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FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Docket No. FDA-2012-N-1040  
Antiseptic Patient Preoperative  
Skin Preparation Products

Public Hearing

Wednesday, December 12, 2012

9:00 a.m. to 12:30 p.m.

DoubleTree by Hilton Hotel  
8727 Colesville Road  
Silver Spring, Maryland

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P R O C E E D I N G S

**Welcome, Introductions and**

**Opening Presentation**

DR. FURNESS: Good morning, everybody.

Please take your seats. We're getting ready to get started.

My name is Scott Furness, and I'm the director of the Division of Non-Prescription Regulation Development in the Office of Drug Evaluation IV within FDA's CDER.

I'd like to welcome you to this Part 15 hearing that will be addressing antiseptic patient preoperative skin preparation products. I'm going to be the presiding officer today, and we have a whole host of distinguished panel of experts from across the agency and from our sister agencies, the Centers for Disease Control, as well as CMS, that are here to listen to the presentations today.

I'm going to first ask the panelists to introduce themselves. Then I will go over some of the logistics, and then provide some background material on the issue that we will be discussing

1 today.

2 DR. LEONARD-SEGAL: Good morning. My name  
3 is Dr. Andrea Leonard-Segal. I direct the Division  
4 of Non-Prescription Clinical Evaluation at FDA.

5 DR. HUSSONG: Good morning. I'm David  
6 Hussong. I direct the new drug microbiology staff  
7 at the Center for Drug Evaluation at FDA.

8 DR. KELMAN: Good morning. My name is Jeff  
9 Kelman. I'm the chief medical officer for the  
10 Center for Medicare at CMS.

11 DR. SHEHAB: Good morning. I'm Nadine  
12 Shehab, Division of Healthcare Quality Promotion at  
13 CDC, Centers for Disease Control and Prevention.

14 DR. ROGERS: Good morning. I'm Colleen  
15 Rogers, team leader in the Division of  
16 Non-Prescription Regulation Development, CDER.

17 DR. CHANG: Good morning. I'm Dr. Christina  
18 Chang. I'm the medical officer in the Division of  
19 Non-Prescription Clinical Evaluation.

20 DR. FURLONG: Good morning. My name is  
21 Lesley-Anne Furlong. I'm the clinical team leader  
22 in the Division of Non-Prescription Clinical

1 Evaluation.

2 DR. FURNESS: Thank you, panelists. We have  
3 had only six speakers thus far register for this  
4 meeting, so we have revised our agenda such that  
5 this meeting will only be held today. Our second  
6 day we had originally scheduled has been canceled.

7 We hope that the speakers will be addressing  
8 the many issues raised in the notice of this  
9 meeting, as well as any other issues that might be  
10 of concern. The panelists will not be making  
11 presentations, but we have left ample time for the  
12 panelists to ask each of the speakers questions, so  
13 that we can develop a full record for this  
14 proceeding.

15 Only panel members will be permitted to ask  
16 questions of the speakers. Once the speakers have  
17 made their presentations, we will have an open  
18 public hearing, so anyone in the audience who has  
19 not registered to speak but would like to make some  
20 remarks can do so.

21 Please make sure you let us know if you're  
22 planning to do that, and there's a sign-up sheet at

1 the back of the registration desk. And we would  
2 ask you to notify us of your intent prior to coming  
3 back from the scheduled morning break.

4 Today's presentations will be posted to the  
5 public docket after this meeting, and the  
6 transcripts will be available for 30 days. Details  
7 on how to access the transcripts are available at  
8 the bottom of the agenda for the meeting. We will  
9 also keep the docket open for a couple of months up  
10 until February 12th of 2013, and we welcome your  
11 comments and any supportive data that you may have.

12 To any members of the press in the audience,  
13 we would direct you to Stephanie Yao.

14 Stephanie, can you raise your hand? Ms. Yao  
15 can meet with you, and we would ask that you meet  
16 with Ms. Yao before contacting any of the panelists  
17 with any questions that you might have.

18 Our goal for today's meeting is to have a  
19 fair and open forum for individuals to present  
20 their views without any interruption. I'll be  
21 announcing the speaker's name and ask the speaker  
22 to come to the podium. At the end of the speaker's

1 presentation, the panel members will be given time  
2 to ask these speakers questions.

3 In terms of the background of the issue  
4 we'll be discussing today, we have called today's  
5 meeting to obtain input on how to address microbial  
6 contamination, a patient, preoperative skin  
7 preparation drug products.

8 Currently, patient preoperative skin  
9 preparations are not required to be sterile. And  
10 despite their inherent antimicrobial activity,  
11 patient preoperative skin preparations may become  
12 contaminated with bacteria.

13 As we indicated in our Federal Register  
14 notice announcing this meeting, a number of product  
15 recalls have been prompted by the identification of  
16 bacterial contamination in these products. And,  
17 unfortunately, we are aware of cases where these  
18 contaminations have been associated with clinical  
19 infections and adverse outcomes.

20 Contamination of patient preoperative skin  
21 preparation occurs by two known mechanisms. The  
22 first mechanism I would point to would be the

1 mechanism of intrinsic contamination. This occurs  
2 where microorganisms gain entry to the product  
3 during the manufacturing process and remain viable  
4 upon storage of the drug product. Avenues of entry  
5 for these bacterial contaminants have been found in  
6 pharmaceutical water supplies as well as from non-  
7 sterile antiseptic manufacturing environments.

8           The second major pathway where contamination  
9 can occur is with extrinsic contamination. And  
10 this occurs when microorganisms are introduced into  
11 the finished product by the end user. And  
12 extrinsic contamination can occur from a variety of  
13 causes, including dilution of the product with  
14 contaminated water, failure to use appropriate  
15 aseptic techniques during handling, as well as  
16 repeated use of non-sterile containers for product  
17 storage.

18           With respect to our existing authority to  
19 address this concern, our current good  
20 manufacturing practice regulations require  
21 manufacturers to have appropriate procedures in  
22 place to prevent the presence of objectionable

1 organisms in drug products that are not  
2 manufactured as sterile. However, it should be  
3 pointed out that the microbial limits test that's  
4 currently in use by most manufacturers, which is  
5 actually a USP test, may not detect very low levels  
6 of microbial contamination. And even more  
7 significantly, it does not screen for the types of  
8 intrinsically antiseptic-resistant organisms that  
9 we've already seen in these products, such as  
10 Burkholderia cepacia, as well as Bacillus cereus.

11 What this means is that a product who passes  
12 the most commonly observed pre-market microbial  
13 limits test may still support the growth of  
14 contaminating microorganisms and may become the  
15 source of clinical infection.

16 So, in summary, the agency has received  
17 reports of contaminated patient preoperative skin  
18 preparations, which has led to a number of product  
19 recalls. And this raises a significant public  
20 health concern.

21 Consequently, we have decided to hold this  
22 public hearing today to hear from interested

1 parties, including healthcare facilities,  
2 healthcare professionals, manufacturers, consumers,  
3 and others about ways that these issues might be  
4 addressed. And we would like feedback on the  
5 following questions, which are divided into two  
6 separate groups addressing intrinsic and extrinsic  
7 contamination.

8 Question number 1 asks, are healthcare  
9 providers and consumers aware that these products  
10 are not sterile and are not manufactured as  
11 sterile? And what measures can be taken to  
12 increase awareness of this fact?

13 Question number 2, in light of these adverse  
14 events, should we require all these products be  
15 manufactured as sterile?

16 Question number 3, are manufacturers  
17 currently producing or planning to produce sterile  
18 patient preoperative skin preparations? And if so,  
19 how will that be achieved, through terminal  
20 sterilization or some validated aseptic processing?  
21 We're very interested to hear about those different  
22 methods that could potentially be used.

1           Question number 4, what are the technical  
2 challenges in producing these sterile patient  
3 preoperative products? For a given manufacturer,  
4 how long will we expect such a switch to occur in  
5 order for this change to take place? And how could  
6 we possibly expect the market to change if all  
7 these products were to be required to be  
8 manufactured as sterile?

9           And lastly, what can the agency do to help  
10 manufacturers overcome this challenge?

11           In the second major group of questions, we  
12 would be interested in hearing from today's  
13 speakers who would be addressing the extrinsic  
14 contamination question, which again occurs from the  
15 end user, an introduction into the products by the  
16 end users of these products.

17           Question number one states, products  
18 manufactured as sterile can become contaminated as  
19 soon as they are open for the very first time.  
20 What steps can be taken to reduce the risk of  
21 extrinsic contamination for these products?

22           Question number 2, excluding the use of

1 these products before surgical procedures or  
2 injections, are these products used for other  
3 procedures in healthcare or home settings? And we  
4 give the example of wound care or maintenance care  
5 for indolin catheters. And if so, what is the  
6 extent of these uses in healthcare in home  
7 settings? And lastly, what settings or uses  
8 comprise the majority of utilization for both  
9 single-use products and multiple-use products?

10 Question number 3, to what extent are  
11 multiple-use products of patient preoperative skin  
12 preparations further processed? Are they diluted,  
13 mixed, or repackaged for subsequent distribution in  
14 healthcare or home settings? And if these products  
15 are subject to these additional operations, are  
16 they handled aseptically? And why are these  
17 products sometimes diluted?

18 Question number 4, should patient  
19 preoperative skin preparations be marketed in  
20 single-use containers only? And what would be the  
21 technical and practical challenges associated with  
22 that?



1 similar to all of you who are healthcare providers  
2 out there. I am also the director of clinical  
3 affairs at Sage Products. And Sage manufactures  
4 medical devices, including the 2 percent CHG cloth,  
5 and the products address hospital-acquired  
6 conditions. And that's pretty consistent with a  
7 preventive healthcare model.

8 As the director of clinical affairs at Sage,  
9 I am responsible in part to support research  
10 efforts that hopefully will glean evidence to  
11 support standard practice.

12 An overview of the agenda, we'll look a  
13 little bit at evidence-based practice. We will  
14 talk about the background of preoperative  
15 preparations, the preparation usages and settings,  
16 contamination risks. We will talk about  
17 sterilization challenges, and I will hand that over  
18 to my colleague, Tim Manthei, who is a senior  
19 director of manufacturing. We'll talk a little bit  
20 about considerations and recommendations.

21 So for those out there who are not  
22 healthcare providers, what is evidence-based

1 medicine? And evidence-based medicine is the  
2 conscientious, the explicit, the judicious use of  
3 current best evidence in making decisions about the  
4 care of our individual patients or patients as a  
5 group. It also allows for individual healthcare  
6 providers to utilize their clinical experience  
7 along with the best evidence from a systematic  
8 literature search. And evidence-based medicine  
9 also seeks to assess the strengths of the evidence  
10 while weighing the risks and the benefits of any  
11 type of treatment.

12 This helps clinicians identify and determine  
13 what is the best way to treat their patients. And  
14 as always, the challenge is to treat the greatest  
15 number of patients with evidence-based  
16 interventions in a cost-effective way.

17 So as a healthcare provider, I certainly  
18 believe that all patients should have access to  
19 these clinically supported drugs, devices, and  
20 interventions, especially when the product provides  
21 more clinical benefit than potential risk.

