interaction of silicone hydrogel lenses with lens care product and ocular physiology are not completely understood yet. The current toxicological test methods do not evaluate the effects of interactions between lenses and care solutions.

We would like to share with you some of the preclinical testing approaches to address lens and lens care solution interactions which are a result of our experience or investigations of contact lens solution in last several years.

Most contact lens wearer use multipurpose solutions for cleaning, rewetting and disinfecting their hydrogel contact lenses. Recently there was a widespread outbreak of *Fusarium* keratitis in daily contact lens wearers using one specific multipurpose solution. The exact cause of such outbreak is not known yet, but it could be multifactorial. It is possible that microbial keratitis was caused by the loss of

antimicrobial activity of multipurpose solution during lens storage. It is possible that the chemical ingredients in multipurpose solution could have compromised corneal epitheal integrity and barrier function resulting in an increased risk of microbial infection. Or, the microbial keratitis could be due to synergistic effects of two factors I just mentioned. Also, patient behavior, like topping off, would be a contributing factor.

Development of an ideal multipurpose solution could be quite challenging. It might be easy to formulate a solution that will kills microbes effectively, but the same ingredients might cause corneal toxicity resulting in unacceptable clinical use of that product. It is about striking a balance between antimicrobial efficacy and ocular toxicity. The multipurpose solution can cause toxicity by direct or indirect contact. The chemicals in a lens care solution can cause cytotoxic effects by direct

contact with ocular tissues. The lens care solution must be biocompatible since some of the solution will be on the lens when the lens is inserted and thus will come in contact with the eye.

Another way the lens care solution may cause toxicity is by indirect contact to contact lenses. Absorption of preservative or other solution ingredients by the lens during soaking in multipurpose solution and release of these chemicals in ocular environment may compromise ocular biocompatibility.

As discussed in the presentation, the chemical compositions, water content and ionic nature of contact lenses dictate the optic and release of various exogenous chemicals. Beside preservatives, other chemical ingredients may also cause corneal toxicity. The breakdown of corneal epitheal barrier can lead to corneal staining. The corneal staining could be overt or mild, transient and asymptomatic. There is

increased risk of associated microbial infections if epitheal barrier function is compromised.

The recent *Fusarium* keratitis outbreaks prompted the ISO Technical Committee responsible for contact lens and care products to form a working group to explore alternative preclinical test methods to assist potential lens solution interactions. The other representation from FDA in the ISO working groups. A draft proposal has been prepared by FDA on cytotoxicity testing of a multipurpose solution to evaluate the potential toxic effects of the solution as well as any cellulo-toxicity that may arise due to the interaction between lens and the multipurpose solution. This proposal was discussed at the ANC Z80 SC7 meeting in March of this year and will be discussed at the ISO meeting in July.

I would like to share the proposal with you a little later and would like to give panel's recommendations.

The potential interactions between a lens care product and various contact lens material should be taken into account in designing the test to fully evaluate ocular toxicity potential of a new lens care product. FDA's 1997 guidance document provides recommendation on toxicity testing of lens care solution alone. FDA's current cytotoxicity proposal focuses on testing the solution alone and in combination with various lenses.

For the in vitro cytotoxicity assay, a new lens care product like a multipurpose solution should be tested with the following groups of lenses. Within the conventional hydrogel lenses Group 1 and Group 4 lenses would be tested. Group 1 consists of low-water, non-ionic polymers and Group 4 consists of high-water ionic polymers. Representative silicone hydrogel lenses with different surface treatments would also be tested.

Now a question may arise regarding the use of silicone hydrogel lenses in the study design if the new multipurpose solution is not indicated for use with silicone hydrogel lenses. The fact is that most of the consumers are not aware of the type of lenses they are wearing and since the multipurpose solutions are over the counter products, they might end up using the product even though the multipurpose solution is not indicated for the type of lenses they are wearing.

I would like to mention some of Agency's thoughts behind the draft proposal. The Agency believes that at this time both in vitro and animal studies raw necessary for evaluation of a new multipurpose solution. Despite severe criticism over the years regarding its poor reproducibility, scientific validity and ethical expectability, the rabbit eye test still remains and acceptable test method by the regulatory agencies around the world.

To date, there is no suitable validated alternative in vitro method available that can completely replace the rabbit eye test. The other in vitro tests available that use eye specific salines or isolated ocular tissues. Some of these assays are currently being used for testing of contact lenses and lens care products.

Although some of these assays are promising, we would like to emphasize the fact that no single predictive in vitro assay has been formally validated for testing of contact lenses and care solutions yet. So for our proposal for cytotoxicity testing, the L-929 mouse fibroblast cell culture model is chosen. This is a well-factorized cell line and this cell line is recommended in the USD and ISO standards for cytotoxicity testing.

Now I would like to present cytotoxicity test proposal for panel's consideration. Here are some of the salient features of the proposal. The test methods

proposed are standard well-established ISO USP test methods and use L-929 cell model. This is the cell model specified in the standards. Tests are designed to evaluate potential cytotoxic effects due to direct exposure to multipurpose solution. Also, there is a test to evaluate cytotoxicity due to indirect exposure to potential toxic chemicals in multipurpose solution through contact lenses. This could happen due to the optic of the potentially toxic chemical from the solution by the lens during lens storage and subsequent release of that chemical in the eye during lens wear. Both conventional hydrogel and silicone hydrogel lenses will be tested in this assay.

This slide shows the assay methods for evaluation of cytotoxic potential of a multipurpose solution by itself. The top diagram is for the agar diffusion assay. This assay is currently used for testing of multipurpose solutions. In this assay, the

test solution is applied to a filter disk and the filter disk is placed on top of an agar surface directly overlying a mono layer of cells. This is not a very sensitive assay. Only advantage is that the test solution could be tested neat that is full strength in this assay.

We would like to add another assay which is more sensitive than the agar diffusion assay. As I mentioned before, a multipurpose solution can cause cytotoxic effects by direct contact with ocular tissue. This exposure could be mimicked by exposing the cells directly to the multipurpose solution by this modified elution assay. This assay is based on the elution assay specified in the ISO USP standards for cytotoxicity testing. The only caveat of this assay is that the multipurpose solution cannot be tested full strength like the agar diffusion assay. Here the multipurpose solution is first diluted with the cell culture media and

then placed directly on the cell mono layer. The result from both assays will be evaluated for assessing cytotoxic potential of a multipurpose solution.

This slide presents the testing approach to evaluate the cytotoxicity of a multipurpose solution by indirect contact through contact lenses. The lens is first soaked in the multipurpose solution. Then the lens is placed directly in the center on the mono layer of cells in cell culture media. The cell set that's directly exposed to any chemical that is written on the lens from soaking in the multipurpose solution. This is called direct contract assay since the lens is in direct contact with the cells. Both conventional hydrogel and silicone hydrogel lenses would be tested with the multipurpose solution by this test method.

Here is a question for the panel. The current cytotoxicity test involves testing on the multipurpose solution by itself and not

in conjunction with various groups of lenses. Please discuss our proposal to include both conventional and silicone hydrogel contact lenses soaked in the multipurpose solution for direct contact cytotoxicity testing to evaluate the multipurpose solution.

Thank you for your attention.

Now I would like to introduce our next speaker, Dr. Marc Robboy. Dr. Robboy is an optometrist in the Division of Ophthalmic and ENT Devices at FDA.

DR. ROBBOY: Good afternoon. My name is Marc Robboy. I'm an optometrist and a clinical reviewer in the Division of Ophthalmic and ENT Devices. And today I'll be speaking to you about the impact of silicone hydrogel contact lenses on clinical study methodology.

I'll begin by revisiting the clinical testing section of our 510(k) Guidance for Contact Lens Care Products. Next, we'll review certain care product

interactions that have been reported with silicone hydrogel contact lenses. This has led to proposed revisions to the clinical testing section of our 510(k) Guidance. Lastly, I'll discuss patient labeling issues that have arisen from the *Fusarium* and *Acanthamoeba* keratitis outbreaks, which impact both the conventional hydrogels as well as the silicone hydrogel lenses.

For the purpose of facilitating clinical trials to obtain 510(k) clearance for new contact lens care products, our current FDA guidance recommends that the new care product is to be testing clinically with contact lenses from FDA Groups 1 and 4, as they represent the extremes of the four groups with respect to both water content and ionicity. So for a new contact lens care product intended for use with conventional hydrogels, we recommend a total of 60 subjects subdivided as shown here by lens group.

This testing matrix has worked

reasonably well over time with the conventional hydrogel lens materials. However, as has been discussed by the other presenters, silicone hydrogel lenses, because of their great complexity, do not interact in the same way as conventional hydrogels with respect to on-eye performance including their interactions with contact lens care products.

As silicone hydrogel lenses have become an increasingly greater percentage of the daily wear market, as we have heard earlier, this has been accompanied by reports of solution-related complications, specifically generalized mild punctate corneal epithelial staining which has been characterized as typically both asymptomatic and transient.

In the Jones publication, 37 percent of subjects demonstrated this type of corneal staining with a specific silicone hydrogel lens that was used with a PHMB-based lens care system. The authors report it as

being consistent with a classical solution-based toxicity reaction. As has been discussed, this standing has been attributed to the lens care preservative being taken up by the lens and subsequently released onto the eye.

This staining phenomena has subsequently led to a lively discussion on the Internet, in the trade press and in the peer review literature regarding the clinical significance of the superficial staining that has been associated with certain contact lens care products. For example, there's a website, staininggrid.com, that displays a corneal staining grid which highlights the severity of staining with various combinations of lenses and multipurpose solutions. Then there's another website, truthaboutstaininggrid.com, that calls into question the clinical relevance of the first website. Similarly, there are reports in the literature that take either side on this

issue. These two references take one side of the argument. In the current publication, the authors retrospectively analyze 609 subjects, and, as we have heard earlier, found that corneal infiltrative events were three times more likely to occur in eyes exhibiting solution toxicity compared to unaffected eyes.

And in the Hall pilot study the authors assessed the effects of lens care systems with different preservatives on corneal epithelial barrier function and measured a significant difference in epithelial permeability between the care systems.

