correlation to washing hands. There was no correlation to rubbing and rinsing. There was no correlation between infection to lens case rinsing or care.

There was only modest correlation to topping off, and I'll quote the authors, "No single hygiene practice was independently associated with disease in our multi-variable model." And more specifically, and this is perhaps most important, our case control studies revealed that sub-optimal hygiene practices were common and similar among case patients and controls. And I think that is an extremely important statement.

There was no difference between the patients who developed infections and the patients who didn't in terms of how they cared for their lenses. And it tells us that we need to look at this, rather, in more detail.

Now, despite this, the industry has risen to the occasion. The industry has recognized that good lens care practice is very, very important, and there has been significant changes among branded products to reflect labeling that is more patient-friendly, labeling that is more respectful of the doctor/patient relationship, and I think that is a very, very important factor.

When we look at no-rub products, OPTI-FREE Express in 2001, no-rub was the headline. OPTI-FREE Express in 2007, it was the small print. So we certainly have made significant advances in reducing marketing issues from the front labeling of packages. And we tend to forget that rub instructions have always been included. In 2001, the directions were precisely the same as they are in 2007, and it included rub steps.

Well, I have given this a lot of thought. I have spoken to my colleagues at Alcon. I have spoken to industry. I have

spoken to my optometric and ophthalmic colleagues throughout the country, and I would like to share some recommendations with you, some of which are seconding some of the excellent recommendations that have been made previously.

Testing and labeling must better reflect real-world challenges and patterns of actual use. Regulation in the absence of understanding what our patients do is regulation that simply will not work. New or revised standards should reflect collaboration among the FDA, ISO Standards Committee, ANSI, the industry, and the eye care community.

In this partnership, we can make effective change, and we can keep patients safer. Testing for acanthamoeba disinfection should be adopted, but we need to establish standards, and we need to validate those standards before we rush in to creating standards that may not be workable, or may not be protective of patients.

Testing with traditional hydrogel lenses should continue. Groups 1 and 4 testing has been very effective historically. We should also test representative silicone hydrogel lenses with the understanding that this technology is evolving. The chemistry of these lenses is quite different, and their interactiveness with solutions is considerably different than what we have experienced with conventional hydrogels.

Disinfection uptake and release is a very important concept, and I think we need to look at it in a number of different ways. Specifically, it gives us insight into the optimum time to look for corneal staining. Now, we don't fully understand the impact of corneal staining, but I can tell you as a clinician, it is the only clinically reasonable way for the average practitioner to evaluate surface damage in the office. And as such, makes for a very, very valuable tool in understanding the relationship between the

contact lens, and the contact lens care product, and its impact on the specific patient.

In terms of labeling and care instructions, labeling should be based on science and testing of individual products, not class labeling. Products did not perform equally. There should be no mandated rubbing and/or rinsing times, because it depends upon the specific product. Class labeling with mandated regimen steps is unnecessary for the safe and effective use of products, and I fear that it will stifle innovation, and that's the last thing we want to do at this time.

Ideally, promotional claims regarding directions of use should be removed from the front panel. They belong in the instructions segment in directing our patients, and in emphasizing professional care.

Practitioners must be involved. There is no question that practitioners play a

very important role. We have to reinforce hand washing. We have to reinforce lens case care and replacement, and we have to discuss the inappropriateness of topping off, because we recognize that as an issue. Labeling should reinforce the practitioner/patient relationship, while providing essential lens care directions. That I see as the purpose of labeling.

A final thought, recommendations from this Panel meeting should take into account the real-world patterns of use. What our patients do, what our patients experience, what they face, and be based upon the scientific data and the evidence. I thank you for this opportunity.

DR. BRESSLER: Thank you. Just before we start, I'll let everyone know we are going to take a break at 10:30. I know it's a lot of presentations, but we want to have a chance for everyone to have an opportunity. With that being said, our next speaker then

will be Dr. Doyle Stulting.

DR. STULTING: Thank you. Mr. Chairman, Members of the Panel and the FDA, I'm Doyle Stulting, Professor of Ophthalmology, and Director of the Section of Cornea and External Disease at Emory University in Atlanta, Georgia. I am or have been a consultant for Allergan, AMO, and Bausch & Lomb. My travel expenses to this meeting were paid by AMO. The opinions that I express today, however, are my own.

I have a PhD in microbiology, as well as an MD degree. I have an academic interest in contact lens-associated infectious keratitis, and the mechanisms by which it occurs. In my ophthalmic practice, I frequently see corneal ulcers in patients who wear contact lenses. When I do, I personally obtain a history of their contact lens care practices, and personally obtain environmental specimens, like contact lens care products, cases, old contact lenses that these patients

might have worn.

I routinely perform gram stains and cultures of corneal ulcers, as well as cultures of environmental specimens when I encounter these patients. I will look at every preparation myself.

During the recent outbreak of Fusarium keratitis, I personally examined about a dozen patients with contact lens-related ulcers during a two week period, initially, and obtained over 50 environmental specimens from them. These became the subjects of laboratory investigations and publications in collaborations with Dr. Zhang, Ahearn, and others.

As a result of my 27 years in practice in laboratory investigations like these, I believe I have developed some insight into contact lens care practices, and infectious complications of contact lens wear.

First of all, we have learned that contact lens care practices are not always

consistent with the labeling of contact lens care products, nor do they minimize the risk of infectious keratitis. Hand washing is not always performed before patients handle contact lenses, and contact lens care is not always performed in a clean environment.

Contact lens disinfection products are not always used as recommended. Specifically, topping off is very common among contact lens wearers, cases are not frequently sterilized or replaced, and contact lens disinfection solutions are misused in a number of ways.

Second, contact lens care solutions have changed over the years in an effort to increase comfort and convenience. They have evolved from highly effective but inconvenient, and potentially toxic disinfection methods like heat and hydrogen peroxide, to more convenient but less effective products, such as multi-purpose solutions.

We have learned that, in some cases, additional ingredients that improve comfort may alter the disinfection characteristics of solutions.

Third, we have seen the introduction of new polymers from which contact lenses are manufactured. These new polymers may interact with contact lens care products, microbes, and disinfection agents in ways that may differ from the ways that previous polymers interacted with them.

Our recent laboratory investigations of the Fusarium keratitis outbreak make it clear that Fusarium is able to survive and replicate in drying films of contact lens care products to varying degrees. Indeed, this particular fungus is able to adhere to and penetrate contact lenses, particularly if they contain nutrients such as we can expect to be absorbed during contact lens wear.

Additives to contact lens

disinfection products that are intended to increase comfort can make solutions difficult to remove from environmental surfaces, providing a safe haven for microbial growth.

Finally, it is noteworthy that the FDA-approved label on many contact lens care products emphasizes convenience rather than efficacy. We and others have shown that rubbing contact lenses significantly improves the ability of contact lens disinfection solutions to remove microbes from the surface of contact lenses, and to inhibit their replication.

Nevertheless, many of your products bear the no-rub label prominently.

In summary, the inherent efficacy of disinfection products has decreased over the years, and conditions of actual use have led to unexpected interactions between contact lens care products and microbes. As a result, we have seen outbreaks of Fusarium keratitis and acanthamoeba keratitis that were shown to

be attributable to contact lens care products and their frequent misuse.

To minimize the likelihood of similar outbreaks in the future, policies and procedures for the approval and labeling of contact lens care products must be changed. I recommend that the FDA review current in vitro testing procedures for contact lens disinfection products. These procedures should be redesigned to reflect conditions of actual use and misuse, including a methodology for testing the ability of the solutions to support the replication of microbes in drying films, and under conditions in which patients top off their disinfection solution.

They should not only include a variety of microbes like acanthamoeba, but also a variety of contact lens polymers, like silicone hydrogels, to determine whether interactions with these polymers themselves might reduce the efficacy of the disinfection products.

I believe it is important that labeling be changed so that efficacy is emphasized rather than convenience. The first such change should be the removal of the no-rub claim, because rubbing contact lenses is a scientifically proven way to improve the efficacy and the safety margin of modern disinfection solutions.

Finally, I think it is time to launch a national campaign to raise the awareness of good contact lens care practices, educating practitioners and patients about the appropriate and responsible use of contact lenses. Thank you for the privilege of speaking at this meeting.