22 There is general agreement in healthcare

1 today that prevention is more effective than  
2 treatment. And healthcare providers are  
3 responsible for providing the best evidence in  
4 treating their patients utilizing evidence-based  
5 medicine.

6 Healthcare providers are also responsible  
7 for remaining current on the literature, and that  
8 is oftentimes difficult to do with the amount of  
9 literature that's out there. And we are always  
10 trying to put our best efforts forth where we can  
11 have the greatest impact.

12 So we all know that addressing hospital  
13 infections today is a priority here in the U.S.  
14 And why is it a priority? It's a priority because  
15 hospital-acquired infections are devastating to  
16 patients, and they also have a negative impact on  
17 healthcare systems.

18 So there has been a call to action for the  
19 elimination of hospital-acquired infections, and  
20 that has been by certain organizations, including  
21 APIC, SHEA, IDSA, as well as the CDC. These groups  
22 have put forth a consensus statement that's been

1 issued by these groups, and there is a plan for the  
2 reduction of hospital-acquired infections. And  
3 that will be done through the promotion of  
4 adherence to evidence-based practices, and that  
5 will be done through partnering and education.

6 So as we talk about hospital-acquired  
7 infections, we next need to move onto surgical site  
8 infections. And we know that preoperative  
9 preparations can help reduce surgical site  
10 infections.

11 How do we know that? We know that because  
12 that's what the literature tells us. And because  
13 of the wealth of literature that has been  
14 published, certain organizations have put together  
15 practice guidelines to help clinicians determine  
16 how best to treat their patients.

17 Some of these organizations are the CDC,  
18 SHEA, and AORN. And what they say specifically  
19 with regards to the guidelines -- we can look at  
20 the CDC recommendations and they require that  
21 patients shower or bathe with an antiseptic agent  
22 on at least the night before the operative day.

1 And we know that, according to a study by Mangram,  
2 where they utilized a clean versus a sterile  
3 surgical skin prep kit, there was really no benefit  
4 one versus the other.

5 The SHEA compendium speaks specifically to  
6 chlorhexidine, and they state that to gain the  
7 maximum antiseptic effects of chlorhexidine, it  
8 must be allowed to dry completely and not washed  
9 off.

10 The AOR guidelines have also made guideline  
11 recommendations, and they state, specific to  
12 chlorhexidine, that patients undergoing surgical  
13 procedures should receive two preoperative showers  
14 with chlorhexidine. And they also acknowledge that  
15 the FDA requires that antiseptic agents be fast-  
16 acting as well as persistent.

17 According to an article in 2011, the comment  
18 is made that additional use of a cloth impregnated  
19 with chlorhexidine is more effective than simple  
20 showering. And that's fairly consistent with  
21 SHEA's recommendation that the chlorhexidine should  
22 remain on the skin.

1           So let's talk a little bit about the  
2 background. What are these preoperative skin  
3 preparations? And these preoperative skin  
4 preparations are over the counter, topical,  
5 antiseptic drug products, and they are used to  
6 reduce the bioburden on patients' skin prior to  
7 procedures, surgeries, and injections. And these  
8 products are used within healthcare facilities in a  
9 variety of settings, and they are also used in the  
10 home.

11           So when you look at the available  
12 antiseptics that are out there, CHG is preferred  
13 due to the CHG's persistent antimicrobial effect.  
14 We know that chlorhexidine is effective against  
15 both gram-positive and gram-negative organisms with  
16 minimal side effects.

17           So pre-op preparations are utilized in a  
18 variety of settings. So if we are looking at the  
19 entire perioperative period, it consists of three  
20 phases. So let's look at the preoperative phase,  
21 which begins when the decision is made to undergo a  
22 surgical intervention, and it ends when the patient

1 is transferred to the OR bed.

2 So patients during this period of time could  
3 be in their home. They could be in a nursing home.  
4 They could be in a hospital. So if you are using a  
5 pre-op preparation during this phase of the  
6 perioperative period, you are using the pre-op prep  
7 outside of the OR.

8 The next phase is the interoperative phase,  
9 and that begins with the placement of a patient  
10 into the OR bed. And it ends when the patient is  
11 admitted to the post-procedure area. If you're  
12 using a preoperative preparation during this phase,  
13 you are using it within the OR setting.

14 The third phase is the post-operative phase,  
15 and that is when a patient is admitted to either  
16 the PACU or the ICU. If you're using a  
17 preoperative preparation during this phase, you are  
18 using it outside of the OR.

19 So preoperative preps along with other  
20 antiseptics are used outside the OR in a non-  
21 sterile environment, and healthcare providers and  
22 patients apply the preoperative antiseptic based on

1 the guidelines.

2 The goal is to decrease the bioburden on the  
3 patients' skin prior to entering the OR as well as  
4 in the OR just prior to the incision. And we do  
5 that because we know that the patients' greatest  
6 risk factor for an SSI is their own endogenous skin  
7 flora. We know that surgical site infections can  
8 also be altered or changed or affected by other  
9 factors as well. And that could be surgical  
10 technique. It could be the virulence of the  
11 bacteria. It could be the patient's own immune  
12 system as well as the environment.

13 So the use of an antiseptic prior to  
14 entering the OR based on guidelines does not  
15 require a sterile product since the application  
16 process in patients' skin is non-sterile.

17 So envision this scenario. You have a  
18 patient who is at home the night before their  
19 surgery. So they or a family member is assisting  
20 them apply the pre-op preparation based on the  
21 recommendations. And they are doing it in this  
22 fashion.

1           They are applying it in a non-sterile way.  
2           Hopefully, their hands are clean. Or they could  
3           potentially be in the shower, applying the pre-op  
4           preparation with non-sterile water from the shower,  
5           from a non-sterile showerhead.

6           So it's clear that this entire procedure is  
7           non-sterile. The patient then is putting on clean  
8           pajamas, getting into a clean bed, but not sterile.  
9           Imagine as well a patient in a similar situation  
10          going to the OR, but they're in the hospital  
11          setting. As an ICU nurse, a previous ICU nurse, I  
12          have sent hundreds of patients to the OR.

13          Prior to sending them to the OR, I have  
14          applied their pre-op preparation per the  
15          recommendations and I did that in a clean fashion.  
16          I put on clean gloves. I applied the preparation  
17          to the patient. I put them in a clean gown, not  
18          sterile, and then brought them to the operating  
19          room.

20          A study comparing clean and sterile surgical  
21          prep kits revealed that there was no difference in  
22          residual microbial skin flora between patients

1 prepped with each type. There was no difference.  
2 I think it's also important to note at this time  
3 that non-sterile does not imply contaminated. It  
4 implies that it's clean.

5 So it's important now to look at  
6 contamination risks. And let's focus on them. And  
7 thankfully, they are rare, but they can't be  
8 minimized. There have been approximately 40  
9 reports of contaminated products both intrinsically  
10 and extrinsically. And certainly, any time a  
11 patient has been harmed or there has been a  
12 potential for harm, that needs to be addressed.

13 What we also know, though, is that  
14 48 million procedures are performed in the U.S.  
15 each year. Or we could say, since 1960, over  
16 2 billion procedures have been performed. So if  
17 there is 48 million procedures performed each year,  
18 that means there is 48 million patients who are at  
19 risk for a surgical site infection due to their own  
20 endogenous skin flora. So it is imperative that we  
21 reduce the bacterial burden on the patients' skin  
22 prior to entry into the OR.

1           So as we look at potential modes of  
2           contamination and attempt to mitigate the risk,  
3           let's look at the intrinsic mode of contamination.  
4           And intrinsic occurs when microorganisms gain entry  
5           into the product during the manufacturing process  
6           and remain viable. And the control for this is  
7           current good manufacturing practices. And  
8           manufacturers should be held accountable to make  
9           sure that they are adhering to these practices.

10           The extrinsic contamination occurs when  
11           microorganisms are introduced into a finished  
12           product by the end user. And the end user can be a  
13           healthcare provider. It could be a nurse. It  
14           could be a patient. It also could be a family  
15           member.

16           The control for that is proper education to  
17           good, proper technique. And we need to hold  
18           healthcare providers responsible for that because  
19           the extrinsic control is easy. That's education,  
20           and healthcare providers really should be held  
21           accountable to maintaining those standards as well.

22           These next slides, when we discuss the

1 challenges, I'm going to hand over to my colleague,  
2 Tim Manthei.

3 **Presentation - Tim Manthei**

4 MR. MANTHEI: Thank you, Dr. Ryan.

5 Good morning, panel. Thank you for allowing  
6 us to speak with you today. My name is Tim  
7 Manthei. I'm the senior director of manufacturing  
8 at Sage Products. Prior to joining Sage, I spent  
9 about 25 years in the large pharma industry in  
10 various positions with terminally sterilizing  
11 aseptically manufactured products, both large-  
12 volume perennials, small-volume perennials, sets,  
13 and devices.

14 My comments today are focused on Sage  
15 preoperative products and processes. As a  
16 manufacturer, we're well aware of the challenges of  
17 making these preoperative products, so I'd like to  
18 share that perspective with you.

19 As you know, there is several different ways  
20 to manufacture sterile products. One of them is  
21 terminal sterilization. Steam sterilization for  
22 CHG is not practical. CHG starts to degrade at

1 about 40 degrees C and, in order to sterilize with  
2 steam or an autoclave, you need to be at least  
3 100 degrees C. So the molecule starts to degrade.

4 Seymour Block, in his book, Disinfection,  
5 Sterilization, and Prevention, Edition 5, talks  
6 about CHG in solution in autoclave, creating  
7 insoluble precipitate at about 1 percent. Our  
8 solutions are at 2 percent. He also talks about  
9 gamma radiation and how that destroys the molecule.

10 Ethylene oxide, which is an older  
11 technology, really can't be used in our product  
12 because you need a permeable membrane in the  
13 packaging for ethylene oxide to penetrate. Our  
14 products have an overwrap that just does the  
15 opposite. We want to maintain a vapor barrier, so  
16 there's no way for the ethylene oxide to penetrate.

17 Another method is aseptic manufacturing.  
18 There's very specific requirements for aseptic  
19 manufacturing. In fact, the agency put out a  
20 guideline, aseptic manufacturing of sterile drugs,  
21 to help the overall industry understand what those  
22 specific items are. And any time you manufacture

1 products aseptically, you have a sterile core, and  
2 then all the pieces and parts, all the components,  
3 have to come into that sterile core. And they have  
4 to be sterilized.

5 With the type of products we're talking  
6 about with this preoperative cloth, we've got a  
7 nylon cloth, a material for overwrap, that's a  
8 film, and a solution that really don't lend  
9 themselves to an aseptic process. The facilities  
10 themselves are very specific and really should be  
11 designed from the ground up when you're going to  
12 manufacture aseptic products. And probably  
13 industry-wide -- again, I'm only speaking for our  
14 products -- we would require a complete redesign of  
15 our facilities and HVAC systems.

16 So as we search for new and better ways to  
17 manufacture, we looked at several different  
18 potential possibilities to make a sterile product.  
19 We looked at gamma and e-beam radiation. Both of  
20 those degraded the molecule. Higher degradation  
21 products, and it reduced the assay.