And these two cited references take the opposing view in this debate. Dr. Ward conducted a survey of the peer-reviewed scientific literature regarding superficial punctate corneal staining and concluded that the literature reflects that this staining does not reflect corneal injury or toxicity. Dr. Levy reported in his review that there has

been no increase in corneal infection in the presence of this low-grade corneal staining. Additionally, he argued that if the solution-related staining represents compromised epithelial tissue, it would be highly unlikely that it could disappear in such a short period. He stated that the apparent misuse of the term "solution cytotoxicity" warrants reevaluation in determining correlation to increased risk.

Because this solution-related staining occurs at maximum severity at approximately two hours after lens insertion, some researchers are recommending that an additional follow-up visit occur at that time. In the Garofalo study, the authors reported that with some combinations of lenses and lens care products, maximum staining occurred between two and four hours following lens insertion. And in the current publication, the authors state that daily wear soft lens wearers should be routinely examined two after

lenses are inserted.

Regarding the assessment of corneal staining and follow-up visits, our current guidance recommends that the visits occur at specific time intervals. For example, at one week, two weeks and four weeks post-dispensing, but does not indicate the specific time of day at which a visit should occur. However, follow-up visits typically occur later in the day; that is, well beyond the two to four-hour window.

Therefore, later the panel will be asked, please discuss your recommendation for and additional follow-up visit at two hours in order to assess for solution-related corneal staining. And please discuss whether this should be included in lens care products and/or lens guidance.

Although Dr. Hutter has indicated the need for Group 5 silicone hydrogel subcategories to better predict lens solution incapatibilities, this will probably not occur

any time soon. Therefore, in the absence of a validated grouping system, we are proposing the interim approach shown here to be used for clinical investigations of new contact lens care products. As you can see, the silicone hydrogel lenses have been subdivided by surface treated and not surface treated, and further subdivided by type of surface treatment. In the case where a manufacturer offers more than one silicone hydrogel lens and similar chemistry, we're proposing testing to one with a higher water content.

As you may recall, our current guidance recommends that a total of 60 subjects be clinically evaluated for a new contact lens care product for intended use with conventional hydrogel lenses. In comparison, this is our proposed approached based upon the convention outlined in the previous slide. Realize, however, that this approach may change with the clearance of new silicone hydrogel lenses with unique

chemistries. Thus, the table may continue to expand or other logical grouping methods may evolve.

Therefore, the panel will later be asked to discuss, to please provide your recommendations on the inclusion of silicone hydrogel lenses and the clinical investigations of contact lens care products.

Turning our attention to labeling concerns, we have heard earlier that FDA has previously cleared both rub and rinse as well as no-rub multipurpose contact lens care products. We've also heard the specific benefits of the addition of the rub step during the microbiology presentation, as well as some of the other presentations.

As you recall, these references show the removal of additional microorganisms, as well as reduce deposition with the addition of the rub step. Additionally, in response to the *Fusarium* and *Acanthamoeba* keratitis outbreaks, as we have heard earlier, various

professional organizations have made recommendations in this regard. For example, the American Academy of Ophthalmology says to consider performing a rub and rinse lens cleaning method rather than a no-rub method regardless of the type of cleaning disinfection solution that you use in order to minimize the number of germs on the lens.

In the paper cited here, although Dr. Butcko and her coauthors acknowledge the conflict of opinion in the literature regarding the need for the mechanical rub step, they cite growing evidence which supports reestablishing the digital rub component to multipurpose solution lens care systems.

Later, the panel will be asked: Currently rub and no-rub care products have been cleared by FDA for marketing in the United States. In light of all the data currently available, please discuss your recommendations continuing to have no-rub

directions on the product labeling.

In summary, I've reviewed the sample size recommendations n our current guidance which are based upon the previously-established lens groupings for conventional hydrogels. We've seen that corneal staining has resulted from certain combinations of silicone hydrogel lenses and lens care products and has garnered significant attention in the literature, as well as having led us to proposed revisions to our guidance.

And finally, we've seen that the recent outbreaks have caused us to rethink some our labeling instructions and to propose additional changes to improve the safe use of these devices.

Thank you.

CHAIRMAN BRESSLER: Thank you very much.

I'd like to thank the FDA and the CDC speakers for their very enlightening and informative presentations.

I'd like to have the panel now ask the FDA and CDC speakers any specific questions they have. We're not going to discuss the questions for the panel. We'll come back and have another opportunity as we discuss the questions for the panel to get additional information from the FDA and CDC speakers. But I just want to be able to answer specific questions that patient may have right now. Then we will take a short break. Then we will come back after that break to begin to address the six questions with some discussion as necessary with the panel.

So I'll start with Dr. Matoba.

DR. MATOBA: May I ask two questions of the same speaker? Okay.

Dr. Visvesvara, I wanted to ask you two questions. The first is, when you evaluated those multipurpose solutions and you concluded that they had no efficacy at 24 hours, you kept the plates for two weeks,

correct? And how confident are you that at that point those cysts are not viable? Because in the environment they can remain like that for months, or years even.

DR. VISVESVARA: That's a very good question. You know, in some of those cases, we have taken those cysts off of the plates, washed them again and put them back on agar plate with bacteria. And if they are viable, they should be able to excyst and then eat the bacteria. We did not see that.

DR. MATOBA: Okay.

DR. VISVESVARA: We didn't do in all the case, but in some cases. And that gave us the indication that most probably, most likely all these cysts are non-viable.

But if you do not expose them to any of the solution, if you let them sit in the laboratory cupboard where all the agar is completely direct, we have been able to recover the *Acanthamoeba* from those cysts which have been sitting on the parchment like

agar plate for 20 years. We have been able to get them to excyst and we are going to write a -- a publication is coming out now. So that is there.

But when they are exposed to, for example, hydrogen peroxide, or PHMB, one of those things, they -- and also, you know, we take a 100 cysts, probably most of them are killed. There are just a subset of populations who are resistant to all these things and they come out.

DR. MATOBA: Okay. My second question is, when you were doing those studies, you were looking at cysts alone, but in clinically probably when you have cysts in the contact lens case they probably also have bacteria because the co-contamination is going to be very common.

DR. VISVESVARA: Right.

DR. MATOBA: So in that setting do you think that the multipurpose solution would be less effective because some of it is being

used to kill the bacteria, or more effective because the presence of the bacteria might induce the cysts to excyst.

DR. VISVESVARA: See, what we do in this case is that we wash out the bacteria as much as possible. So, when we look at the preparation there will be very, very few bacteria. And I think in a few cases we had used as control, just bacteria only. And we did not see any sort of, you know, enhancing the viability of the *Acanthamoeba* cyst because of the presence of bacteria. So, I think what we are seeing is truly the inactivation of cysts by some of these solutions.

DR. MATOBA: But do you think that in evaluating a multipurpose solution for efficacy against *Acanthamoeba*, that which is being proposed, so that there should be some component where testing is done with a mixture or amoeba plus bacteria?

DR. VISVESVARA: I would think so. When you test them, you try to wash up as

much bacteria as possible. When you do a low-grade certification, the amoeba, because of the density, they settle down right at the bottom. And then the suberate will have a lot of bacteria. And then you wash it two or three times. You're getting up most of the bacteria.

And the remaining few bacteria, I don't think is going to interfere with your testing at all.

CHAIRMAN BRESSLER: Thank you.

Dr. Mathers?

DR. MATHERS: Yes, I also had a question for Dr. Visvesvara.

It seems that you tested two peroxide solutions. One of them was effective and one of them was not. Do you have an explanation for that?

DR. VISVESVARA: I do not. The only things I can think of is that there are some other ingredients or some other substances in the lens solution which are

interrupting with the activity of the hydrogen peroxide. That's a possibility. And also we have seen that in many of these cases, especially when we look at the contact lenses, cases and solutions inside them, we see a lot of precipitate which indicates that some of the components are probably precipitating out and they're not really available for the amoeba to act on the amoeba. That's a possibility.

And the third possibility is maybe they did not have the necessary concentration of hydrogen peroxide.

DR. MATHERS: Because you were not looking at a one-step, two-step thing. I mean, you didn't have it in a contact lens case or whatever. You just had the solution?

DR. VISVESVARA: Yes.

DR. MATHERS: Okay. Thank you.

DR. VISVESVARA: The solution, right.

CHAIRMAN BRESSLER: Thank you. Dr.

Szczotka?

DR. SZCZOTKA-FLYNN: My question is for the same speaker.

CHAIRMAN BRESSLER: Your *Acanthamoeba* expertise is needed.

DR. SZCZOTKA-FLYNN: Along the same lines as Dr. Mathers with the peroxide solutions you tested. So can you clarify again, that was 100 percent. But three percent peroxide during the entire soak time, that wasn't how -- was that how a consumer may use it with the neutralization process?

DR. VISVESVARA: Well, I can not give you a definite answer for that because we did not look at the concentration of peroxide there. We just took the solution from the bottle and it said --

DR. SZCZOTKA-FLYNN: So it was not used the way a consumer would use the product? It was used with a four-hour perhaps soak time of simply what was in the bottle?

DR. VISVESVARA: Yes, we took one

ml from the bottle --

CHAIRMAN BRESSLER: Wait one minute. Before you answer your question, we just want to -- the mike went out.

I want to make sure the transcription is -- get it forever, so --

DR. VISVESVARA: Well if I remember what you asked, that we took up one ml from the bottle. Okay? And then just like we took out one ml from all the other bottles, you know, with different companies. And then we inoculated the cysts into those one ml solution. Because we thought when we measured the contact lens cases, each case had probably -- you know, approximately they could hold one ml. That's why we picked one ml as the standard. And we used only 10 microliters, so there was not enough dilution factor. If there's a dilution factor, it could be common to all the solutions to be tested.

DR. SZCZOTKA-FLYNN: So are you aware that the peroxide systems must be

neutralized before they go in the eye and that is not consistent at all with how consumers use those products?