DR. BRESSLER: Thank you, Dr. Stulting. Our next speaker will be Dr. Simon Kilvington.

DR. KILVINGTON: Thank you very much. I'm Dr. Simon Kilvington from the Department of Infection, Immunity and Inflammation at the University of Leicester in

England, where I'm Senior Lecturer in Parasitology. My main research is on the pathogenic free-living amoeba, including acanthamoeba, and I've been variously supported in my research from the contact lens industry, including AMO, who paid for me to come, through an air ticket, to attend this meeting today.

So this is acanthamoeba. It's a free-living amoeba, common to virtually all soil and aquatic environments, characterized by feeding and dividing trophozoite, which, in response to adversity, of course, can transform into this dormant, highly resistent cyst stage. And the resistance of the cyst to extremes of temperature, desiccation and disinfection accounts for this virtual ubiquity of the organism.

So acanthamoeba keratitis, well, it's a potentially blinding infection of the cornea. It affects previously healthy persons, and it's one of the most difficult

ocular infections to, firstly, diagnose, and then treat successfully, due to the resistance of the cyst stage to most therapeutic agents.

And of course, contact lens wearers account for 90 percent of recorded cases. And we know that risk factors to infection are poor hygiene practices, as we've heard, rinsing or storing of lenses and lens storage cases in tap water, and, of course, general noncompliance to recommended use of contact lens care solutions.

Though it is rare - I mean, we've seen figures of one to two cases per million lens wearers here in the U.S.A.- in the United Kingdom, it's about 20 odd times higher, and we get about 30 cases per million lens wearers, and that's due to tap water contamination by the organism. Most homes in the UK have this, a roof or loft storage tank, where potable water is stored, and used to supply bathroom cold taps. And we have shown that these tanks are rich sources of

acanthamoeba, including that one, which is the one in my home.

Now, efficacy testing of contact lens solutions against acanthamoeba, well, unlike bacteria and fungi, there are no standards in existence for testing of solutions against acanthamoeba. And my laboratory and my research interest is focused on this area. And particularly two areas. Physiological response of acanthamoeba to contact lens solutions; what happens to a trophozoite when you drop it in a contact lens solution? And then also developing biocidal methods and regimen methods for assessing efficacy of commercial solutions, and experimental formulations against acanthamoeba.

And because there's no standard, if you look in the literature, there's a wide range of opinions on the efficacy of a particular solution, for example, against acanthamoeba. You will see one report

suggesting Solution A kills acanthamoeba, another one showing that it doesn't.

And to start with, I'll talk about the physiological response. And this is some work we just published, where we took acanthamoeba trophozoites, incubated them in a contact lens care solution, and found that the trophozoites formed cysts, immature cysts, and we worked on this, and showed that it was propylene glycol in the formulation that was causing this phenomenon.

More recently, we have been looking at incubating trophozoites again in care solutions, and there is a slide at the bottom of normal trophozoites in a test tube, and then we found that a particular solution caused mass clumping of the contact lens -- of the acanthamoeba trophozoites. And we have shown that that actually affords the trophozoites protection, safety in numbers, from disinfection.

So the thing that has concerned us

most is developing standardized assay methods. And here, in the top table, shows the efficacy of certain solutions against two different species of acanthamoeba involved in keratitis. And as you will see, castellani, in red there, survived exposure to the solutions, whilst polyphagia was either killed, or only one survived out of the triplicate experiment. So species strain variation.

How we prepare the cysts, we use Neff's constant pH encystment medium for most of our work, and we tend to find that the solutions are effective against this cyst form, that then produce cysts by growing acanthamoeba on bacteriological Agar covered with E. coli, and you find that they are markedly more resistance, although, under the microscope, they look morphologically identical.

So we have developed a kind of screening method for enabling us to evaluate

factors that may affect disinfectant efficacy. And here is a simple one. We take 100 trophozoites or cysts, add them to the solution, leave them for a fixed period of time, neutralize, and then culture for survivors.

And this slide really is to show, not about the efficacy of solutions, but to show, firstly, that in red there, the cysts are more resistant, typically. Not all contact lens care solutions, based on one part per million PHMB, are equal. Some are better than others. One step peroxides, good against trophozoites, but not cysts, and really, if you want to kill everything, you need the two step, three percent peroxide.

That's quite simple. Otherwise, we've got to do the more lengthy biocidal approach, which is akin to the ISO method for doing bacteria and fungi, where we can look at the kinetics of trophozoite or cyst killing. It needs a lot more organism. It's quite

burdensome, but you can see here, with this solution, trophozoites being steadily killed in red there, and in purple, cysts resistant.

Finally, in looking at the regimen, again borrowing the methods from the ISO Standards, we inoculated acanthamoeba in the presence of organic soil to two times the silicone hydrogel lenses, and then subjected the lenses to the manufacturer of the solutions recommended regimen, whether it's rub and rinse, no-rub rinse, or even no rub and no rinse.

And as you can see quite clearly, with both cysts and trophozoites, a solutions, that C and A there, that recommend the rub step, are far more effective at removing acanthamoeba from contact lenses. Take out the rub step, as you see in Solution A there, and they start to fail. Take out the rub and the rinse, and then they also fail.

So in conclusion, acanthamoeba keratitis is a rare but serious condition

amongst contact lens wearers. The contact lens industry needs to address the risk from acanthamoeba keratitis through better education of, not only practitioners and eye care workers, but also lens users. I think we should promote the rub step, and also extended disinfection times, you know, six hours to overnight, to try and get a kill going against acanthamoeba.

We need to develop standardized methods before we can start setting standards for saying that a given solution is or is not effective against acanthamoeba. We need to look at the physiological response of the solution, the biocidal efficacy, and the regimen, against, not only the more susceptible trophozoite, but also the more hearty cyst stage.

And finally, of course, in developing assay methods, we need to address the significant variables of test species and strain, method of trophozoite culture, and

importantly, cyst production, and how we actually conduct these assays. Thank you very much.

DR. BRESSLER: Thank you, Dr. Kilvington. Our next speaker, and I'll just indicate that, after our next speaker goes, we will take a break, so that we'll be around the 10:30 area. It will be a 15 minute break, so I'll announce what time we'll begin again, but this will bring us through about halfway of our public speakers. So thank you again. So Dr. Jim Thimons will be the next one to speak, and then we will be taking a break, and I'll announce the time. Thank you.

DR. THIMONS: Dr. Bressler, Dr. Eydelman, distinguished Panelists, thank you for the opportunity to present today. As a matter of disclosure, I consult for, receive educational grants from, or have conducted clinical research with the following companies in the last 12 months: AMO, Alcon, Allergan, Inspire, ISTA, Carl Zeiss Meditec, and

Synamed.

My transportation here was paid for by AMO, as was my room at the hotel last night, and hopefully, my transportation home.

My concern today is that of clinicians and colleagues throughout the country who are looking for a mechanism to help in the assessment and the evaluation of the ocular health of the contact lens and cornea patient relative to multi-purpose solutions in contact lenses, and specifically, what is the role of corneal staining, what is the relevance of corneal staining, and do we currently have a standard that we can rely on as clinicians to assist in the health of our patients' individual welfare?

This is my body of work over the last 30 years for your review, and this is a short summary of a variety of mechanisms that cam impose itself on the ocular surface. Multi-purpose solutions, as we have had discussed today are certainly one of the

players; the contact lens process itself; the combination of the two; patients with concomitant ocular symptomatology and disease, such as dry eye, systemically mediated or otherwise; concomitant medical therapy, such as topical drugs chronically used, oral medications, both over the counter, and systemically prescribed.

We have additionally systemic factors of an autoimmune nature, and as many of the Panelists have very elegantly stated, we have patient dependant factors, which are unpredictable on the individual, but globally seem to have patterns of behavior that put the patient, in some instances, at risk, in combination, or independently, of the existing factors you see above.

Probably the most important element of this process is the presence of a healthy ocular surface. And the inability to maintain that ocular surface places the patient at risk, both from an immune suppression

perspective relative to the natural protection provided by the tears in the maintenance of a healthy eye, and additionally, in the role of the complexity of a contact lens on the surface of the eye, and the use of adjunctive chemicals to maintain the health of that system.

So my question and statement simultaneously is, is there a standard for assessing biocompatibility in the industry that clinicians can utilize as a biomarker for the maintenance or assessment, and then subsequent maintenance, of their patients' ocular health?