22 EtO sterilization, we talked about, really

1 not practical. And aseptic processing with the  
2 varied components that we have today really does  
3 not lend itself to manufacturing, either.

4 We looked at sterilizing the solution. And  
5 in our specific product, the solution clogged the  
6 filter in about 10 minutes. So we were unable to  
7 do that. And even if we were able to find a method  
8 to sterilize the solution, that's only one step in  
9 a whole gamut of steps to manufacture aseptic  
10 products.

11 Then, like I mentioned, the facilities are  
12 not engineered to manufacture sterile products.  
13 They have to be really designed with the HVAC  
14 systems, floors, walls, ceilings, as you guys know.

15 So I haven't given you much. Right? So  
16 let's talk about something that maybe we could do.  
17 Several years back, we looked at what could we do  
18 to reduce bioburden in our products, from the start  
19 of the product process to the end? And we utilized  
20 quality management of systems approach to try to do  
21 that, and we looked at every step of our process.

22 We found if you use USP purified water or

1 better, that's where you should start with your  
2 bulk solution. Your facilities. We designed a  
3 facility that has engineering controls. It's an  
4 unclassified facility, but it has all the controls  
5 of a normal manufacturing pharma manufacturing  
6 facility: HVAC, walls, floors, ceiling, designed  
7 for cleanliness.

8 We installed a clean procedure, routine  
9 clean procedure, for the facility, CIP and COP in  
10 the solution manufacturing and in the final process  
11 equipment. We look at the water system for  
12 microbial contamination. We monitor both the loop  
13 itself for the system, along with every drop.

14 We environmentally monitor the facilities,  
15 and then we also turn that data and have applied  
16 action levels and alert levels to control it.  
17 Every bulk solution batch that we make is monitored  
18 for microbial contamination. And then our final  
19 product specifications, every batch is looked at  
20 for microbial contaminations, and we don't allow  
21 any objectionable organisms. And we have added  
22 *B. cepacia* to that specification.

1 Questions at all?

2 (No response.)

3 MR. MANTHEI: Then I'm going to turn it back  
4 over to Joyce Ryan.

5 DR. RYAN: Thank you, Tim. So as we attempt  
6 to make decisions, let's look at a couple of  
7 critical points of consideration. So to date,  
8 there is no evidence demonstrating use of a non-  
9 sterile pre-op prep has resulted in a surgical  
10 infection.

11 Intrinsic contamination of antiseptic  
12 solutions is rare. However, it cannot be minimized  
13 and may be underreported. There are significant  
14 technical challenges in sterilizing antiseptics,  
15 and intrinsic contamination events have also been  
16 associated with sterile products. So I think it's  
17 important to note that sterile products does not  
18 necessarily guarantee that a product would not be  
19 contaminated.

20 So, in summary, we all need to use evidence-  
21 based practice. That's standard for healthcare  
22 providers. But what we know now is that the non-

1 sterile products that are on the market work, and  
2 the literature suggests that they work.

3 Antiseptics are used in a variety of  
4 settings, including the home. But we also talked  
5 about the preoperative, the intraoperative, and the  
6 post-operative phase. Non-sterile antiseptics have  
7 been used for decades for skin antiseptics prior to  
8 surgery, without significant issues. And there is  
9 no evidence supporting sterile versus non-sterile  
10 pre-op preparations are superior or less likely to  
11 cause an infection.

12 So there are challenges, too, with  
13 sterilizing antiseptics. So I think, as we attempt  
14 to provide the best care for the greatest number of  
15 patients using evidence-based products that are on  
16 the market already, we need to make sure that we  
17 are not impeding access to those products because  
18 we know that lack of access to those evidence-based  
19 products may cause greater risk of infection.

20 So we all understand why we're here today.  
21 We are all motivated to protect patients and make  
22 sure that they are kept safe. As a nurse, I am

1 intrinsically motivated to keep patients safe and  
2 offer the best care that I can. And as the agency  
3 and as manufacturing companies, they are motivated  
4 in the same way as well.

5 So a couple of recommendations. The agency  
6 could provide guidance for industry outlining GMP  
7 requirements for this class of product or classes  
8 of products. Industry could upgrade their  
9 processes and facilities when necessary to meet the  
10 agency's guidance requirements.

11 And a couple of additional recommendations  
12 is that healthcare providers should use checklists  
13 and maintain adherence to aseptic technique or the  
14 appropriate technique based on this scenario. And  
15 healthcare providers should be accountable for  
16 that. And that is easy to address the extrinsic  
17 potential for contamination. It can easily be  
18 addressed through education.

19 Perform a risk analysis because the effort  
20 to reduce the risk really should be commensurate  
21 with the frequency of the problem. So as  
22 healthcare providers, as the agency, as

1 manufacturers, it's important I think to plan and  
2 put our efforts where we can have the greatest  
3 impact for positive patient outcomes. Thank you.

4 DR. FURNESS: Thank you very much. I would  
5 now like to turn the floor over to the panel for  
6 any questions you may have of these speakers.

7 Dr. Chang?

8 DR. CHANG: Thank you. I have a few  
9 questions for you. Now, on slide 18, when you say  
10 that there's no evidence demonstrating the use of  
11 non-sterile products resulting in surgical  
12 infections, can you explain to me what you base  
13 that statement on?

14 DR. RYAN: That's based on contaminated  
15 products, so we're making the comment that there is  
16 no evidence demonstrating use of a non-sterile  
17 pre-op prep that is not contaminated has resulted  
18 in a surgical infection.

19 DR. CHANG: Have you done a literature  
20 search or is that based on your own postmarketing  
21 reports?

22 DR. RYAN: It was based on a literature

1 search, yes, and also based on Triad and Clinipad,  
2 looking at their information.

3 DR. CHANG: I'm not quite sure that, based  
4 on a literature search, you could arrive at that  
5 conclusion. But let me just ask you about your own  
6 postmarketing reports that the agency received in  
7 2008.

8 There were reports of infections stemming  
9 from Burkholderia cepacia. And I'm just curious to  
10 know, in your reporting process, whether you worked  
11 with the hospitals where those infections were  
12 located to further identify whether those reported  
13 cases were in fact traced back to the product.

14 DR. RYAN: I think I'm going to open this up  
15 to anybody else who works at Sage Products who  
16 might have been there during that particular period  
17 of time and to maybe describe better how it was  
18 traced back. But I think my point here to this  
19 bullet point, you're talking about contaminated  
20 products, and this comment here is really related  
21 to non-contaminated products that have caused a  
22 problem.

1 DR. CHANG: Thank you. One last question.  
2 How did you arrive at the conclusion that Triad and  
3 Clinipad products were sterile products?

4 DR. RYAN: How did I arrive at that?

5 DR. CHANG: Yes. Were you aware that those  
6 were manufactured as sterile products?

7 DR. RYAN: Yes. And I think that's to my  
8 point where I said that there still can be issues  
9 with sterile products. Sterile products do not  
10 guarantee that there will not be a contamination.

11 DR. FURNESS: Anyone else? Dr. Kelman?

12 DR. KELMAN: Very interesting presentation.  
13 I have to admit, until Doug called me, I wasn't  
14 aware that surgical skin preparations weren't  
15 sterile. I mean, I assume most of the people in my  
16 agency think they are.

17 So two issues. One is similar to  
18 Dr. Chang's question, I think. When you say that  
19 there's no risk demonstrated, do you mean that you  
20 really think there's no risk or that there's no  
21 evidence as to now developed as to that risk? In  
22 other words, has anybody done root cause of

1 surgical site infections, to look back to the  
2 presence or absence of sterile surgical skin  
3 preparations?

4 DR. RYAN: Not that I'm aware of. And  
5 certainly no one is saying that there is not a  
6 risk. There's obviously a risk because there have  
7 been reports. There have been approximately 40  
8 reports, and that's probably underreported, as well  
9 as surgical site infections are probably  
10 underreported as well.

11 So I don't think anybody is making the  
12 comment that there is no risk to using a pre-op  
13 preparation. There certainly is risk, and I think  
14 that the point was we can address that risk with  
15 good GMP and adhering to good manufacturing  
16 practices, as well as addressing the extrinsic  
17 potential for contamination through education.

18 DR. KELMAN: I mean, surgical site  
19 infections are a big issue in the department right  
20 now. They cost money. They're bad for health.  
21 And they lead to re-admission. They're part of  
22 value-based purchasing.

1 DR. RYAN: Yes.

2 DR. KELMAN: So I'm also curious -- I mean,  
3 were you suggesting that Sage actually can't make a  
4 sterile product?

5 DR. RYAN: I think we were talking about the  
6 challenges of attempting to do that because the  
7 molecule degrades, so there are issues with  
8 impractical. And I'll hand it over to Tim.

9 MR. MANTHEI: We have no means to make a  
10 sterile product that we know of today. Everything  
11 that we've looked at either degrades molecule or  
12 isn't practical; EtO for an example. Our overwrap  
13 maintains a moisture and vapor barrier. There's no  
14 way to get EtO into the product because of that  
15 moisture and vapor barrier.

16 We've looked at gamma radiation and e-beam  
17 radiation. Both of them degrade the molecule. We  
18 haven't done a lot of work there, so maybe you  
19 could do something where you increase the CHG assay  
20 up front, and then look at the degradation products  
21 after the sterilization. But those also could be  
22 dangerous, too. And so, there would have to be

1 quite a bit more work done on that.

2 DR. KELMAN: Thank you.

3 DR. FURNESS: Dr. Leonard-Segal?

4 DR. LEONARD-SEGAL: Thank you for the  
5 interesting presentation. I want to focus on the  
6 extrinsic contamination part of the comments  
7 because I'm curious. I think it appears that  
8 education is a very reasonable way to go. However,  
9 I can't help finding myself wondering, with very  
10 large volume containers of these antiseptics, I  
11 wonder if education can only go so far.

12 Do you have comments about how one educates  
13 well to avoid extrinsic contamination in large-  
14 volume containers that are multiple-use?

15 DR. RYAN: Yes. I'll let Tim speak to the  
16 large volume, but I'll speak -- and we can take  
17 turns on this. I can answer certainly as a  
18 healthcare provider and as a nurse what training  
19 you undergo in the hospital setting, anyways, to  
20 learn proper technique based on the situation,  
21 whether it's going to be clean technique or  
22 sterile.

1           Also, we can probably address much better  
2           how we teach families and family members how to use  
3           a clean technique when they're using these products  
4           in the home. But as far as a nurse or another  
5           healthcare provider within a hospital system, you  
6           do learn the appropriate technique on how to use a  
7           product, whether it's sterile -- aseptic, or  
8           sterile, or clean.

9           DR. LEONARD-SEGAL: Right. Speaking as a  
10          physician, though, having had a lot of training in  
11          this kind of area, obviously the training has been  
12          there, but it's only gone so far. And so, I'm  
13          wondering if there are other specific educational  
14          points that you can offer beyond what is already  
15          taught with regard to these larger multi-use volume  
16          containers; or whether you have any views as to  
17          whether those larger containers maybe shouldn't be  
18          as large, or shouldn't be as multi-use, or how we  
19          might go about addressing this issue above and  
20          beyond what we have already done.