DR. VISVESVARA: No, we followed exactly what the bottle says. If there is a neutralization, we used exactly the same method that the bottle had recommended. So what I'm saying is that we followed exactly what a consumer would do.

DR. SZCZOTKA-FLYNN: Okay. Well, I'm still very confused then because Clear Care requires a platinum coated disk and their case to neutralize the product and the percent of peroxide rapidly deteriorates within the first few minutes and UltraCare uses a time release coated tablet.

DR. VISVESVARA: Yes.

DR. SZCZOTKA-FLYNN: So, if you're only using one ml of solution taken directly out of the solution without any neutralization steps, then I don't think it's a very representative way to represent these results

because it's not the way that a consumer would have used the product if you did not use any neutralization step.

DR. VISVESVARA: I'm still not very clear. Because see, if there is a neutralization step, we use exactly what the bottle recommended. So I don't think there was any difference from what the consumer would do. Because some of the people who work with me, they are contact lens users. And, you know, we were very careful about doing exactly what the bottle recommended.

CHAIRMAN BRESSLER: I think your points can be taken into consideration when we do the discussion of that.

Okay. Other questions for the group?

Mr. Bunner?

MR. BUNNER: I just have one for Dr. Lepri?

DR. LEPRI: I get my name murdered all the time so I'm probably murdering yours

too; I'll apologize for that.

MR. BUNNER: It's been pronounced worse than that.

I just was very interested in the studies on medical non-compliance.

DR. LEPRI: Yes.

MR. BUNNER: And in the general medical population there's a non-compliance rate or 24.8 percent.

DR. LEPRI: Yes.

MR. BUNNER: And it was stated in the slide that retention depends on doctor/patient relationship and repetition to improve that.

DR. LEPRI: Yes.

MR. BUNNER: So what is the theory on the breakdown in the eye care community where we have non-compliance rates ranging from 50 to 79 percent? Do we think there's less of a doctor/patient relationship or less repetition instruction, or is there any explanation for the difference in that?

DR. LEPRI: What you're saying is that the non-compliance rate drops, is lower, and proved when the doctor reinforces instruction with each follow-up visit.

MR. BUNNER: So is there anything we can assume in the eye care community that shows such a high non-compliance rate? Well, much what we're trying to do, I guess, is to look at patient labeling and patient education.

DR. LEPRI: Yes. Because on one of these studies that I cited it was for eye care, for contact lens care. And they also improved the rate when there was a better doctor/patient relationship and reinforcement. But I don't have the exact rate.

Okay. This was in the study by Collins that reinforcement follow-up visits improved this behavior, but they did not give the rates. It was just a general statement that everything -- the misunderstanding about chemical disinfection, the not washing the

hands. All of those rates dropped to lower levels once it was reinforced the importance of them and the consequences in their follow-up contact lens visits.

Am I answering your question?

MR. BUNNER: I think so. I guess what I was getting at was if we wanted to see an improvement in compliance, it's going to be more than just -- product labeling is going to have a lot to do with the relationship between the eye care provider and the patient.

DR. LEPRI: Yes, that message needs to get out to the clinical community that it's not just to be entrusted to any technician in the office for follow-up visits, but that when you put the patient behind the lamp, these types of warnings may be something to put in the labeling, you need to reinforce. Ask these questions. Are you doing it this way, step-by-step? Are you following these procedures. And if you hopefully get an honest answer from your patient, then you can

reinstruct them.

CHAIRMAN BRESSLER: Very good.

Dr. Mathers?

DR. MATHERS: My speaker isn't working, but I can --

CHAIRMAN BRESSLER: Does it work next -- or the whole side is out? Okay.

DR. MATHERS: I call on Myra Smith.

You were testing *Fusarium* --

MS. SMITH: Right.

DR. MATHERS: -- and as model organism, and I don't see any indication anywhere that some of the organisms that are considered as also suitable to test. Is there a more stringent test besides the *Fusarium* in your opinion, or --

MS. SMITH: Which test are you referring to?

DR. MATHERS: The test for fungal species.

MS. SMITH: Yes.

DR. MATHERS: For viability.

Obviously some species and some organisms are going to be more difficult to kill.

MS. SMITH: Right.

DR. MATHERS: And testing those would be a more stringent test. Is *Fusarium* in the middle? Is it relatively easy to kill? How does it fit in and is there an organism that might be useful that would be more stringent?

MS. SMITH: I don't have a real good answer to that, because there's so much variability in the different strains. Originally in the contact lens original -- back in the '80s, I believe it was, they were doing *Aspergillus niger*. And even with the performance criteria for all these organisms within our tests, there's a very -- either you require either removal or just like a very low number of organisms being killed. So the theory was that most of these multipurpose solutions primary were intended to be bactericidal, not that the fungal organisms in

the yeast would be more -- it's more relied on by a physical removal.

There are some products that have a higher level of efficacy, but within the performance criteria, as they stand now, it's really a very low level. We are really depending primary on -- to get clear -- more of a physical removal. And part of the reason for that was that it was thought that they were less prevalent than the bacterial infections.

DR. MATHERS: Do you think that's also true for the *Acanthamoeba* species? For instance, *lenticulata* is, I understand, more difficult to kill than *castellanii* and I'm sure there is a wide variation as well.

MS. SMITH: There definitely is, even within the same strain. How you prepare it. There are so many variables. The idea is to try to have standardized methods. A manufacturer can always do more testing. Before, more strains were tested at one point.

Maybe that's something we need to look at.

DR. MATHERS: And this is more than strain-dependent. It is dependent upon the circumstances that the organism is set up.

MS. SMITH: That is correct.

DR. MATHERS: Correct as well?

DMS. SMITH: Yes.

CHAIRMAN BRESSLER: Thank you. Yes?

DR. AHEARN: In the case of the *Fusarium*, none of the original containers that the patients used were positive for the organism. What about with *Acanthamoeba*? I didn't --

MS. SMITH: I think you'd have to ask one of the CDC investigators. I don't recall that.

CHAIRMAN BRESSLER: Thank you, Dr. Smith.

Did you want to ask Dr. Verani?

DR. AHEARN: That would be fine, yes.

CHAIRMAN BRESSLER: We will repeat the question.

DR. AHEARN: In the case of the *Acanthamoeba*, were any of the original containers found to be contaminated with the organism, or was this limited to the cases, et cetera?

CHAIRMAN BRESSLER: Just the mike over to your left. All the way over.

DR. VERANI: To my left.

CHAIRMAN BRESSLER: Thank you.

DR. VERANI: No, I was looking for my presentation, because I do have a back-up slide.

CHAIRMAN BRESSLER: Sorry.

DR. VERANI: But I don't know if we have connectivity to the lap top anymore.

CHAIRMAN BRESSLER: I thought you had mentioned testing the cases, that you didn't find that.

DR. VERANI: We did. No, it was present in some -- I don't know -- remember

the proportion off the top of my head, but we did test -- I believe it was about 80 environmental specimens that included bottles of contact lens solution that had been opened and used by the patient, contact lenses and contact lens cases. And some proportion of all three of those were --

DR. AHEARN: Was that the tips of the cases such as with the nozzles, or was this the internal ingredients of the contact lens solutions?

DR. VERANI: Now I'm actually going to defer to Vis because they did the testing in his lab.

Did they test the tips of the cases, or the bottles?

DR. VISVESVARA: What was that?

DR. AHEARN: Internal contents of the original containers, did they contain the *Acanthamoeba*, or was it all cases tips outside?

DR. VISVESVARA: We looked at all

of the solutions and many of them we had *Acanthamoeba* grow back -- I think that -- FDA to ensure that they are --

CHAIRMAN BRESSLER: Dr. Verani, could you repeat his answer just so we get it into the microphone? Or, do you want to come back just to give the answer, please? I apologize.

DR. VERANI: Were you speaking about the unopened bottles of solution, or the solutions that --

DR. AHEARN: Used solutions that were in the hands of the patients. Were the internal contents of the original containers containing the organisms or were they confined to the outside surfaces?

DR. VERANI: My understanding is actually the solution inside that was tested. But we did not -- no, just that outside. Okay. It was done in Vis's lab, so --

CHAIRMAN BRESSLER: Did you get your answer, Dr. Ahearn? No?

DR. AHEARN: I'm not sure.

CHAIRMAN BRESSLER: Okay.

DR. VISVESVARA: Let me tell you what we did. Okay? We did not find -- we took the unopened bottle from the market, that we purchased from the market. We looked at all of the 11 solutions that we looked at. None of them had any bacteria. None of them had any fungal organism. None of them had any *Acanthamoeba*. We did not swab the surface and look at them.

CHAIRMAN BRESSLER: Right. So the unopened ones have no infection.

DR. VISVESVARA: Unopened bottles.

CHAIRMAN BRESSLER: But I think your question was --

DR. VISVESVARA: Was open bottles.

CHAIRMAN BRESSLER: -- in the cases that were opened, what did you test to look for --

DR. AHEARN: No, I'm interested in the initial bottle. Did the contamination

occur back into the solutions within the original containers?

DR. VISVESVARA: Well, we did not look at the opened bottles.

CHAIRMAN BRESSLER: Okay.

DR. VISVESVARA: Okay?

DR. AHEARN: Okay.

DR. VISVESVARA: We did not look at the open bottles.

CHAIRMAN BRESSLER: And you can check. We can come back to the question after the break as well.

DR. HILMANTEL: Just as far as the *Fusarium* goes, there was one of 17 opened bottles of the MoistureLoc; *Fusarium* was found under the cap. And one of five bottles of MoisturePlus, *Fusarium* was found under the cap, but there was no *Fusarium* found inside.

CHAIRMAN BRESSLER: Okay. Dr. Burns, last question?

DR. BURNS: I had a quick question for Dr. Verani.

Yes, I just wanted to check, you ended up in the *Acanthamoeba* study with I think 75 or 74 people in the case control study?

DR. VERANI: The cases, yes.

DR. BURNS: The cases?

DR. VERANI: Yes.

DR. BURNS: Did you just do some simple descriptive statistics of that group relative to the total population of cases that you started with?