And I would submit to you that I don't think that has been made present yet. We have good systems in place. Scanning electron microscopy is certainly an elegant way to assess the ocular surface. You can see differences in outcomes based on product, but quite frankly, from a practical perspective, clinicians don't have access to that level of

technology, nor is the expense/import ratio to a private clinical practice reasonable in that genre.

This is some work by Dr. Behrens, published out of the Delphi Panel, which I think is actually an initial and very good start to the attempt to try to define dry eye, it's impact on the ocular surface, and the whole concept of adjunctive disease relative to contact lens wear, and some of the implications that that presents.

As you can see, the idea of corneal staining is broadly dealt with here, and more importantly, it's dealt with, not only on the cornea, but staining of the conjunctiva, as well, which is really not addressed in any of the current standards that are utilized by the FDA.

This type of staining is in many instances more indicative of an underlying pretension of future disease than corneal staining is, which tends to be more transient,

and relatively less predictable in its impact on long-term health.

We understand as clinicians, and my colleagues have certainly expressed this concern, that over the last several years, we have had numerous of our colleagues attempt to quantify and relay to us their perspective on the presence or absence of corneal staining and its importance to us as clinicians in maintaining the health of the ocular surface.

Unfortunately, and from my perspective, and I think most of us who I have spoken with throughout the country, I think all we have been left with is a relative amount of confusion. And the reason for that, I'll hope to elaborate in the next several minutes, and then summarize at the end.

But we do understand that that is a complex relationship between contact lens solution and the ocular surface. We know that chemical keratitis, toxicity, micro-trauma, and a variety of impact from preservatives can

impact the epithelial health.

There has been some very nice work done by my colleague, Gary Andrasko, also a classmate at the Ohio State University, along with Ryen Garofalo and Lemp in 2006, which demonstrated methodologies to define staining, and to help us elaborate a system that would be useful in our overall assessment and management protocols.

They looked at things like micropunctate, macropunctate and its impact. And quite frankly, if you look at the outcomes of this study and the others that I'm going to reference, none of them really definitively correlated the relationship between clinical staining, and eventual evolution of a microbial event on the corneal surface. And I think that's very important because, at this point in time, part of the reason for this, and you'll see here in just a second, is that each of the studies used a different level of protocol.

Some used 30 minutes, some used two hours, some used 24 hours, some used less. And unfortunately, as other presenters have elaborated, that lack of uniformity in the decision to create clinical studies has left us with a significant dearth of evidence-based medical information that can be used by practitioners nationwide to make sure that their patients' long-term visual welfare is maintained.

This is one of the standard formulations that has been developed to assess corneal health. This is a grid pattern. Dr. Andrasko and the group was originally involved in this, and that grid has been in the public domain, both in peer reviewed and non-peer reviewed literature for the last several years. It has, unfortunately, after having undergone some fairly significant review, been challenged by a number of other authors and left us with, quite frankly, a less than sustainable level of clinical information that

we need to manage our patients' welfare.

This is some work by Garofalo and Dassanayake in eye and contact lens, and you can see that their observations at two hours did show that, quite frankly, most of the patients with staining were typically asymptomatic, which is what I see in my practice. I practice in a secondary and tertiary level facility which basically deals with contact lens-related problems. And the vast majority of patients, symptomatic or otherwise, have some form of corneal stain.

The problem is, and their conclusion directly addresses that, clinical significance of this information was not determined in the study, and I would submit to you that I don't have any information that I have been aware of that directly correlates level, intensity, and type of staining to the risk of progression in microbial disease.

This is the Andrasko staining grid. This was produced -- probably this was

accessed in 2008, but it has been there for several years, and it was a good initial work to help us excite the process. But, as other authors have subsequently reviewed, including the Institute for Eye Research, when you do a contrast and comparison, data from different facilities has varied considerably on the same subject material, the same lenses, and the same solutions.

So that obviously implies that the complexity of the anterior surface needs to be addressed in a larger context, and no single element is capable of defining the risk that our patients undergo.

This is some work by Kislan and Bucci in an AOA poster for 2008, and just a brief review of their data, which also presents a considerable departure from material that has previously been put into the public domain, and has been used extensively by clinicians to assess risk benefit ratio in the management of contact lens patients and

their long-term health.

And you can see here that these numbers widely vary from both the IER data, as well as the original Andrasko data. And all three of these serve as a very nice example of why I believe that the following recommendations, and in summary, my final comments, are pertinent to your considerations, and hopefully, your deliberations and actions to the future.

First and foremost, it's very clear that observation time, variables on entry, materials and solutions all influence outcomes of studies, and I think one could probably say with some confidence that you can produce any outcome that you wish given the selection and the appropriate utilization of materials. There is that large a variability in both time domain, as well as clinical response.

Second, and I think very importantly, the differences in the formulations, which has been very eloquently

addressed by the previous speakers, as well as the materials, need to be evaluated individually. I don't believe that the class evaluation system is an adequate measure of current impact to the ocular surface.

And finally, I don't believe that there is any significant correlation between short-term transient staining, and damage to the eye due to multi-purpose solutions.

I would also like to impose that there is a minimal presence of evidence-based medicine in this regard, and my recommendation, if accepted by the Committee, would be that we develop a collaborative effort on the part of industry, the FDA and clinicians to define this material at a better and more useful level. Thank you.

DR. BRESSLER: Thank you very much. So we will start at 10:35 with Dr. Lally. I would encourage the speakers to be around if the Panel has questions for them, which we will do at the end of our public speakers. We

are about halfway through.

So we would like to take a break now, and we will start with Dr. Lally at 10:35. Thank you.

(Whereupon, the above-entitled matter went off the record at 10:20 a.m. and resumed at 10:35 a.m.)

DR. BRESSLER: Okay. I will remind the public speakers that we will have 10 minutes. You will have a one minute warning at nine minutes, so with a yellow light and we do have to have you stop by the 10 minutes, so we have time for everyone to be fair to have their statement.

So I would like to start then with Dr. John Lally as our next speaker. Thank you.

DR. LALLY: Good morning, Dr. Bressler, Members of the Panel, can everyone hear me?

DR. BRESSLER: His button is on, but it wasn't working.

DR. LALLY: Yes, okay. I think we got it now. Good morning, ladies and gentlemen. Good morning to the Panel and also thanks to Dr. Bressler and the Panel for giving me the opportunity to speak here. My name is John Lally. I am Vice President of R&D at AMO for Ocular and Surgical Devices.

I have worked on -- I have a PhD in chemistry and worked in the Life Sciences industry for 20 plus years or so. Thirteen of those years being in the ocular industry with both Advanced Medical Optics and CIBA Vision.

An outline of the brief talk today is going to touch on that balance we need to achieve between disinfection efficacy and corneal health. We will also talk a little bit about two hour staining and its unreliability in predicting long-term clinical biocompatibility. We will touch on the need to have enhanced or improved disinfection efficacy testing standards. And also we will present data supporting a rub and rinse

regimen introducing microbial load and enhancing effectiveness of all contact lens solutions.

When it comes to formulation development and preclinical testing, there is two main areas really we need to focus on. One is testing beyond the current ISO standards and the FDA Guidelines where we really need to incorporate additional testing for real-life use. And probably the most important thing here in the real-life use situation, it has been touched upon already by Dr. Epstein, and that is that each lens/lens care combination has a unique optic release kinetic profile, depending -- dependent on the physicochemical properties of that lens or polymer.

We also need to, of course, incorporate tests for robustness against potential noncompliance. These include effects of evaporation, effect of topping off and reusing solutions and we need to look at

the effects of shorter rub and rinse times and recommended leveling or for that matter the effect of potentially no rub as a noncompliance situation.

As I said, MPS product development is a balance between disinfection without getting clinical cytotoxicity. If you look at this graph here, we've got our top QII quartile here and that's where we all are, where we are aiming for, at least, getting the optimal combination of high disinfection effectiveness and low cytotoxicity.

However, in some of the stuff that I have heard, you know, one of the big risks we have here is going for really high disinfection efficacy and as a result, we end up compromising the cornea, which will in turn make the eye more prone to infection. I mean, essentially, we don't want to develop a nuclear bomb to kill all our bugs, because we're going to have more problems.