21          DR. RYAN: I will let Tim address that. The  
22          product that we represent is actually a single-use

1 product, so I'll let Tim speak from a manufacturing  
2 standpoint on the larger volume.

3 MR. MANTHEI: Those are great comments.  
4 And, really, what Dr. Ryan said, our product is a  
5 single-use product, so we don't make a multiple-  
6 use. So I really can't comment on the  
7 manufacturing process there or whether it should or  
8 shouldn't be used multiple times. But maybe  
9 somebody in the audience could.

10 DR. FURNESS: I'd like to ask a question of  
11 Mr. Manthei. I'm trying to get a sense of the  
12 generalizability of some of the findings that you  
13 presented on the challenges of sterilizing  
14 chlorhexidine. I mean, what specific products did  
15 you test? And were a variety of different products  
16 tested or were we just talking about a couple of  
17 different of your own, in-house formulations?

18 MR. MANTHEI: Specifically, our in-house  
19 formulations. Two percent chlorhexidine is what  
20 that is. And as far as filtration, we have an  
21 additive in our product that is what actually gets  
22 filtered out, not the chlorhexidine itself.

1 DR. FURNESS: Thank you.

2 Any other questions? Dr. Shehab?

3 DR. SHEHAB: Thank you for your  
4 presentation. I have two questions. We've  
5 anecdotally heard of chlorhexidine products,  
6 sterile chlorhexidine products, being available,  
7 commercially available, overseas. And I'll defer  
8 to my FDA colleagues as to whether they're  
9 solution, or cloth, or if anyone can confirm. But  
10 have you consulted with industry colleagues,  
11 perhaps abroad or elsewhere, as to how they achieve  
12 sterility among chlorhexidine-based products?

13 MR. MANTHEI: We have looked at in-house and  
14 talked to our colleagues in the field. We've not  
15 talked to anybody outside the U.S. And I'm not  
16 aware. I have heard that, that there's a  
17 formulation out there, but I don't know what it is,  
18 or how it's used, or how they got to sterilization.

19 DR. SHEHAB: Okay.

20 MR. MANTHEI: Yes. We'd have to look at  
21 where it actually comes from.

22 DR. SHEHAB: Thank you. The second question

1 is, when intrinsic contamination has been  
2 identified among your products, has there been an  
3 overwhelming root cause? And the reason I ask, we  
4 understand that aseptic processing can be a  
5 challenge, and it sure seems to be a limitation to  
6 terminal sterilization.

7 So is there something beyond the minimum  
8 GMPs that can be identified to mitigate a more  
9 overwhelming cause that's been identified in  
10 manufacturing controls, that's leading to intrinsic  
11 contamination, something that could maybe inform  
12 voluntary guidance of some sorts or other  
13 manufacturing controls beyond GMPs?

14 MR. MANTHEI: Two things I think would be  
15 helpful. The aseptic manufacturing guidance  
16 document that industry and the FDA put together,  
17 something similar to that for the preoperative  
18 products would be beneficial because it becomes  
19 more specific than the 211s. Right?

20 The other thing, specifically on intrinsic  
21 challenges in the factory, what we've done since  
22 2008 is we've put in QMS processes using CAPA and

1 drive the root cause. And so, we drive the root  
2 cause, and then we fix whatever we find was the  
3 issue. So that is very beneficial.

4 DR. SHEHAB: Sorry. One more question.  
5 Beyond the minimum USP, United States Pharmacopeia  
6 elements, does your company engage in any active  
7 surveillance that better identifies bioburden,  
8 again, beyond the minimum USP? Or is that  
9 something that is within your capacity?

10 MR. MANTHEI: On every final product, we  
11 also look for *B. cepacia*, so that's beyond USP.  
12 And then we identify organisms from the  
13 environmental testing also. And if that's  
14 *B. cepacia*, we look at going back to CAPA and root-  
15 cause analysis to eliminate it. So, yes.

16 DR. FURNESS: Dr. Chang?

17 DR. CHANG: Sorry. One last question.  
18 Could you comment on the feasibility of  
19 microfiltration, whether that process could improve  
20 the outcome?

21 MR. MANTHEI: Yes, I can. We tried that  
22 with our solution, and there's an additive that we

1 have in there that plugs the filter, at a .2 micron  
2 filter. So is it possible in other manufacturing  
3 solutions? I can't speak to that. But I can say  
4 that filtration is just one step in producing a  
5 sterile product. Right? If it's going into a  
6 sterile core, so an aseptic product, everything has  
7 to be sterile coming into that core, and then it  
8 has to be put together sterile, and end up sterile.  
9 Right? So there's a lot of pieces, parts, lot of  
10 components that have to come together besides just  
11 a sterile filtration step.

12 Terminally sterilized, you can  
13 sterile-filter up front, but you still have to have  
14 the facilities, and HVAC systems, and processes to  
15 support that.

16 DR. FURNESS: Any other questions?  
17 Dr. Furlong?

18 DR. FURLONG: This one is for Ms. Ryan.  
19 Thank you for your presentation. As a gynecologic  
20 surgeon, you've brought me back to the OR as you  
21 were describing all the events around surgery.

22 I'm curious what you think about how the

1 product is used, though, in the operating room. I  
2 agree that the showers and so on, before and after,  
3 are all in non-sterile settings. But when you  
4 think about the operating room, where you have  
5 sterile gowns, sterile gloves, sterile IV fluids,  
6 sterile complicated drugs in those IV fluids,  
7 sterile instruments, if the patient's eyes are  
8 closed with any topical ophthalmologic product,  
9 that is also sterile. And yet, the product that's  
10 placed on the person's abdomen -- say it's  
11 abdominal surgery -- may have pseudomonas  
12 aeruginosa in it.

13 That I think is the point. At that point,  
14 there's an incision in the skin, which is a natural  
15 barrier. And we're wondering about that, why the  
16 product is used in that setting or starting IVs or  
17 catheters, where the skin is invaded, why that  
18 should not be sterile.

19 DR. RYAN: Yes, and that's a great question  
20 because, in theory, that makes sense. You would  
21 think that if something could potentially be  
22 contaminated, obviously, that would be a risk to a

1 patient. So I agree, in theory, that does make  
2 sense. I think what we have to look at now is what  
3 does the clinical data say? Does the clinical data  
4 say that patients are at higher risk with a non-  
5 sterile or a sterile product? And we don't know.  
6 I don't know that there's been a significant amount  
7 of comparative studies that have looked at sterile  
8 versus non-sterile and determined that one is  
9 better than another.

10 So I think what we have to go with now is,  
11 most of the time or a lot of the time, these  
12 products are used outside of the OR, and sometimes  
13 certainly they're used inside the OR. And I think,  
14 right now, all we can speak to is what the evidence  
15 shows to date.

16 But, in theory, I understand that question.  
17 It makes sense. But speaking to the challenges of  
18 making that product sterile, I think we need to  
19 think about the risk versus benefit. Is that  
20 patient best served by using the products that we  
21 know have clinical efficacy versus the potential  
22 slight risk that a product is contaminated? And

1 that's not to minimize at all the potential  
2 contamination, but the data that we have to date  
3 shows efficacy using the products manufactured as  
4 they are.

5 DR. FURNESS: Dr. Leonard-Segal?

6 DR. LEONARD-SEGAL: Yes. I think that's  
7 where the dilemma lies because we do have efficacy  
8 that these products achieve log reduction and  
9 reduce bacteria on the skin, hopefully by not  
10 introducing additional contaminants that would not  
11 have been on the skin that would then be causing an  
12 infection. And we've accepted that, as an agency,  
13 that that's an okay way to go.

14 The problem that we find ourselves facing is  
15 that we really don't have clinical outcomes. We  
16 have log reduction. And so, it makes it difficult  
17 to understand how to put all this together.

18 Do you have any thoughts on putting this  
19 together with that background information, ways for  
20 us to think about this from an efficacy standpoint,  
21 knowing that we really don't have the clinical  
22 outcomes, and we know that they've been very hard

1 to get? So we've sorted accepted the practicality  
2 of it, but, yet, we have this safety risk.

3 How do we put this together? This is a  
4 dilemma for us.

5 DR. RYAN: It is a dilemma, and I think all  
6 of us working together is probably the best case  
7 scenario to figure that out. And whether we're  
8 ever able to come to an absolute black-and-white  
9 answer that this is better than that, I think we've  
10 outlined some things that we can do immediately.  
11 And Tim focused on some advancements that Sage has  
12 done, and I'm sure other manufacturing companies  
13 have done as well, to make sure that those GMP  
14 practices are really adhered to in holding  
15 manufacturers accountable, but also holding  
16 healthcare providers accountable.

17 We can do a much better job addressing that  
18 extrinsic contamination when it comes to healthcare  
19 providers and patients utilizing products in the  
20 appropriate technique.

21 So I think that there's things that we can  
22 do up front, and it's the things that Tim mentioned

1 as well, is that increased education in making sure  
2 we're addressing that extrinsic potential  
3 contamination, because that's probably an easier  
4 fix and can be done immediately.

5 So those are just some initial thoughts.  
6 And that probably doesn't answer in a black-and-  
7 white way and give an absolute answer, but I think  
8 that there are certainly things that we can  
9 do -- and I'm not saying making them sterile or  
10 non-sterile is the answer, but things that we can  
11 do, at least in the interim until a decision is  
12 made, because we know that these products worked in  
13 their present formulation, focusing heavily on  
14 making sure that GMP practices are adhered to as  
15 well as appropriate technique.

16 DR. LEONARD-SEGAL: So I have one more  
17 question, going back to the education part. So you  
18 talked about a checklist, and checklists are always  
19 a good idea. But I guess that we would be very  
20 appreciative if you could provide us with some of  
21 the elements that you think belong on that  
22 checklist that go above and beyond the additional

1 training, the current training, that people have.  
2 I think we'd be very interested in receiving that  
3 information from you.

4 I know you may not have it right now, but we  
5 would be very interested in hearing those ideas.

6 DR. RYAN: I certainly do not have those  
7 answers right now, but I think we have shown that  
8 with a team approach to healthcare in a hospital  
9 has really shown to be beneficial, where different  
10 modalities work together in a team approach; and  
11 it's shown to be very effective, where nurses and  
12 other healthcare providers hold physicians or  
13 whoever it is accountable when you're, for  
14 instance, inserting a line. If you notice a breach  
15 in aseptic technique, that you're able to speak up  
16 and challenge the person who is doing that  
17 procedure.

18 So I think a checklist has been helpful.  
19 They have shown, certainly, some improvement. But  
20 holding people accountable, but also giving that  
21 autonomy to be able to speak up and address patient  
22 safety as a group.

1           But I think increasing awareness, too,  
2           because there could be healthcare providers that  
3           are utilizing these pre-op preparations, but not  
4           really having a clear understanding of the  
5           ramifications of a breach in technique.