DR. VERANI: I don't have that data with me, but I do remember looking and that they were more or less comparable to the 105.

DR. BURNS: Okay.

DR. VERANI: Yes.

CHAIRMAN BRESSLER: Yes? Go ahead, Dr. Raasch.

DR. RAASCH: You showed us the results from that follow-along survey of the ophthalmology clinics around the country for 2007 and noted that the drop off in the last

seven months after the suspect solution was off the market was pretty radical --

DR. VERANI: Yes, it's --

DR. RAASCH: Are there plans to -- about now for another follow-up survey to see if in the next six months --

DR. VERANI: Yes, about to rise when we're planning to --

CHAIRMAN BRESSLER: Can you just repeat the question, just so that they'll have it in --

DR. VERANI: So the question is about the 2007 data. When you look by month, there's no clear decline in cases in the seven months of 2007 following the recall of AMO Complete MoisturePlus. And we do plan to collect that data. For the reasons that I stated when I did the presentation, you know, there's difficulty interpreting that data from 2007 because of the persistence of the product in people's homes. So we are planning in July to contact those same centers to ask for cases

diagnosed during the first six months of 2008.

CHAIRMAN BRESSLER: And again, we'll have an opportunity to come back as we discuss the questions, because we may have comments. I apologize for the microphone glitch, but it's better to walk over than have somebody ask you a month from now exactly what somebody said, so we prefer the recording.

All right. We are going to take a break now, only for 15 minutes, because we want to start the panel questions. So we're going to start exactly at ten after 3:00.

So, thank you and we'll work on the microphones in the interim.

(Whereupon, the above-entitled matter went off the record at 2:55 p.m. and resumed at 3:07 p.m.)

CHAIRMAN BRESSLER: Okay. We are going to start and although we only have six questions, some of them are multifaceted. Some may be straightforward, some may require some additional discussion.

The way I would like to do this is to have Dr. Saviola introduce the question and then I will turn to the Panel and if someone wants to comment on it, please do. It's not required for everyone to comment on it. And if there's a general discussion that you think is relevant to the question, we will do that. I will try and make a summary of what I believe the Panel is representing.

And I would ask, Dr. Matoba and Dr. Mathers, maybe you could keep little notes on the side and if I'm concentrating on something, I may miss part of our summary and I'll turn to you to make sure we've covered everything, and then I'll confirm with Dr. Eydelman that she has the information that we need and what our concerns are.

So we will do our best and I'll turn it over to you.

DR. SAVIOLA: Thank you, Dr. Bressler.

All right. The first question to

be discussed is: Please discuss whether our proposed directions for use and warnings below are warranted. If yes, please identify any other messages that should be conveyed in the proposed warnings. Then there are five sub-parts regarding reuse and topping off, is the first one, (b) is rub and rinsing times, (c) is lens case care, (d) is water activities, and (e) is specifying a lens care product discard date. And also please provide any other additional recommendations for product labeling that you may have.

CHAIRMAN BRESSLER: So these are proposed directions and we're just going to take one at a time to see if there are comments on them and I'll try and summarize those from the group.

So any comment on the proposed direction for reuse and topping off?

DR. MATOBA: Well, I think there's no question that we've clearly -- that we should have some warning against reuse and

topping off and it should be in a language that I think that's very clear, because not everyone knows -- not all patients would know what we mean by avoiding reuse or avoiding topping off. I think we should start out by saying something like, "Always discard the contact lens solution before you put the lens in."

CHAIRMAN BRESSLER: Any additional comment or contrary comment to what Dr. Matoba said from the group?

Okay. So Dr. Eydelman, it seems that at least for that first part, everyone was in agreement with avoiding topping off and reuse, but avoid jargon. Like reuse may mean something to one person and something else to another.

Go ahead, Dr. Ahearn.

DR. AHEARN: One comment. The topping off also should relate to the case, because the case is one of the areas that gets a heavy residue from the various solutions and

that's a build up. And when you have evaporation on the case, then you have dried films. And when you have dried films, well you've got bacteria and fungi and so forth that develop. Because the integrity of the solution is lost with the evaporation and I think most of the patients that we looked at had dried films on the cases.

CHAIRMAN BRESSLER: And we'll come back to that with (c) as well for lens case care.

So Dr. Mathers, additions to what we've summarized so far?

DR. MATHERS: Yes. In terms of warning, several words were proposed up there what might be used. And I might say that I think this should be strong warning. And saying that you could get an eye infection is not a strong warning. Saying you could go blind is a strong warning. And we need to make it strong, otherwise we know you don't get compliance. So we need to make it a

strong warning.

CHAIRMAN BRESSLER: Okay.

DR. MATHERS: A corollary to reuse might be for part-time wearers. Some instructions for part-time wear if you're wearing them once a week or twice a week, to maybe re-disinfect within 24 hours of wearing the lens. It's sort of reuse of solution to some degree.

CHAIRMAN BRESSLER: So again, I think our summary is, we're all for the topping off. Be careful with, you know, the jargonous use so it's clear and your labeling experts will be able to help in that. And it needs to be a strong warning. There's a concern about this because of the rare infection of causing blindness.

Dr. Eydelman, do you have enough for that first one?

DR. EYDELMAN: Thank you. That's sufficient.

CHAIRMAN BRESSLER: Okay. So rub

and rinsing, including a time.

Dr. McMahon?

DR. McMAHON: Most certainly, there's a growing body of data that suggests the combination of the two maximizes the efficacy of these kind of solutions, particularly with fungal organisms and I think that some minimum times need to put in there that are realistic. At the same time, sponsors need to be providing, you know, sort of low volume rinse times in their evaluations, since that's what the patients are going to do.

CHAIRMAN BRESSLER: Are there additional comments?

Dr. Mathers? No?

DR. MATHERS: Yes. I think that if rubbing gives you one log unit, it's worth it. And it doesn't mean that you can't have an effective solution that gives you more log units, but an additional log unit of efficacy is worth it for a rub.

CHAIRMAN BRESSLER: And Dr. Edrington.

DR. EDRINGTON: One of the things, and again, maybe this isn't the place for it, but the reason for the procedure, so that they understand why rubbing is indicated.

CHAIRMAN BRESSLER: So there's a general -- sounds like a consensus that rubbing and rinsing should also be in there as a do item, and to again indicate why, but the why may be again to reduce the risk of blindness.

And again, this rinsing, I think the only additional thing I might add is you're talking about rinsing with the solution. And this will also be important because rinse to some people may mean rinse in water and I think we've heard a lot of expert information today say don't rinse with water; rinse with the solution. So you're talking about rubbing the lens and rinsing with the solution.

Another comment? Dr. Smith?

DR. SMITH: There was one speaker this morning that referred to rubbing and rinsing after removing the lens and before inserting the lens, Carol Clayton on the rub and rinse time, FDA slide that says current instructions for use. Are there any instructions that say that? Rubbing and rinsing after removal as well as prior to insertion?

DR. SAVIOLA: I'll answer that, if you don't mind.

DR. SMITH: That's all right.

DR. SAVIOLA: Generally there's no rubbing after it's soaked. There's a rinse after it's soaked, but not a rub after a soak.

DR. SMITH: Okay. So I would agree with --

DR. SAVIOLA: Are you looking at page 21 of the hand out?

DR. SMITH: Yes.

DR. SAVIOLA: Yes.

DR. SMITH: And I would agree with Dr. Bressler that this language, and I guess we'll get to it to another section that needs some -- could improve, could be improved.

CHAIRMAN BRESSLER: Are there additional comments or disagreements of what we said?

Dr. Matoba?

DR. MATOBA: The question also refers to rinsing time. And I think a speaker this morning said that 20 seconds is -- one of the solutions has 20 seconds as the rubbing and rinsing time, but that was not realistic because most patients don't spend 20 seconds rubbing and rinsing.

I don't think we've been given enough data to give a recommendation as to the ideal time. And then whatever that time is though that gives you the maximum efficacy, even if it doesn't seem realistic, if it's less than half a minute, I think that is the number that should be put on the label.

CHAIRMAN BRESSLER: Given what we've heard about compliance, then maybe an additional factor to take into consideration is we all heard good data to support rubbing and rinsing with the solution. We don't necessarily have the data yet to give you a time. And I would presume even if people -- everyone just starting rubbing and rinsing without a time, that might be a step in the right direction. Maybe additional studies may come forward to help say what a cut off is, so I think we're okay there.

Dr. Eydelman?

All right. Lens case care. So comments on proposed warnings with the lens case care. This relates to some of the things that we heard earlier.

Any comments? I think this was in terms of discarding the lens case after a certain amount of time.

DR. SAVIOLA: It's on page 22 of the hand out, the proposed warning. "Do not

store your lenses or rinse your lens case with tap water, bottled water or non-sterile solution, etcetera."

CHAIRMAN BRESSLER: Thank you.

DR. MATHERS: What is the current acceptable time to keep a lens case? How long can you keep it now?

DR. SAVIOLA: There's no specific time at the moment. But the question for discussion is do you endorse this proposed warning regarding exposing the case to non-sterile products? If you think that you should include a recommended replacement time, then we'd certainly be listening to that recommendation.

And the advice to patients that was cited in the presentation regarding the outcome of the Fusarium and acanthamoeba, I believe three months was the recommended time for replacement of the case. But that's been somewhat variable across different professional organizations.

DR. MATHERS: I would like to recommend a time replacement. I think it adds to the efficacy of this approach.

CHAIRMAN BRESSLER: So there's a suggestion right now to expand the warning about not only using just the information you have in the warning here, but potentially have some statement about lens case duration.

Comments on that? Dr. McMahon?

DR. McMAHON: Yes, one of the things that we discussed early on is to make our recommendations based upon science. And where it sounds really good to replace lenses, or cases on a regular basis, and certainly all of us have seen the grungy cases that come out of pockets and purses, I haven't seen any data yet that says what kind of time frame we should be talking about. The notion I think is a good one, but I wouldn't know what time frame to use. I agree with --

CHAIRMAN BRESSLER: Okay. Dr. Szczotka-Flynn?