A little bit on our two hour short-

term staining and that it does not reliably correlate with clinical biocompatibility. Industry and academia are continually working on short-term preclinical or clinical models to predict long-term clinical success of products.

When such tests, which has already been mentioned and has garnered much attention, has been a company sponsor to our screen of product contact lens combination for transient staining phenomena. Of course, that's the Andrasko grid. It has also been suggested by the FDA in a recent current task document to maybe look at, you know, the two hour time point for staining.

Of course, as already mentioned by several, the test has been controversial, however, as to its validity on long-term relevance. There has not been a validated clinical study correlating this data to long-term toxicity or acceptability of any lens care solution, contact lens combination.

The other point I want to make is that the degree of staining can vary substantially depending on the time of the observation and I will talk a little bit about that later. In a more recent report of staining grid in the IER Matrix, this matrix indicated that two hour studies do not reliably predict long-term solution, induced corneal stain responses for the majority of lens and solution combinations evaluated.

IER Matrix data certainly seems more clinically relevant with the three month wear time and represents a truer longer term indication of the real-world clinical situation.

To better illustrate this point, if you look at the release kinetics and how they influence the degree of staining at various time points, we have two entities here, disinfectant entities for multi-purpose solution A and B.

If we look at the -- if we plot the

release kinetics of these two MPS activities, MPS B releasing early may exhibit high staining effect at the 30 to60 minute time point. The other, MPS A, the blue line here, releasing later may exhibit high staining at two to four hours. So if I'm a company who sells and promotes MPS B, I may record represent staining at two to four hours or if I settle for MPS A, I may record to present staining at half hour, for example.

As a further extension of this work on uptake/release kinetics, clinical testing should include worst case lenses for release of the primary active entity. In these examples, for example, MPS A should be tested with lens E and then MPS B should be tested with lens A. And if you take this one step further, microbiology testing should include worst case lenses for uptake of the -- hold on a second, I think, yes, microbiology testing should include worst case lenses for uptake of the primary active entity.

In these examples, MPS A should be tested with lens A and MPS B should be tested with lens D. I may have skipped a slide there. I apologize for that.

Most of you are reasonably familiar with this and that evaporation can reduce antimicrobial effectiveness. Partial evaporation multi-purpose solutions may occur in scenarios of topping off, reuse of solution or inappropriate storage. This experiment shows the ME of some solutions to be impacted substantially with component concentration for evaporation.

Notably, the dramatic reduction in microbial efficacy of MPS X, which is, of course, they recall a product. Similar experiments have been reported by other groups including Bausch & Lomb.

It seems certainly that in the last year we are making progress in acanthamoeba testing. A review is about to be published and reiterated by Dr. Kilvington and others is

that non-standardized microbiology methods for soft contact lens disinfection efficacy against acanthamoeba continue to produce highly variable data from study to study.

Recent publication "Knowing Contact Lens" recommended that all lens care products be tested for propensity to induce acanthamoeba encystment. Finally, of course, we should not forget that acanthamoeba is ubiquitous and reducing the incidence of acanthamoeba keratitis is multi-faceted.

It includes, of course, implementation of standardized solution disinfection requirements, as potentially outlined by Dr. Kilvington, also education of soft contact lens wearers in the hygienic wear and care of the lenses. And there has been some suggestion also by the Chicago group that we should pay some attention to the quality of our water.

Rubbing and rinsing is paramount to successful and safe contact lens wear. This

slide shows data from a study conducted by Don Ahearn's group at Georgia State in collaboration with John Stulting and others.

And the picture is obvious that the inclusion of the rub step resulted in substantially reducing the level of fungal contamination or colonization.

Taking this one step further, in evaluation studying the importance of the rub step in care regimens it is important that real-world potential microorganism adheres to simulators. A recent study at AMO shows that if microorganisms are allowed time to interact and adhere to contact lenses, the contribution of and importance of the rub step is magnified.

The contribution of the rub step towards lowering the microbial load to -- a part of disinfection was more evident when lenses were soaked in an inoculant overnight, a more realistic situation.

The concern of this result is that

the current guidelines quote remarks of a "10 minute direct inoculant" incorrectly or inappropriately favors testing of products where rinse only or a rub is part of the labeled regimen testing.

In summary, I just want to emphasize really that in addition to industry, academia, FDA, etcetera, and other bodies working together, at the R&D level it's the clinicians, the ocular surface biologists, the microbiologists and the chemists, particularly those uptake/release or control release chemists need to work closely together to get us to a better place. Thank you.

DR. BRESSLER: Thank you very much. Now, our next speaker will be Dr. Mark Willcox.

DR. WILLCOX: Thank you. And thanks for the opportunity to talk to you. Some of the research I'll be talking about today has been sponsored by CIBA Vision or AMO.

In my talk today, I'm looking at aspects of contact lens disinfection solutions and their interactions with the cornea, especially solution and lens interactions. I'll be talking particularly about solution induced corneal staining and the apparent association between solution induced corneal staining and corneal inflammatory events.

And finally, I'll talk a little bit about rub versus no-rub efficacy of solutions and then come up with some recommendations or conclusions.

You've heard a little bit about the IER Matrix Study today. It's a series of daily wear trials examining the performance of contact lenses and disinfecting solutions. To date, we have done seven lenses, mostly silicone hydrogels, but we have also included Acuvue 2 in this and six solution types. One one step hydrogen peroxide solution, a PHMB solution and two polyquad/Aldox solutions.

About 40 patients are in each lens

solution combination and the duration of the testing is for three months and we see the patients at two weeks one month and three months and the lenses are replaced either on a two week or monthly basis, depending on the lens type.

You have seen this as well before in the previous speaker's talk. This is the rate of what we call solution induced corneal staining. Others have called toxicity staining in our matrix study. As you can see, it's highly dependent on solution and lens combinations.

It appears that the hydrogen peroxide, the one step hydrogen peroxide solution causes the least solution induced corneal staining, followed by PHMB solution with the exception of when that is used with Purevision lenses. And the polyquad Aldox solutions are somewhat worse in producing this solution induced corneal staining, again, especially when used with the Purevision

contact lenses.

You can also see that the lenses are important, so Acuvue Advance produces the least amount of corneal induced -- solution induced corneal staining, rather. Another lens and solution combinations produce different amounts.

We have looked at that and examined it in relation to the Andrasko two hour staining grid and see that this is not as John said last time, does not always predict the three month clinical findings.

For example, there is a relatively poorer performance with OPTI-FREE Express using Acuvue Oasys or Purevision lenses compared to the two hour data that is in the Andrasko staining.

We have recently published this toxicity staining, as we called it at that stage, which is the same as solution induced corneal staining, was associated with the production of corneal inflammation. So in

this graph here or in this table here, you can see that the risk of getting any infiltration, the toxic staining group or the solution induced corneal staining group was about three times the risk of getting infiltrates in the non-staining group.

And that was really driven by the production of asymptomatic infiltrates, which is about five to six times the risk if you've got corneal staining. And there was no association, in fact, with symptomatic staining.

We have looked to see if our three month data could, in fact, be looked at at earlier times to see the same prediction, but as you can see from this, actually, we do need to run the studies for around about three months to get any association between at least the asymptomatic corneal infiltrates and corneal staining.

And this is the data split at the two week, one month to three month data

points. And you can see that it is only at the three month data point that there is about the three times risk with a significant p-value there.

Well, then if you like turn this on its head in some ways and said okay, what are the risk factors associated with corneal inflammation in daily wear? And there are several, but I just want to point out the main one today, which is the fact that the use of multi-purpose solutions, those Aldox, polyquad or the PHMB shows about a 10 times greater risk of producing corneal inflammation. Usually, those asymptomatic infiltrates compare to using hydrogen peroxide.

And interestingly, if we remove those eyes that have got solution induced corneal staining from that analysis, you can see that we actually don't really affect the level or the risk of getting the inflammatory response. And we think that really points to the fact that whilst it's clear that multi-

purpose solutions produce both corneal staining and inflammation, they are not necessarily a causative relationship here. And it may, in fact, be different aspects of the solution, which produces both of those factors.

Indeed, we have looked at corneal staining to see if it's an associated risk factor for microbial keratitis. And we have conducted over a number of years clinical trials in both Sydney and India and have had about 10 microbial keratitis.