6           DR. FURNESS: Thank you very much.

7           Dr. Chang?

8           DR. CHANG: One more question. Thank you  
9           for spending so much time. So, currently, do you  
10          have any strategies that you have in mind in  
11          communicating to healthcare providers, or any  
12          consumers who may be using this at their home, to  
13          help them make the benefit risk decision, even in  
14          the face of a potential risk that has not been  
15          adequately quantified?

16          DR. RYAN: As a healthcare provider, we have  
17          a team of nurses, actually, at Sage, and we work  
18          under the research and education department at  
19          Sage. And oftentimes, when these products come  
20          into use, our team is actually a resource to  
21          healthcare providers and the company as well.

22          But oftentimes we are brought in when they

1 are implementing some type of initiative; say  
2 they're going to implement chlorhexidine as a  
3 pre-op preparation within the hospital system. So  
4 our nurses are actually able to go into those  
5 hospitals and help educate the other nurses that  
6 are going to be the end users of these products.

7 So that's something that we do on a pretty  
8 frequent basis.

9 DR. FURNESS: Dr. Hussong?

10 DR. HUSSONG: Thank you for the  
11 presentation. I have a couple concerns, and they  
12 link. One relates to intrinsic and the other is  
13 extrinsic. When I started this job several decades  
14 ago, I would have been hard-pressed to accept that  
15 an infection could come from an antiseptic. I  
16 mean, they kill bacteria.

17 But several years ago, there was a recall on  
18 some antiseptics. And the only reason it was  
19 noticed is that the surgeon, when opening the  
20 container, found the solution smelled putrid. And  
21 it turned out bacteria had grown tremendously, to  
22 great numbers.

1           There are bacteria that grow in many of  
2 these antiseptics. And my concern is that if you  
3 don't eliminate this bacteria, which means sterile,  
4 they will grow. And that does not seem acceptable  
5 in a surgical setting.

6           If GMPs can control this -- and keep in  
7 mind, a non-sterile product can pass into a system,  
8 and the organisms can grow over time during shelf  
9 life -- how can those GMPs, assuming you're using  
10 non-sterile GMPs, protect the patient? Is that  
11 something that can be worked around?

12           The other issue that relates to this is the  
13 extrinsic. Studies of injection products returned  
14 to the pharmacy after use in the clinic reveal  
15 rates of contamination in those injection products,  
16 as high as 10 percent. Normally, it's about 2 or  
17 3 percent. And certainly, the clinical  
18 associations are working very hard to control that,  
19 and they do it through education. My concern is  
20 time. Shelf life of the product is where the  
21 organisms grow, and in-use life.

22           Based on the use of a product, can we

1 control time to keep that growth down, keep it  
2 safe?

3 DR. RYAN: I will give that question over to  
4 Tim.

5 MR. MANTHEI: I'd like to go back to your  
6 first question, if I could. How could you better  
7 control to make sure that the patient is safe? I  
8 really think a guidance document like what was  
9 designed with industry and the agency on aseptic  
10 manufacturing practices would be beneficial for  
11 pre-op products; internal controls that we as an  
12 industry either do have or could have better  
13 controls; and final product testing, where we would  
14 test for all the organisms that we find do  
15 contaminate product.

16 We do AE testing on the preservatives, so we  
17 have an understanding of how long the preservatives  
18 last and how effective they are. And then perhaps  
19 a pre-op prep is different from an OR prep, and so  
20 maybe that's a possibility also.

21 DR. HUSSONG: Thank you. I think that's a  
22 really interesting concept, the pre-op versus

1 surgical, pre-surgical -- or, I'm sorry, operating  
2 room versus pre-op. Thank you.

3 DR. FURNESS: Thank you very much, Ms. Ryan  
4 and Mr. Manthei.

5 DR. RYAN: Thank you.

6 DR. FURNESS: At this time, I would like to  
7 call Dr. John Thomas, who is the director of  
8 International Tri-University and the Biofilm  
9 Research Consortium.

10 **Presentation - John Thomas**

11 DR. THOMAS: Good morning. Can you all hear  
12 me in the back? My name is Professor John G.  
13 Thomas, and I'm from West Virginia University  
14 School of Medicine and quite proud to be a Welshman  
15 who also travels internationally, to Cardiff  
16 University, where I have an appointment.

17 My issue is that, throughout my career, I've  
18 been involved in microbiology for almost 50 years  
19 now. And the reality is that my 50 years of  
20 microbiology led me to involve myself with wounds,  
21 particularly because I happened to serve as a  
22 captain in the United States Army during the

1 Vietnam War. And although I have been trained as a  
2 microbiologist, I found out that war environment  
3 and wounds for the wounded warrior are quite a bit  
4 different.

5 So I'm going to address not only my concern  
6 about the use in the rather sterile environment of  
7 our hospitals, but also for those who are involved  
8 in the impact area of microbiology.

9 My interest, per se, has evolved around  
10 biofilms because microbes don't grow just as single  
11 organisms. And one of the points I hope to make to  
12 you is that we've dealt with our assay systems and  
13 our log reductions by using, basically, a Robert  
14 Koch approach. In the world of microbiology today,  
15 we're dealing with anti-Koch multiple organisms  
16 growing as a biofilm, and in wound management and  
17 in preparative assessment, that's a very important  
18 feature.

19 I'd also like to point out that as I started  
20 to develop this biofilm research consortium, that  
21 we wanted to make sure that we were, in the upper  
22 left-hand corner, dealing with biofilms in lungs

1 and endotraches. And it's led us to understand  
2 about legislation. You cannot legislate compliance  
3 of use products, and that's an issue. And on the  
4 lower left-hand side, the idea that in chronic  
5 wounds, the development of a biofilm is critical in  
6 assessing what management style would work.

7 Also, the point I'd like to make is that we  
8 want to look downstream about the outcomes  
9 associated with these processes so that when you,  
10 at the beginning, begin to associate with a  
11 particular kind of management style, does it really  
12 impact on the patient?

13 The point is, as a microbiologist I guess,  
14 what tools do we assess to determine the bugs that  
15 are associated with this process or the ones that  
16 are really there?

17 So what I'd like to do is, I'm a professor.  
18 You can tell. I was going to bring my puppets, but  
19 probably my wife said, "Don't you dare do that." I  
20 like to teach to students -- medical students,  
21 nursing students, pharmacy students -- with  
22 visualization because they remember a picture much

1 better than a particular statement. But I want to  
2 point out, every slide I ever start with starts out  
3 with this thought, "We live in a microbial world.  
4 You cannot legislate out the fact that bugs are  
5 around us, and, in fact, very helpful."

6 I want to address some comments -- figures  
7 don't lie, but liars can figure -- about assessment  
8 of data. I want to look at what happens with these  
9 biofilm-associated organisms on the skin. And I  
10 want to talk about changing paradigms in the  
11 clinical world of microbiology that I'm in. And  
12 so, let's get going and really kind of look at  
13 this.

14 So here's my statement. We live in a  
15 microbial world. It is their world. It's an  
16 important environment that we deal with. And the  
17 world of defining this microbial world is changing.  
18 We are now using metagenomics. And I want you to  
19 realize that cluster analysis of microbes on a  
20 wound site is where it's at, single organism  
21 identification. To say that pseudomonas is going  
22 to be a pathogen and produce an outcome associated

1 with a bad scenario is not correct. We need to  
2 upgrade the assessment of bugs and disease process.

3 So you all know that we live in this  
4 microbial world of which our patients have four  
5 classic reservoirs, which was based on historical  
6 evidence, and we teach that there are these  
7 barriers. And, folks, that's wrong. We have now  
8 recognized that when we really look at the body,  
9 there is a continual interaction of organisms  
10 throughout the entire source, so that skinned  
11 organisms are in effect recolonized with organisms  
12 from other sites.

13 So we need to expand that recognition that  
14 there is, in fact, this great diversity. And  
15 cleaning that skin may in fact alter to some  
16 degree, but the organisms present are still going  
17 to be the ones that we deal with. And the point  
18 that I'd make out to you now is that as we go into  
19 metagenomics and new molecular tools in the  
20 laboratory, the names of the organisms on the skin  
21 are very different and expanded considerably beyond  
22 what we have used in our traditional sense of staph

1 and pseudomonas.

2 So the reality is, as you know, there has  
3 been historically now a huge direction in clinical  
4 science to use molecular methods, to identify  
5 microbes beyond what they have been.

6 In the upper left-hand corner, the human  
7 metagenomic study has redefined how we approach  
8 diagnostic microbes and how we should track  
9 outcomes relative to product assessment. And to  
10 continually use staph and E. coli and pseudomonas  
11 as markers for good or bad is simply limited and  
12 doesn't recognize the microbial pool in the world  
13 in which we live.

14 So, in reality, what I teach our students,  
15 our pharmacy students, our medical students, I  
16 teach them, point out to them, that in fact the  
17 normal flora that you address with products is in  
18 fact a part of our normal defense mechanism. And  
19 we teach our students today that normal skin flora  
20 is an organ system. It should be maintained with  
21 integrity so that cleaning it should, in fact, as  
22 we provide a protective environment for our

1 patients, should address the reality we need to  
2 maintain some normal flora.

3 I tell the students, "You want to get rid of  
4 a problem, autoclave your patient. It won't help,  
5 but the microbial world is gone. You won't worry  
6 about an infection." But the reality is, please  
7 reconsider how we address safety issues in patient  
8 management because the tools up to now, to measure  
9 this, have been rather restrictive and approached  
10 from sort of a Robert Koch perspective. We're no  
11 longer in that environment. We're in an anti-Koch  
12 environment.

13 So I point out that the normal flora that  
14 you really want to assess is a very established and  
15 necessary environment, and it is part of the  
16 defense mechanism of the host.

17 So I loved this slide when I was a freshman  
18 in college, which, as I told you, was a long time  
19 ago. I was told by a chemist -- gosh. As a  
20 microbiologist, I hate chemists, but we must get  
21 along. The reality is, I asked the professor how  
22 should I prepare my first exam. And he said,

1 "Clearly, repetition is the mother of all  
2 learning." And the second point he said is,  
3 "Figures don't lie, but liars can figure."

4 And so, the reality is, I've sort of, again,  
5 as I try to teach our students, pointed out to them  
6 that there's a very important formula in infectious  
7 diseases and in microbiology. And that is, if you  
8 want to assess the evaluation of potential outcome,  
9 we need to go  $N$  times  $V$  over  $I$ . It is so simple.  
10 What is the number? What is the virulence over the  
11 immunity or resistance of that environment?

12 In Robert Koch's era, it was simply logs of  
13 bugs times a single organism, which had a virulence  
14 factor, all over the immunity or in fact the  
15 established susceptibility or resistance of the  
16 environment of the patient. That is no longer the  
17 simplicity now because we involve, as I show you in  
18 a moment, with our patients who are being treated  
19 with biofilm-associated infections, which now is  
20 multiple organisms. So the end may be different  
21 for each species, and the log reduction associated  
22 with potential outcomes is not the same for each

1 organism. And when you put them together, that  
2 changes the rules.

3 So my point is, the tools that we've had to  
4 assess where we are need to be upgraded as a  
5 microbiologist. I'm sort of humbled by the fact  
6 that we've been doing the same thing since I was in  
7 the Vietnam War with our wound management, almost  
8 40 years ago, and we haven't changed. Why is that?  
9 What tools don't we have?