DR. SZCZOTKA-FLYNN: My question refers to the air drying recommendation here. I know most groups say to rinse with solution and air dry. There is no data showing this, but I know when I let my case air dry, there's still a film in it. And I'm wondering if that's enough film to support continued microbe growth. I did read somewhere that some groups actually recommend swabbing it with like an alcohol swab, or turning it over so that the case at least can drain even that excess solution.

So I think there needs to be a little bit more recommendation in terms of just letting your case air dry, or more data to support other ways to let it dry.

CHAIRMAN BRESSLER: Go ahead, Dr. Burns.

DR. BURNS: I just want to make a comment on the wording of these kind of instructions; and that is, it's ambiguous. For instance, in sample one you say never use

tap water. You said solution, so don't say never use water. Don't leave it open that they say, okay, it's not tap water and use it. Say never use water. I think there are several cases like that.

CHAIRMAN BRESSLER: Dr. Matoba.

DR. MATOBA: Because bottled water has bacteria in it, too. So I think your point is well-taken.

DR. SMITH: But the proposed change has bottled water and any non-sterile solution in the warning part. But the current language says never use tap water.

And my question about the current language is about the top for those tops that are screw tops. Do people interpret rinsing your lens case with including rinsing the top of your lens case, not the ones that snap down, but the screw-top ones, case and top for any -- because that's all exposed to that area.

CHAIRMAN BRESSLER: So you may need

some clarification then on what is a lens case. But again, we're trying to just give some advice to help based on the science. And so I will come back to the lens case care, because we haven't resolved the drawing bit yet. I mean, the replacement bit yet.

DR. MATHERS: Yes, I was going to suggest that I think my esteemed colleagues are completely correct. We do not have data on this. Perhaps we could ask the FDA in conjunction with industry to do relatively simple things to determine how long it takes an average case to build up a certain amount of debris that can't be cleaned and what a suitable replacement time would be. I think it seems easy.

CHAIRMAN BRESSLER: So to try and summarize, but correct if I'm wrong, it sounds like there's a general favor for the warning that you have, but to clarify some of the language in terms of avoiding water, that there is insufficient information at this time

to comment on how often a lens case should be replaced or how it should be dried or air dried or the concerns that are mentioned. And that comes up every day. So additional information may be helpful. That only allows you to put the warning in that you have, but we don't have enough data to advise about replacing the lens case.

Dr. Eydelman, okay?

All right. Dr. Smith, another comment on that and then we'll go to the next.

DR. SMITH: The last comment is the last statement there says use of non-sterile solution can lead to serious eye infection. It might be helpful to add "and loss of vision" with that. I mean, that's several places eye infection and most people don't know that -- they'll think that's pink eye. They won't --

CHAIRMAN BRESSLER: Dr. McMahon, comment on that?

DR. McMAHON: Can I touch again on

the drying for a second?

CHAIRMAN BRESSLER: Yes.

DR. McMAHON: I'd love to hear what Dr. Ahearn has to think about the idea of air drying cases, since his thin film stuff is very much akin to that.

CHAIRMAN BRESSLER: So air drying?

DR. AHEARN: I don't recommend air drying with solutions that have been -- cases that have been stored for prolonged periods of time. And what those prolonged periods are, I'm not exactly sure of. But I do know that most of the solutions can dry down in a relatively short period of time, so evaporation can have an effect and you can have growth on the outside of the case, which then can seed the inside of the case later, and very time you handle it,

CHAIRMAN BRESSLER: So it still sounds like we have insufficient data to comment on what the care should be so far in terms of, you know, drying the case.

Okay. So water activities? And just refer us to the page again? It's on page 23, I believe?

Do not wear your lenses during any water activity.

Okay. Comments on this? Let's start with Dr. Edrington.

DR. EDRINGTON: The showering, since we have people wearing 30-day lenses, are we not recommending they shower? I don't know.

DR. SAVIOLA: That's part of the difficulty of the total water activity, because then you bring up the most difficult point to address.

CHAIRMAN BRESSLER: We didn't get an answer yet, but don't worry. We're going to continue to discuss this so we can come up with some recommendations.

Dr. Szczotka-Flynn?

DR. SZCZOTKA-FLYNN: Well, my question was exactly the same. I think if you

give the message that you don't want them to shower with the lenses, it just adds confusion to those patients we've already told they could sleep in their lenses. So at the current time I would probably take showering out of this warning, unless you want to revise your extended-wear guidelines, too.

CHAIRMAN BRESSLER: Not yet, but let me get -- okay. Dr. Mathers?

DR. MATHERS: There is a real problem with removing your lenses for water activities. People are not going to do that. So the reason they have their contacts is so they can go skiing and water skiing and this sort of thing. Otherwise, they could wear glasses in many cases.

So although I think that water exposure is one of the strongest causes of acanthamoeba keratitis, if we are to say something useful, we might consider saying that if we can strongly recommend that they don't do it. But if they do, then immediately

after the water activity they remove and discard those lenses. It's a compromise, but it -- or --

CHAIRMAN BRESSLER: Dr. Matoba commented that perhaps you could re-sterilize.

DR. MATHERS: -- re-sterilize.

CHAIRMAN BRESSLER: So I want to just expand this for a second, you know, I want to review sort of the epidemiology that we heard. In at least the logistic regression analyses, we didn't hear that there was additional risk of the water exposure. That doesn't mean that it isn't a risk. But I agree with your first comment that we're weighing here what we're recommending. And for example, let's just take swimming in a pool. If we told everyone in the world and they were all compliant with taking their lenses out, and now they can't see that well, what other risks, you know, occur from that? You know, do they not see where their, you know, child is, or do they bump into someone

new that they didn't know they were going to meet? But it is quite a lot to say we want you to remove this because there's this one in 10,000 or three in 10,000, you know, risk of an infection compared with -- you know, I don't know what the other risks are by removing it and taking away the person's vision. So that has to be balanced.

Dr. McMahon and then Dr. Szczotka-Flynn.

DR. McMAHON: I mean, it's clearly a conundrum. I mean, the water environment is the environment for acanthamoeba and Fusarium in particular. So you have sort of an implied risk. It just hasn't been spread with a statistical, you know, significance at this point.

And then we have the issue that Dr. Szczotka brought up, that you know, we have this group of patients that are going to be sleeping with lenses. I would actually suggest that we not specifically say disinfect

them, though that would be effective for bacteria, but for things that are on the market now it's not going to be effective for acanthamoeba, which is the primary, you know, concern at that point. So I'm unclear as to what to recommend with this whole topic.

CHAIRMAN BRESSLER: Dr. Szczotka-Flynn.

DR. SZCZOTKA-FLYNN: If you want to go back to the science or evidence-based, I think the CDC evaluation showed, at least on univaried analysis, that lakes and streams were more risky. And I know other groups in Australia have shown that as well in those kind of bodies of water. I'm not familiar with anything yet that is showing statistical significance in univaried or multi-varied analyses on showering, or even pool water, for that matter.

But just to qualify what I said earlier, perhaps you can, in the daily wear patient, recommend, you know, attempted

removal during showering and of course all those other water activities. But I would clarify in the daily wear patient, if you wanted to go that route.

CHAIRMAN BRESSLER: Dr. Mathers and then Dr. Edrington.

DR. MATHERS: The strongest indictment of water is the experience in Britain. They have a ten-fold increase over the United States and it's mostly considered to be the water supply. And in my clinical experience, I think that water exposure matters a great deal, even though it is perhaps a little difficult to document.

I think we should err on the side of safety in assuming that exposure to dirty water is a risk and if we can help patients deal with this, it would be a good thing.

CHAIRMAN BRESSLER: Dr. Edrington and then two over here, and I'm going to try and give you a proposed summary of what we've said. So additional comments?

DR. EDRINGTON: Perhaps something about, "Please discuss this with your eye care practitioner." Because you have a lot of people that are, you know, going scuba diving on their trip to Hawaii and you'd sort of like to help them, although it does put maybe you and the patient at a little bit of risk. But they should discuss it with their eye care practitioner.

CHAIRMAN BRESSLER: Dr. Smith?

DR. SMITH: I think you could be consistent with the case. You're telling them not to use tap water. You could say something like, "You should avoid water contact with your contact lenses." I mean, it's a consistent message. We know that people are going to do these things, but that cannot control our recommendations. As clinicians, all of us know people do things. They do all kinds of things with their medications. You don't tell them it's okay to do that. You say well, I'm recommending that you take the

dosage that I gave you. If you take that dosage, these things might happen to you. And you know, I understand we're trying -- you know, we're trying to do real case scenario, but I also think we have a responsibility to say what we recommend. If a person doesn't follow it --

CHAIRMAN BRESSLER: Okay. And Dr. Burns?

DR. BURNS: Yes, sort of swinging the other way and supporting the idea of discussing it with the eye care is what are people going to do with their lenses if they're at the beach or at the pool when they take them out. I think there's a real risk there that may be larger.

CHAIRMAN BRESSLER: Yes, we don't want them to put them in their mouth.

Dr. Matoba.

DR. MATOBA: I wanted to agree with Dr. Mathers about this issue. Because compared to the 1980s epidemic, when the

epidemic was clearly linked to non-preserved saline and once they stopped doing that, then the epidemic went away. This time it's associated statistically with one contact lens solution. You take that off the market, but it's not clear that the epidemic is over. And the Chicago people have suggested that there may be a change in our water supply in the United States due to the changes made by the EPA in terms of decreasing the stringency of the system and they felt that that would allow bacteria to overgrow, this allowing acanthamoeba to feed on the bacteria and then increase the biofilm within the water supply.

And that hasn't been clearly studied or eliminated as a possibility. So I think we do have to be concerned about the possibility that, like England, that in the U.S. the water supply may be contributing to the current epidemic, which may not yet be over.

CHAIRMAN BRESSLER: So it sounds

like there's general consensus of there being a risk of water for the eye infection. There's a concern about telling people not to do something in the warning, like don't shower or don't swim or something and that that may be why there's this judgment to say, you know, let that be an interaction with the eye care provider to tell them why there's this risk.