This graph shows for the first two columns the level of corneal staining, the controls and the corneal infiltrating event group. And you can see that those overlap and they are not significantly different. And then the staining, the level of staining that you can see with the microbial keratitis cases was the level of staining actually visit prior to them coming in with microbial keratitis.

And I think you can see from this

that there is a wide range of corneal staining here and it wouldn't be predictive of them getting microbial keratitis.

So just on to the rub versus no-rub or rub/rinse versus no-rub dichotomy here. We have recently performed some studies in the laboratory looking at two different MPS solutions, OPTI-FREE RepleniSH and ReNu MultiPlus with the so-called panel of microorganisms that -- we have also included acanthamoeba in this and used a five second rub and a five second rinse. So a five second rinse by itself or a five second rinse and a five second rub.

For the MultiPlus stage I hope you can see here that the top panel here is the rinse only data and the bottom is the rub and rinse data, but it's clear that rub and rinse reduces greatly the level of bacteria or other microorganisms that are present on the contact lens compared with the rinse only.

Another obvious finding here, in

fact, is that the lenses themselves are different. We have used O2Optix here, Acuvue Advance and Acuvue 2. And you can see in general for the bacteria, Acuvue Advance appears a lot less and has less effect of rinse only or rub and rinse, whereas O2Optix and Acuvue 2, for the bacteria at least, adhere a lot more.

For the fungi, there is not such a significant difference nor for the acanthamoeba. But overall, as I said, what I wanted to point out was the rub/rinse for whether it is bacteria, a fungi, yeast or acanthamoeba is much better at reducing the number of microorganisms on the lens than the rinse only.

Similarly, for RepleniSH, at least for the candida albicans, you need a rub/rinse step to reduce the level. But again, you've got differences in the lenses and lens -- in the lenses with the use of that solution.

So finally on recommendations, we

believe that the solution induced corneal staining, whilst associated with infiltrates in the cornea, that association is probably not causative. We also think that the reliance on solution induced corneal staining as a measure of inflammation is therefore somewhat questionable. And as others have pointed out today, the clinical consequences of this solution induced corneal staining are really still not known and more research needs to be done.

We also believe strongly that a rub/rinse combination is much superior to no-rub in disinfecting contact lenses and should be recommended to all wearers. Thank you very much.

DR. BRESSLER: Thank you again. Our next speaker will be Dr. David Hansen.

DR. HANSEN: Thank you, Dr. Bressler and Dr. Eydelman and distinguished Panel Members. First of all, I am Dr. Dave Hansen. I was a clinician, practicing

optometrist in Des Moines, Iowa for over 30 years in a multi-specialty practice focusing on contact lens and contact lens research. I have experience working with almost all of the companies.

I now have the distinct privilege of working as the Director of Professional Services at Advanced Medical Optics, AMO. Hopefully today I'll present a clinician and industry view of this very unique and very welcome Panel discussion regarding contact lens products.

I would like to focus specifically, because of the time, on the science and compliance of contact lens care and specifically focus on one particular area and that being the importance of rub and rinse. It has been outlined here today, but I would like to reiterate two of the focus studies that have appeared in the peer reviewed journals in the last year.

One of the things that was said in

the Ahearn/Zhang report in Cornea last year was that the failure to use a manual cleaning disinfecting procedure may help to explain the increase incidents of Fusarium keratitis. And even went as far as to say that vigorous rinsing with a multi-purpose solution without the rub regimen is possibly the cause for some of the fungal attachments.

Most clinicians know that the research has demonstrated that with a rub, controlled rub/rinse regimen, you can remove almost 99 percent of the microbes and the attachments for deposits on contact lenses. Also presented in this particular report was the rinsing of hydrogel contact lenses alone was not significant in the rinse process, therefore, advocating a rubbing step in the multi-purpose solution disinfecting system with hydrogel and possibly silicone hydrogel lenses.

The recommendation by another study in the Eye & Contact Lens journal also said

that on reviewing all of the available data, it would appear that failing to rub lenses as a part of the cleaning process with concurrent absence of adequate rinsing does not seem to be prudent behavior. So this is a combination of the system of rub and rinse, but is really only a small portion of the entire compliance system.

Many professional organizations, as has been pointed out today, throughout the entire world, the American Society of Cataract and Refractive Surgeons, the American Academy of Ophthalmology, the American Optometric Association, the Academy of Optometry's Cornea and Contact Lens Section, the British Contact Lens Association and others throughout the world have recommended a rub/rinse regimen in this compliance system.

The rub/rinse is only one portion of this six step process. The literature clearly defines the six step process in compliance: A clean environment for the

patient, this means in an area where the patient is using their contact lenses, applying, removing and storing their contact lenses needs to be in a safe area.

Also, the proper hygiene, using proper cleaning methods with a rubbing action from the center of the contact lens out to the outer edge and using non-lanolin soaps, washing their hands appropriately and drying with lint-free towels.

The rub/rinse regimen that we have been talking about is also prior to taking -- to putting in a lens or applying a lens and also after removal. The other parts of this entire six steps program is the disinfection of contact lenses and the replacement of contact lens case is an integral part of this entire compliance recommendation.

And the final is the documentation of records within medical and optometric and contact lens practitioners' offices and also of triaging patients to other areas when they

leave the practice for specific follow-up care to allow the patient and the practitioner to know exactly which contact lens material, wearing schedule and care system is utilized.

AMO has been a proponent for communication with clinicians, office staff, professional societies, educational institutions, including optometry schools, residency programs and ophthalmology and optitionary residency programs, as well as their educational meetings. But the most important part of this communication process is with our patients.

We have had a very concerted, initiated effort in the last year to reach over 26 countries worldwide with a consumer education program to again reinforce this compliance system, which is known as the Practitioner's Standard of Care.

These practice educational materials, which we have instituted and initiated, include placemats for practitioners

to ensure that they know how to educate their patients regarding these systems; patient brochures which could be taken home, given to the family members as well as the patients; compliance contracts with the patient and the practitioner to assure a better compliance system; educational compliance posters and educational materials for offices throughout the country; and also an acrylic lens that demonstrates in front of the patient how to rub and rinse the debris and the particles off of these lenses, which can give a better risk value for the compliance system.

We also have included in our packet of information patient reminder cards to follow-up and the care systems don't stop with leaving the office, but also need to be seen on a regular basis.

As a result of this, we have also taken a further step. We have led the industry in trying a new packaging to assure compliance in the rubbing and rinsing of

contact lenses, storage, replacing of contact lenses on a scheduled basis. We recommend that not only do contact lenses need to be replaced as per the practitioner's recommendations, whether it be a one day, two day, three week, four week, monthly, whatever is decided upon by the manufacturer and the practitioner.

We have also recommended that the cases which contain the contact lenses need to be replaced on a systematic basis and have provided a free case within our compliance packs and also our retail packages. Also on the labeling as shown here, we show again and remind the patient how to rub, rinse and take care of their lenses.

In summary, we believe that the important three elements of compliance include a rub/rinse regimen; the replacement of a contact lens case on a scheduled method; we believe in teaching general hygiene that includes overall hygiene as well as hand and

eye and face hygiene; we have targeted groups throughout the world, including professional organizations, clinician staffs, educational institutions and more importantly, patients and family.

We believe that these instructions need to be easy to be read in front of the patient in the office. They need to be dramatic. They need to be shown how to manipulate their contact lenses and their care systems and we believe that there should be multiple channels for this information throughout the world, including news letters, patient brochures, websites and other media avenues.

We believe truly that this is a reinforcement message that has to be for new contact lens wearers as well as previous ones. We look forward to working with your agency in following up with the care and changing of behavior of contact lens patients, which we believe can be changed like other behaviors

have been changed throughout our health care system. Thank you for the opportunity to share a few things with you today. Thank you.

DR. BRESSLER: Thank you, Dr. Hansen. Now, our next speaker will be Dr. Francis Mah.

DR. MAH: Good morning, ladies and gentlemen, Dr. Bressler, Dr. Eydelman, distinguished Panel Members. I would like to first commend the hearing to try to and continue to improve patient safety in this difficult topic.

Francis Mah coming from the University of Pittsburgh. I'm in the Department of Ophthalmology and the Department of Pathology. I'm the Medical Director of the Charles T. Campbell Ophthalmic Microbiology Laboratory. We did help the CDC in both of the contact lens associated outbreaks.