10 So let's look at this molecular detection  
11 and where we are with clones and clusters. And if  
12 we look at simply skin -- be it dry, be it glands,  
13 or be it moist -- and we look at the organisms that  
14 are associated in that, I want you to realize that  
15 these are not staph E. coli pseudomonas and  
16 serratia or whatever. These are organisms that  
17 have potential given clusters. They exist together  
18 to produce a potential outcome.

19 The reality is, what we have done is we have  
20 so focused on standard microbes at a particular  
21 concentration, it's given us sort of a fail-safe  
22 method that may need to be replaced with the

1 reality of what happens in patients. And if you  
2 look at the difference of organisms in the list  
3 that's provided there, we are now saying to our  
4 colleagues, and to our physicians, and to you who  
5 work in this environment, that as a cluster  
6 analysis, as anti-Koch, we need to be with multiple  
7 species that have the ability to either maintain an  
8 environment or to produce an infectious  
9 environment. And it's a world that must be  
10 refocused because we've used the same tools for  
11 way, way, way too long.

12           So the issue is, then, in your environment  
13 and mine, who needs these tools and how can we help  
14 them utilize this data? And as I pointed out  
15 there, I loved it because look at the last one.  
16 When we started in infection control, do you know  
17 the tools we used? Remember those sticky floor  
18 mats? I mean, we'd walk in and there was a  
19 sticky -- I look at the audience. You're not that  
20 old.

21           There used to be floor mats on the floor.  
22 Do you remember those? And they were sticky, and

1 we'd pull off one piece of paper. And we used to  
2 say, "Shoe covers are absolutely mandatory," and a  
3 wide variety of old things that we don't do any  
4 more. But the reality is we still need to address  
5 the option of what happens when we follow protocol,  
6 and do we have a down-field outcome that can be  
7 measured appropriately?

8           You cannot legislate compliance. I want to  
9 repeat that a thousand times. You can't legislate  
10 compliance. And our biggest issue with products  
11 and looking at infection control is the use of the  
12 product appropriately.

13           So the products are there, and what I want  
14 to point out to you is we have, though, tried to  
15 upgrade these products. And one of the things that  
16 I've been very, very lucky to be able to associate  
17 with because of my travels is a gentleman at Purdue  
18 University, very well known for particular types of  
19 image analysis. He's come out with a system, and  
20 now it's beginning to be utilized in the clinical  
21 world, which uses laser diffraction of microbes.  
22 It gives us real-time assessment of four things of

1 bugs.

2           So if you just picture it, take a plate, put  
3 a laser beam under it, and the colony morphotype  
4 separates by harmonics wavelengths that can be used  
5 to identify microbes.

6           So what we can do now within a time frame  
7 that somebody was addressing is, we can look at  
8 organisms, in the middle left, identify their  
9 mechanisms of resistance in their ID. At the top,  
10 we can identify if it's from the same source within  
11 the patient, blood and wound.

12           On the lower right hand, middle right-hand  
13 side, we can associate whether the pattern of  
14 diffraction defines whether it's within WVU's same  
15 floor or different floors within the hospital. And  
16 then, ultimately, within West Virginia, is it a  
17 pattern of identification that is associated with a  
18 particular outbreak, which has occurred elsewhere?  
19 After we've found a viable organism, it takes us  
20 about five seconds per organism.

21           So the tools are beginning to be developed,  
22 although I will point out to you that the United

1 States, in my assessment, is the slowest in the  
2 microbial world of assessing new methods into  
3 clinical reality. And I'm sort of embarrassed  
4 about that. I've been doing this almost 50 years,  
5 and when I go to Cardiff -- I just came back from  
6 Australia -- and look at the tools that these  
7 places are instituting for rapid detection of  
8 downstream outcomes, it's remarkable how slow and  
9 out of phase we are with the rest of the world.  
10 I'm a little bit embarrassed at times to have to  
11 say that.

12           So the disease process, as I bring my part  
13 to an end, of now is recognizing the bugs and their  
14 outcomes are not Koch, but rather anti-Koch. And  
15 if you want to really assess this, we've begun to  
16 put together some hypotheses that are being  
17 well-established in the published literature. And  
18 that is the endogenous skin flora, which as you now  
19 know is so diverse and cluster-oriented.

20           What's going to happen, ladies and  
21 gentlemen? We're going to identify bugs by their  
22 phyla. When we came down to the, do you remember

1 the orders and the class, et cetera? You all said,  
2 "I'm going to forget my microbiology. I'm never  
3 going to do it again." We need to recognize how  
4 these group within each other.

5 Species names is not necessarily the correct  
6 way to go. But the bottom line is, we now know  
7 that the depth tissue pH of that wound site,  
8 associated with the stress of that environment and  
9 nutritional support, particularly for the biofilm,  
10 eases us into what's now internationally called  
11 critical colonization. And the point is, we've  
12 used in micro 10 to the 4, 10 to the 5, log  
13 reduction. It doesn't work that way when we have a  
14 biofilm formed on a skin surface. And if we want  
15 to assess product clarity and effectiveness in  
16 maintaining its sterility, you've got to look at  
17 who's present and who the players are. And we  
18 haven't been doing a good job with that.

19 The reality now is, in a time period of  
20 about five to seven days, this multi-species  
21 environment on skin, having received the  
22 environmental support, or lack thereof, produces,

1 as you go into the blue, the scheme of staging in  
2 biofilms. And the biofilm formation that is part  
3 of this assessment now is addressing multiple  
4 issues.

5 I can show you best on that -- because this  
6 is the SEM of a wound bed.

7 (Cell phone rings.)

8 Dr. THOMAS: My mother said there would be  
9 somebody like that, but that's okay.

10 The bottom line is, as you know, this tissue  
11 environment looks like this, but in the reality of  
12 when we look at it, using some rather sophisticated  
13 issues in the wound development at the bed side,  
14 what we find is that we can stage the biofilm  
15 development much like tumor development.

16 The reality is, as the biofilms form this  
17 multi-species, anti-Koch environment, they go from  
18 stage 2, middle stage 3, to stage 4. And, ladies  
19 and gentlemen, biofilms develop their own capillary  
20 system. They have angiogenesis, and you can see on  
21 the lower right-hand side, actual means of  
22 capillary without a wall support for the multi-

1 species biofilm.

2 So when we look at wounds, and we look at  
3 how we need to assess management and preparatory  
4 assessment, you've got to be looking at who the  
5 players are. And right now, I'm sort of concerned  
6 we don't do that.

7 So my issue, as I bring my part to a  
8 conclusion, is, I'm really, really concerned that  
9 if we don't use the right tools, we won't make the  
10 right decisions based on the players. And the  
11 players are microbes, living in a multi-species  
12 community world.

13 The bottom line is, as I put my part  
14 together here, I wanted people to realize that,  
15 from my 50 years just about, the important parts of  
16 this program are the patient and the microbes.  
17 What are we looking at for our patient? What are  
18 we looking at for the organisms, and how they play  
19 their game, if you will?

20 The need, from my perspective, is downhill.  
21 I want to know what you're going to do. Will it  
22 change the outcome of the patient population? And

1 we didn't go into it, but obviously one of the  
2 issues of bugs and multiple species is what we call  
3 colonization resistance. It's not your traditional  
4 multi-resistant organism. It's multiple bugs  
5 living with an extra polymeric substance. We call  
6 that colonization resistance. That's a huge  
7 problem for any group of bugs that has the  
8 potential to live together. It's different than  
9 what we have associated with one bug, one organism.

10           The need is for real-time tracking. And you  
11 asked me what my recommendations are and where we  
12 need to place our emphasis on the time we're  
13 addressing here. My concern is time. And we could  
14 spend hours. Our pharmacy and therapeutic  
15 committee yesterday was talking about the time it  
16 takes to get the information to the people who need  
17 to use it to make a change, if it's necessary. And  
18 some of the newer tools are a major issue for us to  
19 get them online.

20           So my point is, in tracking and what we do  
21 in West Virginia, versus what you do in Washington,  
22 versus what you do in other states, we don't have

1 the tools that other countries are putting in  
2 place. That's where I'd like you to put your  
3 effort. Where is the method of tracking and  
4 maintaining data to get evidence to prove the  
5 benefit of what we're doing? We have so many loose  
6 ends that need to come together.

7 The need is for tracking, as I've pointed  
8 out. And in my perspective, having seen the  
9 wounded warrior as sort of the impact of what this  
10 means to me, is do we change here, up front, and  
11 make a change in the end-stage result? And I think  
12 I need help downstream, not upstream.

13 So I think, with that, I hope you don't mind  
14 my teaching style. That's what I do every day, and  
15 I'd be glad to address any questions that you might  
16 have.

17 DR. FURNESS: Thank you.

18 Questions from the panel? Dr. Rogers?

19 DR. ROGERS: Thank you very much for that  
20 presentation. I'm just wondering, then, with what  
21 you've provided, do you feel that we should have  
22 more of a targeted approach to organisms prior to

1 surgeries, rather than sort of this mass --

2 DR. THOMAS: Yes. Right. Really good  
3 question. I've thought about that a lot, so should  
4 we use one set of bugs or two sets of bugs, or one  
5 organism or multiple organisms? And, clearly, the  
6 point that I would make to all of us is that we're  
7 assessing products now.

8 We're assessing them using a method called a  
9 poloxamer, of how they grow on a biofilm, because  
10 in the wound environment, that's what they're  
11 doing. So to assess them with what we've standard  
12 used is -- so I would rather we use three  
13 organisms: staph, pseudomonas, and the other  
14 organism we haven't addressed here, candida  
15 albicans. We now know candidas are a major player  
16 in biofilm formation. And how many times do we  
17 look at candida albicans in its usefulness?

18 So to answer your question, three bugs I  
19 would use; I would use staph, pseudomonas, and  
20 candida albicans. And here's the other point.  
21 Thank you for asking that question. Not every bug  
22 forms a good biofilm. Staph is not staph, is not

1       staph, is not staph. Pseudomonas is not  
2       pseudomonas. So we have these classic  
3       American-type culture collection isolates that we  
4       do query about sometimes.

5                So we do use clinical isolates. I think  
6       that's a tool, but the reality is, we should also  
7       assess them, do they make a good biofilm. Because  
8       not every pseudomonas, not every staph, not every  
9       candida makes a good biofilm.

10               So classifying their biofilm capacity using  
11       a multi-species, at least three organisms, grown in  
12       a biofilm, is where I would go.

13               Sir?

14               DR. FURNESS: Dr. Kelman?

15               DR. KELMAN: Dr. Thomas, very interesting  
16       presentation. And by the way, I remember the  
17       sticky floors.

18               (Laughter.)

19               DR. THOMAS: You do? I'm sort of glad.  
20       Thank you. You make me feel better.

21               DR. KELMAN: Based on your hypothesis, is  
22       there necessarily any value at all in preoperative

1       antiseptis?

2               DR. THOMAS:  There's a rule here in  
3       teaching.  If you ask a professor a question he  
4       can't answer, that's a bad thing.  Clearly, to  
5       maintain sepsis has been the goal of all of us, but  
6       to recognize the limitations of what it can be.