And so, Dr. Eydelman?

DR. EYDELMAN: There is a bit of a concern on my part with that, in that we usually refer to specific interaction between patient and physician if the patient's case is unique. I think what I'm hearing is that for the lack of our ability to reach a consensus, we're deferring it to individual discussion. In other words, would one person's risks of water activities be necessarily different than another patient with an identical situation. But we do hear your concerns and we'll try to come up with some kind of language to take all of that into --

CHAIRMAN BRESSLER: Okay. Dr. Mathers, last comment on water.

DR. MATHERS: We haven't discussed this at all yet, but I believe it would be the opinion of a lot of practitioners who deal with this that single use lenses under these circumstances have advantages. And while we are not in the business, you know, to promote a particular product perhaps, that isn't actually a particular product, perhaps there is some way to get this message that a truly disposable single-use lens has an advantage if an environment is going to be contaminated.

CHAIRMAN BRESSLER: Very good. Yes?

DR. SAVIOLA: So for clarification, fundamentally do you propose a warning regarding water exposure? Yes. Okay. Thank you.

CHAIRMAN BRESSLER: And the last was specifying a lens care product discard date. Comments on this from an engineering

point of view. Dr. Smith?

DR. SMITH: When that was suggested, I was thinking about how other situations and other types of bottles of things that clinicians do use in evaluating patients. We often open and put a date on it and they are often discarded way prior to the expiration date. So it's a practice that we do for other things already. It seems like a good idea to me.

CHAIRMAN BRESSLER: Okay. Other additional comments on that?

Dr. McMahon.

DR. McMAHON: I mean, I like the idea and I think it's potentially beneficial. Again, the evidence issue of what does this mean and the fact that it's very common practice for, you know, patients to go to a big box store and buy five bottles of stuff and then it doesn't get opened for six months. And so how do you establish that discard date?

If there's some evidence to suggest that after opening, the relative efficacy of the solution fails over a certain period of time, that can be put in the particular labeling and maybe a space on the bottle saying, you know, write that discard date.

CHAIRMAN BRESSLER: So a consideration of when it's opened.

Dr. Mathers?

DR. MATHERS: Is there a current limit on the volume that can be put in a single bottle?

CHAIRMAN BRESSLER: Is there a limit on how large that solution can be?

DR. SAVIOLA: No, there's not a limit. In Europe where it's mandated they have a discard date upon opening, they follow and established ISO standard to establish that date. So if it's a certain size to be considered, like if, you know, use it for like a month for a smaller size bottle versus like three months for a larger size bottle.

DR. MATHERS: Because another way to achieve this is to have relatively small bottles, not a large bottle that would be an economy pack. But if you make the bottle smaller and you have a discard date, it does encourage compliance and might be helpful.

CHAIRMAN BRESSLER: Although they may open that one that they had for the travel case and forgot when they opened it.

Dr. McMahon?

DR. McMAHON: Well, the downside to Dr. Mathers' suggestion is is if they have a smaller bottle, they can rinse with a lower volume.

CHAIRMAN BRESSLER: One question I have about the logistics, because Dr. Smith pointed out that we often may label, for example, ophthalmic drops in the clinic before instilling them and we know when to discard, so we use a pen. It might get smeared. I don't know many people have a pen in their bathrooms. And if they don't have it, they

may not do it. And this is the whole compliance issue as well. So there may be other ways of indicating this like, you know, scratching off while you're there on the bottle that it was, you know, January and it was, you know, '08, or I don't know. But I would certainly take that into consideration as well, that it's easy to say you recommend a discard date, but how you get it there in a compliant fashion in the bathroom is important.

Other comments? I think we finished question No. 1.

Dr. Eydelman?

DR. EYDELMAN: Except for any additional recommendations for product labeling that we might have.

CHAIRMAN BRESSLER: Okay. So I'll open that up to the Panel. Any additional recommendations, warnings? Yes, Dr. Szczotka-Flynn?

DR. SZCZOTKA-FLYNN: Well, I don't

know if this is the correct place to bring this up, but I think you could put these warnings a little bit better on your website as well, because kind of right now they're hidden. So on your risks page, there's two or three statements where they're hidden. And then again on another page, they're hidden. If you kind of had a stand-alone page of your recommended activities in regard to these products, it would be helpful.

DR. EYDELMAN: This actually hasn't come up in our previous presentations, but our intent is to incorporate all of Panel's recommendations and modifications and update of our contact lens website.

CHAIRMAN BRESSLER: Good suggestion.

Okay. Why don't we go on then to No. 2?

DR. SAVIOLA: Now that we did the easy one, question No. 2: 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.

CHAIRMAN BRESSLER: Comments on having no-rub directions from the presentations today.

Dr. McMahon, you can give a summary and then we'll see if anyone disagrees or wants to add something, please.

DR. McMAHON: The quick summary is, is that rinsing works somewhat; rubbing works even better. The combination of the two is best of all and not doing either is worst of all. And so the issue is, is there a gold standard for the amount of log reduction to bugs on the surface of a lens?

And my view would be is, you establish that benchmark fairly high based upon rinse and rub and if a solution can meet that benchmark with no rub, then fine. I

don't think they're going to get there.

CHAIRMAN BRESSLER: Dr. Mathers?

DR. MATHERS: I would second that. I like the idea that the industry competes for safety. If they can do it, that's fine.

CHAIRMAN BRESSLER: Dr. Smith.

DR. SMITH: The other thing that I would add, if there are other mechanisms of removing material that don't involve rubbing like other things we know that people do work on, that would eliminate the need to go back and say, well, you now have a product that says you can shake it 10 times upside down or irradiate or whatever. So I really like the idea of establishing, you know, a really nice objective benchmark for that because that makes it easier, I think, for the FDA in the future to evaluate additional products.

DR. MATHERS: Ultrasound.

CHAIRMAN BRESSLER: Dr. Mathers?

DR. MATHERS: Ultrasound, heat, can be revisited. I think that would be an

opportunity to look at this again.

CHAIRMAN BRESSLER: And Dr. Szczotka-Flynn, yes?

DR. SZCZOTKA-FLYNN: I haven't seen anyone present any data on whether rubbing removes biofilms, and most of the bacteria are simply adhered for a few minutes. So I think that there needs to be more work in that area to show that rubbing actually removes biofilm which has been shown to be implicated in keratitis.

CHAIRMAN BRESSLER: We are going to come back to that, yes.

Dr. Matoba?

DR. MATOBA: Okay. I'd like to ask a question though, because I agree with Dr. McMahon's comments, but for those products that are already approved for no-rub, can you do anything about that, or is this just going forward, in which case you're going to have some no-rub products or rub that are more stringently tested than the ones that are on

the market now?

DR. EYDELMAN: You actually touched on a very interesting subject because if the Panel's recommendation is to come up with a higher bar for the micro-efficacy, then that inadvertently precludes us from taking immediate action. Because obviously it's going to take us some time to decide on where that bar is and then take appropriate action, as opposed to having a general recommendation of rub versus no-rub. We could take action at this time.

CHAIRMAN BRESSLER: So it sounds, so far, that the Panel generally was in favor based on data that had been presented to say there's a certain level of improvement obtained so far with rub and rinse compared with the current rinse alone with solution. I think that's what was presented.

And so, the bar is not being set by the Panel except in general advice to say allow things other than rub and rinse if they

meet whatever that standard is that is come up with that's rub and rinse.

Is that a fair summary, Dr. McMahon?

DR. McMAHON: Well along those lines, I mean, maybe I'm saying the same thing as on the short term that we can encourage rub and rinse for products right now and that the notion of no-rub go away. And that in the long term as benchmarks are established that that particular approach can reemerge.

CHAIRMAN BRESSLER: We agree.

Okay. No. 3.

DR. SAVIOLA: No. 3 has three parts. First part regarding clinical issues. Please discuss your recommendations for an additional follow-up visit at two hours in order to assess for solution-related corneal staining. Second part, please discuss whether this additional follow-up should be included in lens care products and/or lens guidance. And the final, part three, please provide your

recommendations on the inclusion of silicone hydrogel lenses in the clinical investigations of contact lens care products.

CHAIRMAN BRESSLER: Okay. Do we have someone to make a comment starting with the assessment of solution-related corneal staining?

Dr. Edrington?

DR. EDRINGTON: This is a recommendation to practitioners?

DR. SAVIOLA: This would be implemented in the clinical study design for manufacturers.

DR. EDRINGTON: Okay.

CHAIRMAN BRESSLER: Comments on this?

Dr. Mathers, I'm not a cornea expert. My take on it was there wasn't a lot of correlation with corneal staining and subsequent understanding of these problems from contact lenses.

DR. MATHERS: I think that's

correct, that the issue of staining, toxicity and risk of keratitis seem, at first glance, to be a linear progression, but are not necessarily so. And there may even be factors like the release of materials that may even in theory be beneficial to an impeding keratitis even though they produce a small amount of staining.

So I think the links haven't been established correctly, or solidly, and therefore making a recommendation for two hours is not valid at this point.

CHAIRMAN BRESSLER: Dr. Eydelman first and then I'll come back to the Panel.

DR. EYDELMAN: If I can just clarify the question. We're not asking the Panel to set the bar; i.e., what amount of corneal staining at two hours would warrant a decision (a) or (b), but rather in light of the confusing evidence at the time, is it worth adding a two-hour visit for the evaluation as part of the pre-market

evaluation.

CHAIRMAN BRESSLER: Okay. Dr. Szczotka-Flynn?

DR. SZCZOTKA-FLYNN: I think if you're going to add a two-hour visit, you have to add even more than that. Because as we saw data, some preservatives might be released at different time points. So you might add even more time points, perhaps a half-hour, perhaps four hours in addition to two hours. But what you do with that data, I'm not sure. So I don't think you should use it as a condition for approval.

The other information that no one has brought up today was that what we might be seeing is not actually staining of the cornea. There was an ARVO poster that showed that PHMB binds to mucin and then fluorescein combined to that complex. So what we might be seeing is basically the preservative somehow binding to this mucin and that's what's staining and that's why it goes away so

quickly.