I'm here representing the American Society of Cataract and Refractive Surgery and its 10,000 members.

As far as disclosure, I have no financial interest in any of the topics or items discussed today or in my talk, but I have received research support for Alcon Laboratories and Allergan for non-contact lens associated areas.

As previous speakers have mentioned, I would like to first just review some of the impact and then detail some of the issues of the topic at hand, which is the contact lens associated outbreaks and then come up with some recommendations from our society.

As far as the impact, approximately, 34 million contact lens wearers are in the United States. Annually, there are, approximately, 30,000 cases of bacterial ulcerative keratitis, compared to non-contact lens wearers, there is an approximately 80-fold increase risk to develop microbial keratitis.

The risk of infection varies in the

literature. Unfortunately, in the United States, there is no prospective epidemiologic data which we can grasp on to and so therefore, the risk varies depending on studies anywhere from 1 to 25 per 10,000 contact lens wearers.

As far as the impact, up to half of contact lens-related keratitis best corrected visual acuity ends up being 20/60 and a quarter of patients have 20/200 or worse. This again varies on the data which one reviews in the peer reviewed literature.

Corneal opacification and perforation from bacterial keratitis result in, approximately, 330 corneal transplants a year in North America.

As has been reviewed previously, fungal keratitis on March 8, 2006, the CDC received a report from an ophthalmologist in New Jersey regarding three patients with contact lens associated Fusarium keratitis. During the preceding three months, this also

coincides with an outbreak of Fusarium keratitis associated with contact lens wearing in Singapore.

The FDA announced that in May of 2006 that there was a global recall because of the association with the Fusarium keratitis cases and ReNu with MoistureLoc contact lens cleaning solution. And as has been previously mentioned, the cases of Fusarium keratitis have significantly decreased since then.

Acanthamoeba keratitis. Recently, there was an increase in contact lens-related cases. May 26, 2007, the CDC announced an association with AMO Complete MoisturePlus Contact Lens Solution. Because of this, our task force, the Infectious Disease Task Force, which I chair with these other members, came up with recommendations for the 10,000 or so ASCRS members. This was released in July of 2007 to the members. And these are some of the recommendations associated with the outbreak.

Regarding acanthamoeba keratitis, remove and return any AMO Complete MoisturePlus Solution from offices and places of work. Interestingly, the CDC did do follow-up phone conversations and many of the patients who had been using the AMO Complete MoisturePlus had continued to use it, despite the numerous news and media sources, which had explained the recall.

Advise all patients and especially contact lens wearers of the association of acanthamoeba with the contact lens solution, AMO Complete MoisturePlus Solution, so they may dispose of remaining solutions. Recommend that all contact lens wearers rub their lenses with an alternate cleaning solution and avoid the no-rub technique advocated by manufacturers. This has been repeatedly stated today by other speakers.

Although suspicion should be kept high due to the risk of acanthamoeba keratitis, bacterial infectious keratitis is

still the most common etiology and should remain on the top of the list of differential diagnosis for clinicians. Be on the lookout for early signs of acanthamoeba keratitis and use vital dyes, such as fluorescein, lissamine green and rose bengal, some examples have been shown today, to help differentiate these lesions from those caused by herpes simplex keratitis.

With cases of acute keratitis, unless it is of an abnormal appearance, larger than two millimeters in size, moderate to deep stromal melting or is central or paracentral, treatment should begin with intensive application of a topical broad spectrum antibiotic.

If the keratitis does not respond or has any of the unusual characteristics, corneal scrapings for vital stains and cultures should be obtained to identify the pathogen. Confocal microscopy can be an aid in the diagnosis of acanthamoeba.

For any contact lens patient with a suspected infection, contact lenses, cases and cleaning solutions should be collected for culturing as has been mentioned previously.

Steroids should not be used in these cases and they should be used with caution and preferably only if the organism has been identified and if the patient is clinically responding to treatment. Early diagnosis is the key to improved outcome, so consider earlier referral to a specialist than usual, especially in these unusual cases.

Treatment involves extended and frequent dosing of at least one of the cytocidal biguanides (PHMB) and/or chlorhexidine and at least one other agent, such as neomycin, propamidine and/or clotrimazole for weeks to months.

In addition, the treating clinician may consider judicious use of oral itraconazole as an adjunct to topical therapy.

Some issues which we brought up in

our white paper: (1) Which is obviously being done today and will be continuing is to bring together federal, clinical, research and industry leaders to determine the scope and the direction that we should move forward. Approve or at least allow appropriate treatment. Now, currently, there is no approved treatment for acanthamoeba keratitis, such as propamidine, chlorhexidine and/or PHMB.

Mandate teaching of better hygiene, including forbidding tap water rinse, showering, bathing, swimming with contact lenses by clinicians as well as industry and the FDA. Recognize confocal as a valuable tool in diagnosis. Unfortunately, this is not widely available and it is a valuable tool in diagnosis.

Establish adequate standards for amoebic disinfection of contact lens care solutions. Research should be done to combine efforts in contact lens material technology

and solution advances, such that optimal combinations can be determined and several of those speakers have mentioned this fact as well. Thank you very much.

DR. BRESSLER: Thank you again. Next, Dr. William Benjamin will speak and then Dr. Louise Sclafani will follow as the next public speaker. Dr. Benjamin?

DR. BENJAMIN: Yes, I'm William J. Benjamin from the University of Alabama at Birmingham representing the American Optometric Association's Commission on Ophthalmic Standards. Dr. Louise Sclafani is the Chair of the Cornea -- I mean, the Contact Lens and Cornea Section of the AOA and will be giving our talk today. Since we are both representing the same overall organization, we thought it would be better if we just combined our two talks.

I come forward to disclose and the first disclosure I would like to make is that I am an expert witness for J&J Vistakon in

patent-related litigation in the U.S., Europe and in Australia.

Secondly, I look over the room here and I only see one company that has not, in the past, at one time or another, not funded my lab at the university. And so I don't think that's a real conflict of interest, but it could be considered so by some.

The only company that I haven't seen here that did not fund me is Advanced Medical Optics and I don't think that's one reason for the acanthamoeba keratitis.

Dr. Sclafani will be giving our talk today and I'll just go ahead and introduce her right now and have her come up.

DR. BRESSLER: Thank you very much. Dr. Sclafani?

DR. SCLAFANI: Good morning. I'm an Associate Professor at the University of Chicago Hospital and I have served on advisory panels for Alcon, Allergan, AMO, Bausch & Lomb, CIBA, Cooper and Vistakon.

On behalf of the American Optometric Association, I would like to identify several areas of concern to doctors of optometry and the patients we serve. It has become apparent that contact lenses and care products are as important as the lenses we prescribe. Thank you for realizing this relationship and being responsive to our needs, as demonstrated by this hearing today.

We have seen as a result in the past two years solutions may be getting to the shelves too soon. This may be due to pressure on industry to develop novel solutions and go to market before they have been adequately tested. With over 30 million contact lens wearers in the U.S. it seems that this would be an area that could cause a true public health issue and warrant attention.

We would like to suggest to the FDA, industry, contact lens practitioners and patients to look at strengthening the pre-market testing of care regimens in three basic

areas. Testing of solutions under more realistic conditions; testing under known conditions of noncompliance; and improved labeling.

I will now address the potential methods of strengthening the guidance document by testing of care regimens under the above conditions that may contribute to adverse events. The use of the American Type Culture Collection Isolates are limited and needs to be updated as the strains have become overused and new ones prevail.

Based on climate and resistance, the common may become less. In fact, serratia has become a more prevalent pathogen for contact lens induced microbial keratitis in countries such as Australia, where historically it has been pseudomonas.

We know that acanthamoeba keratitis may be uncommon, but given that more than 90 percent of the infections are in contact lens wearers, to our patient population it is

significant. We know it is difficult to kill this form, and that there are many variations in how these organisms are cultured.

We feel that a more standardized testing process should be developed and used by the FDA prior to approval, as well as to compare efficacy between products, so that a practitioner can make better judgments when prescribing.

A product's viability should be testing and reported under no-rub and no-rinse conditions to assure greater antimicrobial ability. It is known that most patients do not rub and rinse, even when advised to do so. The AOA firmly believes there are additional benefits from rubbing, including the removal of biofilms and deposits, especially with the increased use of silicone lenses.