7               The gentleman, sir, you were asking, if you  
8       find a product, an organism in a solution that can  
9       grow, is that an issue?  Of course, it's an issue.  
10      But the reality is, not every bug can do that.  And  
11      how many times is that apparent becomes the issue.

12              But do I think antiseptis is important?  Up  
13      to the point that it makes a good contribution to  
14      the product end-stage, yes.  But does every product  
15      need to be sterile?  The answer is absolutely no.

16              DR. FURNESS:  Dr. Leonard-Segal?

17              DR. LEONARD-SEGAL:  I'm not a  
18      microbiologist.  So this is going to sound maybe  
19      like a very naive question.

20              DR. THOMAS:  You know what the professors  
21      always say; there's never a naive question.

22              DR. LEONARD-SEGAL:  Thank you.

1           So with these biofilms as a potential risk,  
2           as a source of infection on their own, is there  
3           something that we ought to be looking at? I mean,  
4           we've been worried about contamination in the  
5           antiseptic, however it got there. Is there a way  
6           that we should be looking to study whether that  
7           contaminant is interactive somehow with a  
8           preexisting biofilm, such that it would be of  
9           particular risk?

10           DR. THOMAS: Great question.

11           DR. LEONARD-SEGAL: Thank you for saying  
12           it's a great question. I'm not sure I understand  
13           the basis of why I asked it, but I'm asking it.

14           DR. THOMAS: No, no. So the question is  
15           really quite good, actually. And the bottom line  
16           is where I'm really coming from, because certain  
17           organisms don't interact well with the preventative  
18           biofilm that you and I have on our body. I mean,  
19           we are a walking biofilm.

20           So that's a really important point, is, are  
21           the bugs that we need to associate with, as  
22           addressed here, those that don't get along well?

1       Because if they don't get along well, they're not  
2       going to be able to compete with the organisms that  
3       are on the skin, and they will basically be  
4       refused.

5               If they get along well with the pre-  
6       established human biofilm, reduced in bioburden but  
7       still present -- you can't autoclave our  
8       patient -- those are the bugs that I am most  
9       concerned about. And what concerns me now is we  
10      haven't really done that experiment, where we've  
11      looked at the traditional organisms that we do deal  
12      with, and see how they interact with the biofilm of  
13      the patient.

14             Now, here's the problem. And I didn't go  
15      into this, but I love this. You are a biological  
16      microbiologic clock. Your flora changes with age.  
17      And at the flora that we'd looked at with a newborn  
18      versus the flora we'd looked at with my age is  
19      different. So you can't just assume that if we  
20      assay it at one time, it's going to have the same  
21      outcome. If that bug from the contaminated source  
22      has a challenge to a newborn versus a challenge to

1 an adult, and would they interact favorably or not  
2 so, we have to test them, recognizing that you and  
3 I are a biologic clock, and our bug pool is going  
4 to change a bit. But we know now what those pools  
5 are, so we can do that. But it would take some  
6 sophisticated and specific challenges.

7 DR. LEONARD-SEGAL: So do you have  
8 suggestions as to how we ought to be thinking about  
9 doing testing moving forward?

10 DR. THOMAS: Yes, I really do. And one of  
11 the things would be, clearly, as the young lady was  
12 addressing here, that biofilms are part of the  
13 target that we should be assessing. And the  
14 mixture by which the biofilms and the organisms  
15 that could be a contaminate will actually produce a  
16 constellation that is a detriment to the patient.

17 Look. The presence of a bug does not  
18 indicate it's a pathogen. And as our tools expand,  
19 we're going to find bugs. We live in a microbial  
20 world. So the issue isn't, are they there? The  
21 issue is, are they there, and in an environment to  
22 a patient, produce an outcome? And it's my opinion

1 that, most of the time, those bug combinations do  
2 not produce a bad outcome.

3 We have to track it. And that's why I said,  
4 one of the things I'd love to be able to do at West  
5 Virginia University is to track all the hospitals  
6 within the state, or all the hospitals within a  
7 reasonable control system, so we can begin to  
8 assess better what the bugs are; and if we have  
9 contamination, can they be of consequence to the  
10 patient? Bug present in a solution doesn't mean  
11 it's going to be an issue for the downstream issue  
12 of the patient.

13 DR. FURNESS: Dr. Hussong?

14 DR. HUSSONG: First, I'd like to thank you  
15 very much for your comments and presentation. And  
16 as a microbiologist in an agency that was  
17 originally called the Bureau of Chemistry, I  
18 appreciate your comments of chemists.

19 DR. THOMAS: You know where I'm coming from.

20 DR. HUSSONG: Been there, done that.

21 I think it's very important, when you're  
22 talking about infectious potential with your

1 simplified calculation -- appreciate it -- our  
2 concern here is large numbers of atypical  
3 microorganisms that become an infectious dose.

4           Again, a few bacteria generally don't cause  
5 a problem. It's when something overwhelms the  
6 system. When getting your teeth cleaned, you get  
7 an immediate septicemia that most people can handle  
8 without a problem.

9           But the concern that I'm addressing is,  
10 again, the potential for microorganisms that don't  
11 belong and that do proliferate somehow. Delivering  
12 even small numbers of microorganisms to a site of  
13 an indwelling catheter can be a big issue.

14           Your discussion really I think sheds some  
15 light on how we have to look at this. I almost  
16 wonder if maybe we should be looking at probiotics  
17 or something like that to control or suppress  
18 infection. I didn't know if you wanted to make  
19 any --

20           DR. THOMAS: Give me my card back. And the  
21 oral area is the issue. And without getting lost  
22 and going too far, the bottom line is yes.

1 Maintenance of the bioburden of a particular  
2 site -- and they do vary -- is critical to the  
3 health of the patient for a variety of reasons.

4 I must say, again, that the Europeans, and  
5 particularly in oral health, have refocused on  
6 maintaining biofilms by establishing a probiotic.  
7 And in the European literature, and particularly in  
8 oral health, you cannot give in the U.K., where  
9 Cardiff is -- you can't give an antibiotic for a  
10 patient who has periodontal disease. You are  
11 licensed almost to give a probiotic. And there  
12 are, in the U.K., in studies that we've done at  
13 Cardiff, over 300 well-established clinical trials  
14 that in dental periodontal disease proved the  
15 benefit of a probiotic.

16 We won't get lost here, but that's one of  
17 the issues that makes me madder than holy heck, is  
18 that our clinicians use the word "probiotic." It's  
19 like using the word "antibiotic." No one would  
20 send a patient out to buy an antibiotic. They  
21 would prescribe a particular type, given a  
22 particular dose, that's used for a particular time

1 frame. But in the United States, unlike Europe, we  
2 have not decided whether probiotics are medical  
3 management or, in fact, food additives. And so,  
4 the reality is, there is no guidelines for using  
5 probiotics in the U.S.

6 Now, addressing your question, I've  
7 addressed the concept of putting a probiotic in a  
8 dressing to re-establish a bioburden that is non-  
9 detrimental to the patient, which would over time  
10 be very removed by the environment.

11 So I think looking to the future, I think  
12 probiotics in wound management, in dressings, is a  
13 potential option. And I think it's something we  
14 should be looking at, very much so.

15 DR. FURNESS: Thank you very much. We don't  
16 have any other questions. I'd like to thank  
17 Dr. Thomas.

18 DR. THOMAS: You're very welcome. Thank  
19 you.

20 DR. FURNESS: And we are running a little  
21 bit behind schedule, and I would suggest that we  
22 take our planned break at this point. And we'll

1 pick up at where we left off in 15 minutes. So  
2 that would be about 10:45. Thank you.

3 (Whereupon, a brief recess was taken.)

4 DR. FURNESS: In the interest of time, we  
5 need to reconvene. And at this time, I'd like to  
6 call Dr. J. Hudson Garrett, senior director of  
7 clinical affairs at Professional Disposable,  
8 Incorporated, PDI.

9 **Presentation - Hudson Garrett**

10 DR. GARRETT: Thank you very much.

11 Well, good morning, and thank you to the  
12 panel for this opportunity to discuss this very  
13 important clinical issue.

14 I'm going to take a little bit of a similar  
15 approach to Dr. Ryan from Sage and talk to you a  
16 little bit about the clinical aspects of the uses  
17 of these products. I've had the opportunity to  
18 work with the Association for Perioperative  
19 Registered Nurses on this actual guideline that  
20 they actually use for perioperative registered  
21 nurses in the operating room setting and outside.

22 So you can see my objectives here. I'd like

1 to go over a little bit of the clinical aspect of  
2 this. And I think some of the questions that were  
3 already asked this morning are very spot-on with  
4 some of the challenges that we see with this.

5 I also think, though, it's important to note  
6 the role of the skin in this whole equation. I'm  
7 not a microbiologist, and I certainly can't follow  
8 the absolutely outstanding presentation right  
9 before the break, but I hope to shed some light on  
10 the role of the skin in the patient as well.

11 Then last but not least, I think we've  
12 talked a great deal this morning about education,  
13 and I think there's a tremendous opportunity for us  
14 to partner with the agency on education.

15 So when you think about healthcare-  
16 associated infections, each one of us could be a  
17 consumer. I was just a consumer of healthcare two  
18 weeks ago. I had a surgical incision made in the  
19 back of my neck, met a dermatologist for the first  
20 time, asked her some very specific questions, and  
21 she started to ask me, "Well, what do you do for a  
22 living?" when I started to ask this.

1           She actually did an outstanding job, I  
2 think, of following good practice for medicine.  
3 She applied the skin prep using a non-sterile  
4 technique. She applied the drape. She did all the  
5 things that she was supposed to do, and she took a  
6 tremendous amount of time at the end of the  
7 procedure and educated me, even knowing what I do  
8 for a living.

9           It happened to be a family nurse  
10 practitioner with a background like Dr. Ryan. And  
11 so, I certainly knew the risk, knew what the wound  
12 care was. But I really appreciated the fact that  
13 she actually took that additional time with me as  
14 the patient and said, "Here's some things that you  
15 need to do to actually prevent further infection."

16           But when we live in the United States and 1  
17 out of 20 hospitalized patients continue to get a  
18 healthcare-associated infection, to me, that's  
19 absolutely unacceptable, and I think that we have a  
20 tremendous opportunity associated with that.

21           I know we have a colleague here from CMS,  
22 and I know that the Department of Health and Human

1 Services has put forth the HA action plan. And  
2 that's definitely something that we have to  
3 consider. And we know that healthcare is also  
4 delivered in a variety of other spaces outside of  
5 the four walls of the hospital.

6 So when I think of education for this  
7 preoperative skin preparation, I think of the  
8 people outside of the four walls of the hospital as  
9 well. And those are consumers of those products  
10 that we have to be considerate of.

11 So when we look at the skin -- this is a  
12 pretty elementary diagram, and I'm not going to  
13 talk microbiology, per se, but I do want to go back  
14 to a little bit of the anatomy and  
15 physiology -- you really have those two fundamental  
16 layers of the skin. You have the epidermis and the  
17 dermis.