So we don't really even know what that staining is; there's controversy about that. So another reason to reinforce why we shouldn't try to make correlations between the staining and a product's performance.

CHAIRMAN BRESSLER: And Dr. McMahon?

DR. McMAHON: Two comments. One, I don't think there's enough evidence to support adding this particular item. And number two, Dr. Szczotka-Flynn to my left actually has the best supportive information that staining has some predictive value with infiltrative keratitis, but that's in the extended wear and cumulative and I don't think it actually really has anything to do with this here.

CHAIRMAN BRESSLER: Seeing no other comments -- oh, sorry.

MS. NIKSCH: Barbara Niksch. I would just like to agree with Dr. McMahon and also just say that in the rationale for the

two-year period doesn't seem like it's well-justified based on literature or basically what Dr. Mathers had indicated. Also I think it would be overly burdensome for sponsors to ensure compliance to that within a protocol.

CHAIRMAN BRESSLER: So the Panel generally does not endorse adding this visit for the reasons that were discussed.

Okay. Whether this should be included in lens care products or lens guidance, the same. Okay. And inclusion of silicone hydrogel, it's the same. Oh, I'm sorry. Not for staining.

Okay. So let's go to (c). So recommendations on inclusion of silicone hydrogel lenses in the clinical investigations.

Dr. McMahon, you want to start us on --

DR. McMAHON: Absolutely, and I liked the grid that was presented by FDA as a model.

DR. EDRINGTON: The five.

CHAIRMAN BRESSLER: Other comments? Dr. Szczotka-Flynn?

DR. SZCZOTKA-FLYNN: Of course I think they need to be included; they're very different animals. I actually liked the CLI's breakdown with the -- I think they had four categories. And the difference with that was that the supposed third generations, the enfilcon and confilcon A, which are non-TRIS based and used siloxy macromers, I think are quite different animals and may behave differently. So I'm in support of the four subdivisions.

CHAIRMAN BRESSLER: But there's a recommendation to continue to evolve, right, as there's other classes that could be developed by manufacturers.

DR. SAVIOLA: Yes, actually, for clarification, we had the four categories in our chemistry presentation as well, so we didn't have an update in the clinical part.

CHAIRMAN BRESSLER: So there's consensus here to now break out the silicone hydrogel lenses?

Dr. McMahon?

DR. McMAHON: Again, I think for now right now whether it's three, four or five, whatever is most efficacious, I'm fine with. But I think if companies can provide by equivalency for a particular product then, you know, I think that they can individually negotiate a lower number of classes to be looked at.

CHAIRMAN BRESSLER: Okay. Dr. Mathers, you're in agreement?

DR. MATHERS: Yes, I would agree with that strongly because it's going to get very complicated and it may be irrelevant; we don't know, but we will be able to find out.

CHAIRMAN BRESSLER: Thank you.

Dr. Eydelman, you're okay on No. 3.

No. 4, microbiology issues. And I think we'll again take one at a time after you

go through them.

DR. SAVIOLA: Okay. Microbiology. Please discuss your proposal to revise the current Regimen Test in order to improve predictability of "Real World" performance and include the following topics in your discussion: First point, testing marketed silicone hydrogel lenses. Second point, defining worst case rub and rinse times; for example, five-second rub and five-second rinse, total time.

B, in microbiology, please discuss your recommendations for adding acanthamoeba as a challenge organism in disinfection efficacy testing.

C, please discuss our proposal for developing standardized test methods to evaluate the effects of preservative uptake by contact lenses on disinfection efficacy. Additionally, please comment on use of these tests to determine post-disinfection storage times in an unopened lens case.

And finally under micro, please discuss our proposal for modifying disinfection and preservative efficacy testing by two points testing at the lower end of the active ingredient specifications to simulate worst case conditions. And second point, including more resistant clinical isolates in these tests.

CHAIRMAN BRESSLER: Okay. So we'll start with the part A, which was getting to the fact that not everyone follows the recommendations, so should there be real world performance tests.

DR. MATOBA: This is where we would include Dr. Szczotka-Flynn's comments about the biofilm needing -- so that -- because I think currently the contact lenses are being exposed to organisms for 10 minutes, but it really takes hours or 24 hours for some biofilm to build up. And that greatly increases the resistance of the organism to sterilizing solutions. You might want to

elaborate.

DR. SZCZOTKA-FLYNN: Well, I perfectly agree and there's multiple places where the biofilm data comes in, both just looking at stand-alone efficacy of the solution, as well as the rubbing and the rinsing. So if we're just talking about rubbing and rinsing here and looking at the Regimen Test, I would propose that you do rub and rinse on formed biofilms.

CHAIRMAN BRESSLER: Other comments or recommendations to add about having a real world test? Dr. Mathers?

DR. MATHERS: Are we assuming then that the real world test will actually be with contact lenses in an environment where they are dirty, where they have soil, where they have protein and the protein has allowed to deposit? I mean, none of this is done now. So I think that what we're proposing is a radically different approach to this.

CHAIRMAN BRESSLER: So do you think

that's of value here to evaluate the solution?

DR. SZCZOTKA-FLYNN: But I thought FDA proposed that? I thought your --

DR. SAVIOLA: The real world test was a describe test where the lens is sitting in the case with the solution. It's not just challenge directly as it is in the stand-alone right now. So that's what we're working toward that, that ring test that mentioned earlier. Now what I hear is some additions is some additions beyond that regarding biofilm formation.

CHAIRMAN BRESSLER: So there's, again, consensus to do that specifically with no-rub, no-rinse and having a biofilm to test the effects of the solutions.

Dr. Matoba?

DR. MATOBA: And in regard to the acanthamoeba testing, as Dr. Visvesvara said, I think you might want to consider testing acanthamoeba along with other bacteria. Because in the real life that's what happens

is you've got bacteria contamination that's at a very high rate, and then amoeba on top of it. And they may behave differently in that setting.

CHAIRMAN BRESSLER: So we'll had that comment into part B, which at first was acanthamoeba alone, and recommendations for adding this as a challenge organism in disinfection.

Would somebody like to start that?

Dr. McMahon.

DR. McMAHON: Yes, I would wholeheartedly support using the acanthamoeba as a challenge organism. In addition, I would like to encourage both corneal isolates from infected patients as well as environmental organisms that have specifically been taken from corneas.

CHAIRMAN BRESSLER: Dr. Mathers?

DR. MATHERS: Yes, I would like to strongly endorse including acanthamoeba. I think what we're seeing here is just the tip

of iceberg actually with amoeba infections. And currently it may be reported in a few cases, but most cases of acanthamoeba are not reported and the incidence is much higher than as generally quoted and has been quoted today. There are places in the literature where this is inferred or directly stated, but I would imagine that the real rate is more like one in 20,000, 30,000 or 40,000 contact lens wearers. And that there's probably in addition to this a broader spectrum of less virulent organisms that are really only seen by PCR or confocalmicroscopy that are there and are below our radar, but they are participating in disease. So they definitely should be included. I definitely think that we ought to test for this, not just with culture and not just with the current approaches, but with PCR and perhaps encourage confocal, although I don't think that's going to be effective. And that we should use more virulent organisms, organisms that are more difficult to kill.

This is not that difficult to establish. And that as Dr. Kilvington has indicated, the preparation of the cysts and their resistance is strongly variable by circumstances and this ought to be taken seriously.

CHAIRMAN BRESSLER: Dr. Matoba?

DR. MATOBA: So currently -- well the ATCC strains are used for reproducibilities and because they're readily available to all people who want to do testing. So I guess the FDA would have to undertake to isolate or identify test organisms every few years and then provide it to all people who want to -- how would that work?

DR. SAVIOLA: The devil would be in the detail. At this point I don't think we have to burden ourselves with considering the logistics, just taking the recommendations. So if you think you want to include clinical isolates or virulent strains, then that would be the recommendation.

DR. MATOBA: I just didn't want to recommend something that was not very practical for the FDA.

CHAIRMAN BRESSLER: So we're recognizing that, Dr. Saviola, we don't want to be, you know, burdensome in just recommending something, but we have a strong recommendation that acanthamoeba needs to be tested, other virulent organisms related to that as well. And there was also a comment to even consider combining that when there's bacterial and acanthamoeba. I think that's the general advice so far.

Dr. Burns?

DR. BURNS: just to clarify, I think everyone's talking about the cystic form when they're saying acanthamoeba.

DR. MATHERS: You need to test both the troph and the cyst, but almost always the trophs are easier to kill, so it's the cyst that is the problem, but not just any cyst. How the organism encysts is also relevant and

it varies widely.

CHAIRMAN BRESSLER: And Dr. Szczotka-Flynn.

DR. SZCZOTKA-FLYNN: I again support acanthamoeba as the rest of the Panel.

Just a comment about the resistant strains. I think some of the ATCC isolates are irrelevant and I think the point is using a relevant strain. It doesn't necessarily have to be an isolate from, you know, most recent outbreak, but a very relevant strain. An example is the Fusarium strain was from 1970 in Nigeria from a corneal ulcer before contact lenses were even around. So just a relevant strain, I think, and ATCC may be able to provide you that.

CHAIRMAN BRESSLER: Okay. Any other comments? Yes, Barbara.

MS. NIKSCH: Barbara Niksch. Just a comment on practicality that obviously before testing is actually required for pre-approval, that the test method obviously be

standardized and accepted and recognized. Obviously there's a lot of input here today, but to actually implement that so that sponsors can use that. We want to make sure too that sponsors all are using the same methodology. Otherwise, it doesn't mean anything.

CHAIRMAN BRESSLER: Exactly, I think what we were adding to the comment that it wasn't just a easy thing to say, oh yes, why don't you test for it? It's a very important problem. It can be tested, we think, and we're not going through the fine tuning of it, but it obviously needs to be something that industry can know what they're supposed to test.

DR. MATHERS: I would also like to recommend that the log reduction units here be meaningful. In the past, they've talked about a Fusarium reduction of one log unit. I'm surprised that they would even admit that that was done that way. But if you're going to

have a meaningful reduction, it must be in the order of three to four or so log units so that you get a real standard that's going to have some effect.