Although the AOA always recommends a rub and rinse step for all care regimens, testing with the lack of one should hold solutions to a higher level of efficacy.

The cidal activity should be tested utilizing in vitro organic soil to better simulate those conditions in which microorganisms are more viable. As we have seen with some recalled solution, the gradients may have contributed to proliferation of microorganisms because they had a source of nutrition. This should be part of standardized testing.

The creation of a biofilm on the lens case and bottles also contributes to contamination, increased virulence and reduced bioavailability of the cidal agent. The ability to stimulate these conditions and test efficacies could be -- should become standard.

In addition, there are trends emerging in antimicrobial technology using silver, selenium and cationic peptides as coatings, as composite materials in lenses and cases and solution bottles. As these novel ideas come to market, they should be retested with the intended solution and labeling should

reflect if compatibility has been achieved.

Hence, we are hopeful that microbial issues of today will be made inconsequential by new technologies of the future. It has become apparent that the materials and solutions will be exposed to the actual lens and case is another area of concern.

Recent studies by industry and practitioner experience has shown that undesired effects from poor lens and solution combinations can occur just as medications have poor drug interactions. One area that should be investigated is the amount of solution that is being absorbed by the contact lens or case, thereby reducing the availability of the biocide.

Toxicity due to lens uptake and changes in lens parameters are two other possible effects. We are requesting testing of preservative uptakes. This information should be available to the practitioner, so

that they can make the appropriate choices.

The uptake has been linked to corneal staining, yet there is no definitive consensus as to what the clinical implication of solution induced staining is. A number of grids have come up and this thought process has been paramount in getting practitioners to really think about their prescribing patterns.

Doctors need to feel safe with their prescribing practices and much of this information is overwhelming yet needed. As we continue to learn what the consequences are, if any, of staining, we would then ask the FDA to incorporate this into the guidance document and then in a balanced and truthful manner, the doctor could make solution choices and follow through with their own clinical findings.

The final area of whether a solution is going to be effective is in the hands of the user or patients. Practitioners are fully aware that compliance is an area

that can affect safe wearing. Although the recent events have -- had solution failure as a probable cause, improper use of solution and poor compliance cannot be ignored.

Patients are overloaded with information, but in the end, they want shortcuts. They feel that the directions are too time consuming. Often caution will guide them and they will vary from improper usage. They do want to follow the advice of their doctor who should be an authority and guide them through the disinfecting and handling process, since this should be part of the overall contact lens prescription.

One of our goals at the AOA is to stress to our members the importance of giving direction and taking control to emphasize the significance and the overall picture. The focal study showed that more and more Americans are receiving their medical advice from the Internet and the UK reports said the general public reviews George Clooney as a

medical expert.

An astute observer may pose the question, when approving a solution, should the guideline be that known habits should fit the product or should products be designed to fit the habits? As eye care professionals, we believe we should take control of these issues. However, this challenge may be a slow and incomplete process and therefore, we are asking for the FDA to test the products under those situations of intractable noncompliance, such as poor hand washing and dirty cases.

Some recent work by Phil Morgan at the University of Manchester may shed some light on the potential for improvement. He surveyed common habits of lens wearers, relative risk associated with noncompliance as evidenced by peer reviewed research and the potential to modify behavior in these subjects. These two factors ranked very high.

Studies by Stapleton and Chang have shown that patients do not properly wash their

hands prior to insertion and are even less likely upon removal. In 2001, Wayne showed a four times increase in relative risk for infection for those who did not clean cases properly.

We are suggesting testing of products under these circumstances. Although the AOA gives cleaning instructions and recommended discard dates for cases, this havoc could be modified if cases were more readily available as a result of a requirement to have them accompany every full size bottle.

Now, knowing that patients often find the easy way out by not closing the bottles or cases properly, and by topping off their solutions rather than refilling with new, we pose that solutions be tested under these such circumstances. Chang showed that in the Fusarium issue, these conditions may have facilitated the growth of biofilms and promoted Fusarium inherence into the lens.

The FDA is responsible for

solutions to be safe and to perform well, but also to ensure that similar labels meet minimal standards of clinical performance. The present guidance document for contact lens products are from 1997.

I will now address some potential methods of strengthening the guidance document by improved labeling care regimens. Although there is an expiration date on bottles of solutions, the U.S. does not require a mandatory discard date after opening. The only requirement is that it has a preservative or is packaged to reduce contamination.

This has been a vague and confusing area for both patients and practitioners with evaporation contamination and possibly reduced efficacy occurring, the idea of discard dates that are prominently labeled on the bottle.

The most efficient and consistent method for improving compliance is by standardization of labels, clearly marked on the front label in large font should read at

the minimal or in some similar verbiage the following: "Wash hands before handling products and lenses. Do not top off solutions and rub and rinse is recommended by your eye care professional."

With so much emphasis on compliance by both the professional organizations and industry, this seems we should be able to implement these guidelines. The simple modification with universal messaging has the largest capture rate with hopes of reducing complications.

And finally, the past few years have reminded both the public and the eye care professional that contact lenses and solutions we use are medical devices with both benefits and consequences. Safe and effective products are needed to prevent mild complications in those that are devastating. The public trusts that these solutions and lenses be thoroughly tested before becoming available for use and that the laws that protect them from getting

harmed be fully enforced, such as the Fairness to Consumer Contact Lens Law.

Post-market surveillance and ease in reporting of complications should be made mandatory to improve communication between interested parties. When prescribed appropriately, contact lenses greatly improve.

DR. BRESSLER: Thank you very much.

DR. SCLAFANI: Thank you.

DR. BRESSLER: Thank you very much. Our next speaker then will be Dr. Charlotte Joslin. Dr. Joslin?

DR. JOSLIN: Okay. Thank you very much. I would like to take the opportunity to thank Dr. Bressler, Dr. Eydelman and distinguished Panel Members for the opportunity to present today.

I will be presenting on behalf of the American Academy of Optometry. I'm an Assistant Professor at the University of Illinois, Department of ophthalmology and a PhD candidate in epidemiology at the School of

Public Health. I am also the primary author on two publications in which, together with colleagues, we detailed the Chicago acanthamoeba keratitis outbreak over the last two years.

I have no commercial disclosures. Travel support was provided by the American Academy of Optometry. And my support for the research funding has been through a series of private foundations and a career development award through the National Eye Institute.

As detailed earlier today, the recent reports of an increase in incidents of Fusarium keratitis and acanthamoeba keratitis have resulted in general sight threatening -- general concern regarding the incidence, severity and prevention of these sight-threatening conditions.

A withdrawal of the contact lens solution multi-purpose, ReNu with MositureLoc by Bausch & Lomb associated with 57 percent of Fusarium keratitis cases by the Center for

Disease Control and Prevention reduced the incidents of Fusarium keratitis.

Advanced Medical Optics also voluntarily recalled Complete MoisturePlus as a result of the association reported by the CDC with culture confirmed acanthamoeba keratitis, in which 58 percent of soft lens wearers reported its use.

Unlike the MositureLoc recall, however, which effectively decreased Fusarium keratitis cases, acanthamoeba keratitis cases continue. Although the magnitude of Fusarium and acanthamoeba keratitis cases is low, the respective causes are likely multi-factorial and have not completely been eliminated, although certain trends exists. The FDA can be very influential in further reducing these infections.

How did these problems occur? There are likely many potential factors involved, but two are probably contributory. In vitro studies demonstrate that acanthamoeba

are largely resistent to multi-purpose systems. Cysts are notably more resistant than trophozoite, although some solutions have demonstrated efficacy against acanthamoeba.

Notably, hydrogen peroxide and particularly two step system appears to be more effective against cysts as are rigid gas permeable solutions.

In addition, most efficacy testing is performed with strains or methods that attenuate organism virulence, such as extensive laboratory organism cycling or axenic acanthamoeba culture growth, which may reflect -- which may not reflect the virulence of wild type organisms or wild type strains that are causing infection, which was shown with the Fusarium keratitis outbreak.

Stressors which decrease organism virulence may overstate the apparent solution efficacy and this is particularly evident when compared against real-life situations in which solution effectiveness may be further

challenged by patient noncompliance with other factors.

Proper contact lens hygiene and patient compliance are important. Yet, failure to maintain adequate lens-related hygiene both in healthy and microbial keratitis cases has occurred historically and continues to occur with noncompliance ranging upwards of 80 percent in multiple studies.

Inadequate lens care hygiene was contributory in recent Fusarium and acanthamoeba keratitis outbreaks likely by either failing to remove environmental microbial lens contaminants or providing milieu permissive to microbial growth. Microbial growth were reduced by cidal efficacy.

Although only overnight lens wear and solution reuse have been identified as risk factors for various types of contact lens-related microbial keratitis, concerns exist with other forms of noncompliance, such

as not to replacing lenses as prescribed, inadequate cleaning, disinfection and replacement of the storage case, failure to wash hands before handling lenses and cases, exposure of the lens or lens case to tap water and elimination of the digital rubbing step.

Similarly, concerns exist that passive verification of contact lens prescriptions may result in a failed opportunity to promote disease prevention for patient education regarding appropriate contact lens-related hygiene.

Additional lens-related hygiene issues that increase the relative risk of acanthamoeba keratitis include contact lens exposure to contaminated water, whether through recreational activities, such as swimming or hot tub use or exposure to contaminated tap water.

Historically, higher incidence rates of acanthamoeba keratitis in the United Kingdom, as we have heard today, have been

attributed to contaminated tap water and water storage practices. Among acanthamoeba keratitis patients, 30 percent of homes sampled had acanthamoeba positive water samples and acanthamoeba cultures, isolates cultured from the tap water were genetically identical to isolates of the cornea in six of eight patients.

Contact lens solutions must protect against common environmental causes of microbial keratitis, with the exception of MoistureLoc, multi-purpose system-based disinfectants are unchanged since their introduction in the 1990s. And their in vitro efficacy against acanthamoeba has always been poor.

Yet, aside from recent solution recalls, multi-purpose systems have been effective enough to largely prevent against acanthamoeba keratitis outbreaks since their introduction, even despite this general lack of efficacy. This increase in acanthamoeba

keratitis cases has continued and is occurring with all lens care products following Complete MoisturePlus recall.

This continuation of cases together with the general and multi-purpose solution inefficacy, yet, the lack of historical acanthamoeba keratitis cases suggests an overall increase in organism load. An increased environmental exposure from acanthamoeba and biofilm overgrowth in water distribution systems has been hypothesized potentially resulting from changes in disinfection practices to meet US Environmental Protection Agency Disinfection Byproduct Regulations.

Despite the strong association with specific solutions leading to recalls in both the Fusarium and acanthamoeba keratitis outbreaks, inadequate patient compliance appears contributory in both outbreaks. Although inadequate patient compliance does not fully account for recent outbreaks and

individual hygiene practices are generally constant over time at the population level, breaches in contact lens hygiene decreased solution effectiveness against microbial organisms.

This fact cannot be overemphasized, particularly in considering if or when an environmental pressure will increase the microbial load and also the ability of the in vitro efficacy testing to predict solution effectiveness and prevent against future microbial keratitis outbreaks, regardless of the magnitude of microbial exposure.

In vitro laboratory studies demonstrate greater acanthamoeba adherence to hydrogel versus rigid gas permeable lenses and demonstrate a further increase in acanthamoeba microbial adherence with first generation silicone hydrogel lenses. Whether due to surface treatments or increased wetability, surface treatments increasing wetability or increased lens oxygen permeability providing

superior in vitro organism growth is unknown.

To date, however, there is minimal epidemiologic evidence that is supportive for either acanthamoeba keratitis or general microbial keratitis.

The importance of rubbing and rinsing or cleaning step following by rinsing with the multi-purpose solution is highlighted by the relative lack of efficacy of currently available multi-purpose solution system against acanthamoeba and also patient compliance factors that decrease solution effectiveness against all microorganisms.

Studies published over the past two decades document the benefit of the rub and the rinse step in the removal of bacteria, fungi and acanthamoeba from the lens surface. A full rubbing and rinsing and disinfection regimen results in few surviving microorganisms, which in comparison elimination of the rubbing and rinsing steps allows hundreds of thousands of microorganisms

to survive.

Rinsing alone is not adequate as Fusarium and other organisms remain adherent after rinsing alone.

It is evident as a result of the information provided in this position statement that contact lens multi-purpose systems represent a contributing factor to the recent outbreaks in microbial keratitis. Therefore, the American Academy of Optometry recommends that all multi-purpose systems be required by the FDA to have a rub and rinse on the label mandating that patients perform both procedures after lens removal.

In addition, it is recommended that solutions must also demonstrate efficacy against acanthamoeba as a requirement for FDA-approval.

And finally, development of an ongoing surveillance system is recommended as it will provide data that are useful in identifying trends in microbial keratitis

disease patterns and helpful in more rapidly identifying microbial keratitis outbreaks and contributory factors. Thank you.

DR. BRESSLER: Thank you again. Our next to last public speaker scheduled will be Dr. Dwight Cavanagh.

DR. CAVANAGH: Thank you. I'm Dwight Cavanagh. I'm the National Optometrist Chair Professor and Vice Chair of Ophthalmology at the University of Texas in Dallas and Associate Dean for Clinical Affairs at the Medical School. I'm also a member of most of the organizations, in fact all of them, that have testified today. And I speak for none of them. I'm here on my own.

I have had an interest in this topic for roughly 30 to 40 years. And as I stand here today, I look at Don Ahearn and I think it's deja vu all over again in 1986 and we will come to that in a minute.

Now, the best data to solve problems with is peer review data and

impeccably good journals is the best of all. I want to share with you quickly some new data that has just come out in a few months. You may not be familiar with it. It appeared in the journal Investigative Ophthalmology and Visual Science. It's an NCT, National Clinical Registered Trial. It's a randomized doubly masked prospective and all the other good things that go with that type of design.

Can I have the next slide, please? The single center rate of 115 patients and basically the question is this, we have had the idea that daily wear is safer than extended wear. Suppose we put a group of patients on day one in daily wear for a year and monitor them and then a group of patients in 39 extended wear from day one and monitor them?

And we do so in a group that has no preserved care solutions, no MPS hydrogen peroxide. Now, these studies I'm reporting are in distinction to the 10 years of prior

studies or papers in ophthalmology and eye and contact lens using preserved solutions.

So the idea here was to find out if the preserved solutions had some effect on the only thing that I know of or has been published and accepted as a predictor for future infection in the eye, which is pseudomonas binding to shed cells exfoliated non-invasively from the corneal surface with lens wear.

Next slide, please. What we found was in the multi-purpose solution groups, there is a consistent rise over the first one to three months followed by a trailing to baseline. This is true for all studies over the last 10 years. What is suggested for the first time was there was an adaptation to lens wear and since these p-Values were highly significant, it was obvious that there was an effect of length of lens wear that had not been assessed by previous epidemiology studies.

My colleague professor, Fiona Stapleton, in Australia has paper in press now in ophthalmology, a companion paper to one from England of John Dart that establishes that a p-Value of $p<.01$ that the under six months wearers have more risk of developing microbial keratitis than those over six months.

Now, this effect is abrogated. It's zero if you use non-preserved solutions. In fact, it looks like over a year then in non-preserved solution wear a/k/a hydrogen peroxide, you do nothing to disturb the surface of the cornea under the lens that makes it want to bind more avidly to Fusarium, which still remains the most common cause of microbial keratitis.

So certainly, even in bacterial systems, there is an effect on the corneal surface altering bacterial binding with the lens being worn that needs to be considered.

Now, next slide. Suppose we go to

a situation, we take 10 medical students, 20 medical students, 10 males and 10 females, and we simply sign them randomly to lens care solutions with no lens wear. They put in the drops four times a day for a few days and you simply rinse the corneas and ask if the cells that come off the cornea bind pseudomonas more avidly or not.

Well, we had thought the negative control in this study would have been the boric acid, but in point of fact, next slide, this a was randomized masked study done very tightly and I think you can see for yourself that every single solution increases bacterial binding to shed cells exfoliated from surfaces that have been, shall we say, irritated by a preservative, common preservatives used in most of the lens solutions that have been described.

Therefore, I think your smoking gun, your missing link you are looking at it. I think that it is not a good idea for a lens