CHAIRMAN BRESSLER: Very good.

Okay. Dr. Saviola, let's go to C, which is the proposal for standardizing the test methods for evaluating the effects of preservative uptake on disinfection efficacy.

Comments?

Maybe, Dr. Eydelman, you could expand on the question. We're not getting an instant response to provide advice.

DR. EYDELMAN: I think the best is if you can go back to Myra Smith's presentation. She had for Panel consideration and I'm going to try to flip to that slide to read it for you.

DR. SAVIOLA: It's on page 47, 46-47.

DR. EYDELMAN: So essentially, as she summarized, this infection and

preservative efficacy testing at low end of active ingredients specification and testing more resistant clinical isolates. And as a result, hence this question. I don't know if that clarified it for you.

CHAIRMAN BRESSLER: Not yet. I want to confirm with Karen that we have the question discussion or -- Dr. Smith?

MS. SMITH: One of the key things about this is talking about incorporating lenses into the testing when we're looking at efficacy. And you know, that was a major part of the discussion. And that's for the first part, because right now we don't feel that the lenses are adequately incorporated when we're looking at actual efficacy instead of just in physical removal in the Regimen Test. And we're saying that when you soak a lens over a period of time, you have less preservative available and this is one of the key concerns we have, because when we're looking at the current tests, in the stand-alone test there's

no lens. So a product could have great levels of kill to begin with, but the minute you put it into a lens case and soak your lens, the preservative may be uptake -- you know, the preservative uptake may cause two problems. One, you're inserting more preservative into your eye; and two, there's less in your case that would be available for disinfection.

CHAIRMAN BRESSLER: Okay. Thank you for clarifying. Now I think we've got it.

So comments? Dr. Matoba.

DR. MATOBA: Well, my question is, when you are testing the contact lens in a solution with bacteria, are you really concerned about how many bacteria are left in the solution, or how many are on that lens when you take it out and rinse it and try to put it in your eye? And have you looked at that? And if the microbicidal component, or the preservative that's taken up by the contact lens, maybe if you don't have too much toxicity it's really not that undesirable if

the contact lens has more antimicrobial material on it.

MS. SMITH: There are concerns because it's never really been adequately tested to know what type of a problem that uptake would cause. And it may be different with different lens materials. As far as the soak solution, because the reuse of the lens case there would be more of a chance of biofilm formation. I think one of the most important things is that we can only have a certain amount of expectations for these solutions unless we -- they're not high-level disinfectants. So we can say we want to test all the most resistant organisms in the world, but in reality either you have to have a system where you have to assure that it's completely removed or you need to have some sort of balance where you are getting a reasonable amount of kill and trying to predict what is going on.

CHAIRMAN BRESSLER: Okay. Dr.

Mathers?

DR. MATHERS: Well I think you're correct that we are asking industry to come up with something that works and the gold standard would be sterility. And --

MS. SMITH: I think with regard to that, this is not a -- I don't think we're looking for sterility because we're dealing in an everyday situation. I think we're looking for a hygienic situation.

CHAIRMAN BRESSLER: Right.

DR. MATHERS: I understand.

CHAIRMAN BRESSLER: Well, he was getting there, right.

DR. MATHERS: But if the gold standard is sterility, but that -- and maybe that can be achieved with peroxide or heat, or something like that. Maybe that is possible. But if it isn't possible, then there has to be at least a limit on the duration that that lens can sit in that case and you still consider it to be a useful time frame and that

is something that you could determine. Because really what you're asking is how long can you let the lens sit there before you've got to go through the thing again. And that should be a relatively short period of time. None of this 30-day stuff where it sits there.

MS. SMITH: That's why there's the second part of that question, because right now when we're -- we've established that 30-day disinfection, no lens is included in that testing. And I think that's something that we could easily correct.

CHAIRMAN BRESSLER: Dr. McMahon?

DR. McMAHON: Recently I'd learned something I had never even thought about, that actually applies to this particular question, and that is some of the preservatives that are used in these solutions, the molecular weight at any given point in time can vary quite a bit. So there can be selective absorption of relatively more effective variance of a molecule that goes into the lens that then

makes the area around it potentially less biocidal. Now, I'm not a chemist; I can't speak to the validity of that statement, but if that is true, then this type of mechanism where you introduce a lens to the process makes a lot of sense. It's sort of a back door way of getting around that issue.

CHAIRMAN BRESSLER: So the general advice from the Panel is to include these as you're suggesting and to come up with perhaps some general guidelines of times, as Dr. Mathers suggested.

Okay. And then part D? This I think is again asking for trying to get into worst case conditions or more real world conditions. Is that right?

MS. SMITH: That's similar to for high-level disinfection. You usually do try to establish -- or reprocessing of other medical devices, you try to look at for microbiology the worst case would be the lowest concentration. It's the highest

concentration that could possibly be there for toxicity, but it's the lowest concentration for microbiology. And sometimes you would have a range or over, you know, depletion of time and you know, all manufacturers have specifications. And if you happen to be at the higher end and it's supposed to be set, if you have it maybe a little bit higher, I mean, then you need to -- may assess whether -- how you're setting your specification to justify that whatever within the realm of this predictability of this test you can do.

CHAIRMAN BRESSLER: Okay. So are there comments then on this proposal from the FDA in favor of it? Dr. Szczotka-Flynn?

DR. SZCZOTKA-FLYNN: I wanted to bring up again, it goes along -- this topic is the peroxide issue and you know, that might fall in this lower end of the spectrum because I think there's not consistency between how you test peroxide systems and how you test these multipurpose systems because of the

neutralization process that's occurring. So if you're looking at a peroxide system, I think you have to incorporate somehow proposals for standardizing the neutralization effect of that solution and how quickly the peroxide changes from three percent to something lower. So in terms of the lower end of the efficacy of that, somehow incorporating this issue of the neutralization steps that need to occur to show consistency between the solutions and also on the lower end of the efficacy scale.

MS. SMITH: That would be addressed in looking at the kill curve in terms of the neutralization process for a peroxide. We know that if you have a disk or you add in a neutralizing tablet, we look at release rate. You can't ask to look for, you know, what the release rate is of the catalyst and how it compares to the level of kill. So that would be incorporated into the testing right now. But there would be no lens involved.

DR. SZCZOTKA-FLYNN: Along the same lines, if we're looking at, like Dr. Mathers brought up, how long you can keep a lens stored in the solution because of the uptake of the preservative, we also have to contrast that with the peroxide systems where they have no preservative after their disinfection cycle. And there's just a little bit of comparing apples to oranges.

CHAIRMAN BRESSLER: Dr. Mathers?

DR. MATHERS: Yes, I agree with you and in addition, this is going to come up if you're talking about something like an ultrasound solution or some ultrasound system, or even heat. I know no one ever talks about this, but it wasn't that long ago that we thought this worked. Even though contact lenses may not last as long, people don't wear contact lenses as long. And the industry may decide this is a reasonable approach. But it would require a different kind of standard because you don't have anything afterwards.

But I think the FDA could certainly address that and come up with a reasonable approach.

CHAIRMAN BRESSLER: So the Panel generally agrees with going to the lower end of these testings. And the exact considerations I think are, you know, broad, including the hydrogen peroxide statements that Dr. Szczotka-Flynn made.

DR. EYDELMAN: Thank you.

CHAIRMAN BRESSLER: Okay. So No. 5.

DR. SAVIOLA: Question 5. 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 lens group into subcategories.

CHAIRMAN BRESSLER: So earlier the Panel was in favor of, you know, separating out the silicone hydrogel lenses. Is there something different about this recommendation?

DR. McMAHON: Yes, CLI's

classification was four separate silicone hydrogel groups, whereas FDA's was three silicone hydrogel groups and a Class 4 HEMA group. And I guess, do you want direction as to which of those two this Panel prefers, or --

DR. EYDELMAN: Well, the question doesn't specifically ask you to address that, rather than just to comment on our work, on our plan to stratify it further. However, if you wish to give a comment, we're certainly willing to listen.

DR. SAVIOLA: If I may, Tim, you're thinking back to the one slide that Marc showed. That was the clinical categorization for the test, agreed? Of the three CLI into one?

Yes, what we're talking about here really isn't pertaining specifically to the clinical study, per se. It goes back more toward Dr. Hutter's slide where he had the four groups in the effort to break the

silicone hydrogel out.

DR. McMAHON: As I said before, I conceptionally support the notion of breaking down the groups, the details --

CHAIRMAN BRESSLER: Other comments?

DR. BURNS: Just support. Yes, I think it makes sense to try to stratify these.

DR. EYDELMAN: Okay.

CHAIRMAN BRESSLER: All right. Straightforward.

Last but not least.

DR. SAVIOLA: Question 6. The current cytotoxicity test involves testing on the multipurpose solution by itself and not in conjunction with various groups of lenses. Please discuss our proposal to include both conventional and silicone hydrogel contact lens soaked in a multipurpose solution for direct contact cytotoxicity testing to evaluate multipurpose solutions, or any care product for that matter.

CHAIRMAN BRESSLER: So comments?

Because we've had some tangential comments on this with the previous discussions.

I think there was general agreement that the Panel did think that that should be incorporated in conjunction with the lenses.

Okay. I don't see other further comments.

Dr. Eydelman, Dr. Saviola, do you have other questions that you want to address with the Panel for now?

DR. EYDELMAN: I would just like to take this opportunity to thank the Panel for your deliberations and for your prompt -- it was quite an extensive agenda and I'm very impressed that you have been able to conclude answering and deliberation on all of these questions.

CHAIRMAN BRESSLER: We certainly didn't want to rush it. And I want to thank the Panel as well for all their time in listening and then giving advice, and to the CDC and FDA and all the public speakers who

came and gave us input to put this together. So thank you very much.

So I will say that this meeting of the Ophthalmic Devices Panel is now adjourned. Thank you.

(Whereupon, the above-entitled matter was concluded at 4:10 p.m.)