18 When we think about the use of these types  
19 of products, we're really trying to target the  
20 transient flora in the epidermis. So we're never  
21 going to actually sterilize the skin. And I think  
22 that's a very important piece that we have to think

1 about.

2 The whole purpose of this process is not to  
3 sterilize. I think we've acknowledged the role of  
4 good flora on the skin, but we also recognize that  
5 most of the infections actually come from the  
6 patients' own flora. They're not coming from  
7 sources outside of the patient.

8 So when you look at current utilization, so  
9 where are these products used, now, there's been a  
10 lot of discussion about the operating room. But I  
11 know many of you on the panel are physicians by  
12 background, and so you know that these products are  
13 used in other outpatient settings. They're used in  
14 ambulatory surgery. They're used in primary care.  
15 They may be used in cardiac catheterization  
16 laboratories.

17 So it's not just the four walls of the  
18 operating room in which these products are used.  
19 And so, we have to think about what types of  
20 clinicians might actually be using these products.  
21 What are their skillsets? What are their  
22 educational backgrounds? Are they exposed to

1 continuous education? And I think that's a  
2 question that we have a lot of opportunity to do in  
3 collaboration with the agency.

4           You think about the different types of  
5 procedures in which these products are used, and  
6 there's a large variety. And so, it actually  
7 changes the way that we might educate as well. And  
8 like Sage and many of my other colleagues here from  
9 industry, we spend a tremendous amount of  
10 resources. I have a team of medical science  
11 liaisons that actually educate the users of these  
12 products to ensure that they're doing it correctly,  
13 and we take that extremely seriously. Now, is  
14 there room for improvement? Absolutely and that's  
15 something we'd like to collaborate with the agency  
16 on.

17           When we look at aseptic technique -- now, I  
18 mentioned to you before, I was just a consumer of  
19 healthcare. So the timeliness of this meeting is  
20 pretty ironic. But I think about the whole  
21 principle of aseptic technique in general. So what  
22 does that mean? Are we really accomplishing what

1 we're setting out to? What's our objective?

2 Well, our objection is really to reduce the  
3 bioburden present on the skin to a safer level  
4 prior to the actual procedure, whether it be an  
5 injection, an incision, whatever it may be. And  
6 so, that's really what we have to think about. The  
7 skin will never be sterilized. Skin preparation is  
8 not designed to be a sterile procedure, and you'll  
9 see one of the guidelines here in just a minute.  
10 But what we are trying to do is minimize any  
11 potential source of contamination.

12 My background is not in manufacturing, and  
13 so I'm really speaking more as a clinical expert to  
14 say that there's a lot of opportunity on that side  
15 of the house to actually improve practice.

16 So when we look at antiseptics in general,  
17 no surprise to you it needs to be broad spectrum.  
18 So when it is applied to the patients' skin, what  
19 type of efficacy are we achieving? What type of  
20 log reduction are we actually seeking? There's not  
21 a magical number that says, if you achieve this log  
22 reduction, you're going to prevent a healthcare-

1 associated infection. And that, to me, is a  
2 challenge that we need additional research. I know  
3 we have a colleague here from DHQP at CDC, and  
4 that's something that I always ask myself. What  
5 else can we do to challenge ourselves to create  
6 that resource, that evidence-based practice?

7           We know that it needs to be quick. If you  
8 apply a skin antiseptic to a patient and it takes  
9 an hour to dry, it's not necessarily going to be  
10 the most appropriate antiseptic. It has to be easy  
11 for the clinician to use. An example of this is,  
12 if the products' instructions are so prohibitive  
13 that it takes several minutes to read them, the  
14 clinician's not going to adhere to them. And so, I  
15 think we have an opportunity to have more  
16 educational labeling that can actually be present  
17 on these products as well and educate the actual  
18 clinician. And I think we've also brought up a  
19 good point this morning about the potential patient  
20 that may be taking these products home from a  
21 pharmacy or their outpatient setting and utilizing  
22 them.

1 Persistence is one of those words. Well,  
2 what does that mean? Well, we know that if an  
3 antiseptic can continue to provide antiseptic  
4 properties on the patient's skin, that that  
5 provides some benefit. Again, we don't know what  
6 that magical number is, but we do want it to  
7 obviously be compliant with the TFM.

8 Another thing that we have to think  
9 about -- especially if it's done by a patient,  
10 maybe in a homecare environment, where we're  
11 teaching the patient and educating them to actually  
12 take care of, for example, their own wound -- is  
13 that antiseptic going to maintain its activity in  
14 the presence of organic matter? And so, that's a  
15 challenge that we face. And then last but not  
16 least, from a patient safety perspective, the  
17 antiseptic needs to be non-irritating.

18 So I told you that I had the opportunity to  
19 work with AORN on their guideline for a  
20 perioperative skin antisepsis, and they're very  
21 stringent about this. And just as Dr. Ryan  
22 mentioned earlier, the studies show that when

1       you're using preparations, there's really been no  
2       difference between the application in a non-sterile  
3       versus a sterile manner.

4               Now, when you think about it, antiseptics  
5       typically are wet. So if you are in a sterile  
6       gown, sterile gloves, sterile mask, and surgical  
7       attire, there is a high risk for contamination that  
8       can exist with that antiseptic and actually  
9       contaminating, whether it be the drape or actually  
10      the sterile gown.

11              So AORN actually says that you should have  
12      the non-scrub personnel apply the skin antiseptic,  
13      according to the manufacturer's label and  
14      instructions. And so, that's something that,  
15      again, we're never going to sterilize the skin. So  
16      we want to apply that antiseptic, following the  
17      manufacturer's instructions for use, in an aseptic  
18      manner that's going to not additionally contaminate  
19      the skin or the field.

20              When you think about skin antisepsis, we've  
21      spent a lot of time talking about surgical site  
22      infections this morning, but another thing to think

1 about is central line-associated infections, which  
2 these products are also used for. And if you think  
3 about this, there are lots of opportunities for  
4 bacteria to invade the skin. We certainly agree  
5 that if you have intact skin, that's a great  
6 natural barrier for microbic contamination.

7 But what happens when you actually put a  
8 catheter or you put some type of prosthetic device  
9 or things like that in there? You're creating a  
10 break. You're creating an opportunity for  
11 organisms to invade that area. And so, the use of  
12 skin antiseptics does not just stop prior to the  
13 procedure. It actually continues post-procedure,  
14 maybe through things like dressing changes or site  
15 care, or things like that. And so, those are  
16 additional sources of contamination that we have to  
17 think about.

18 When you think about CLABSI or blood serum  
19 infections, I give you a statistic. Most  
20 infections actually come from maintenance. So that  
21 means it's not at the time of insertion. It's  
22 actually at the time post-procedure that other

1 clinicians are actually caring for that site or  
2 that wound.

3           So we have a lot of opportunity to educate.  
4 And I think that the notion to have a checklist is  
5 a great one. When you look at some of the great  
6 work that colleagues have done with CLABSI, over  
7 50 percent of CLABSIs have been reduced due to a  
8 checklist, due to things that are on there to help  
9 standardize that approach to preventing those types  
10 of infections.

11           These are just a few risk factors. So we  
12 were talking about, obviously, intrinsic and  
13 extrinsic sources. Well, I would call your  
14 attention to the fact that there's a tremendous  
15 growth opportunity in providing more education.  
16 One of the things that we find -- and I think that  
17 my colleagues from industry would share this  
18 concern -- is that there's a lack of understanding,  
19 in some cases, of the proper use of skin  
20 antiseptics, when to use them, how long to use  
21 them, how to apply them, when they should be  
22 re-applied, and, more importantly, how to really

1 understand some of the label instructions.

2 So we do a tremendous amount of education  
3 around that to ensure that clinicians do understand  
4 how to appropriately use these so that they are  
5 actually achieving the outcomes that the label  
6 indications claim.

7 So when you look at some of these risk  
8 factors, some of these are controllable; some of  
9 them honestly are not. But we certainly can do  
10 more to actually help control some of the ones at  
11 the patients' bedside and really bring more  
12 attention to that. And I think that as more and  
13 more procedures are done outpatiently, we have to  
14 also think about how we can educate the consumer as  
15 well, because they may be receiving these products  
16 in pharmacies and places like that, as I mentioned  
17 before.

18 So I know some of the questions that were  
19 asked by the panel, if you think about, should  
20 these products be sterile, that's a fundamental  
21 question that you've asked. And I think it's a  
22 very good question and a very logical question to

1 ask.

2 I know one of the comments made earlier was  
3 that there's many sterile supplies and things like  
4 that, that are in the operating room setting. But  
5 the operating room itself is not a sterile  
6 environment. I mean, we try to make it as sterile  
7 as possible, but it's certainly not possible to  
8 make the entire room sterile. And so, when you  
9 think about skin antiseptics, again, the skin cannot  
10 be sterilized unless you autoclave it, as my  
11 previous colleague mentioned. And so, that's  
12 obviously something we can't do with the patient.

13 So what's the next best thing? Well, we  
14 need to apply it using the best manner that we  
15 have, using the best solutions that we have that  
16 are most appropriate for the patient, following the  
17 instructions for use.

18 So while sterility does provide an added  
19 layer of benefit, it's certainly not going to  
20 eliminate the risk for contamination. You think  
21 about sterile products that come packaged today. I  
22 hate to pick on needles and syringes, but we have

1 needles and syringes that are clearly labeled  
2 single-use, sterile, disposable, for one patient,  
3 that, in this country, continue to be reused. And  
4 that's an issue for us that continues to cause  
5 adverse events. Poor user education, opportunity  
6 for improvement, opportunity for collaboration, and  
7 so, we have to think about that.

8           The other thing, though, is that  
9 contamination can actually change, and it can occur  
10 over time. If you think about an antiseptic -- and  
11 I'll show you a slide here in just a moment to  
12 further describe that -- there's single use, and  
13 then there's multiple-patient use. And I'll talk  
14 about that in a minute.

15           But we know that with multiple patient use,  
16 there's more of an opportunity for contamination  
17 because there are storage issues involved. There's  
18 continued exposure to that actual solution. And  
19 so, it's a larger solution, of course, and so every  
20 time you open that, you're breaking that system and  
21 you're exposing it to the atmosphere. But again,  
22 storage and education have to be accompanied with

1 that.

2 So when you think about what would be the  
3 requirements, I think Sage did a nice job of  
4 outlining some of the manufacturer requirements.  
5 That's not my area of expertise, so I'm certainly  
6 not going to touch on that. But I really think  
7 that with the issues with drug shortages now,  
8 there's going to be some tremendous manufacturing  
9 challenges with moving in that direction to a fully  
10 sterile solution.

11 So I don't clinically feel that that's  
12 actually the best course of action. And the reason  
13 being is that we haven't taken all the necessary  
14 steps to actually educate and fully involve the  
15 users that we can. And that may be things like  
16 educational classes that can be delivered, that  
17 many of us are actually providing. It can be  
18 additional labeling opportunities that we can work  
19 with the agency on, to say, "How can we further  
20 improve the clarifications required to the proper  
21 use of these products?"

22 We also know that clinical education is

1 continuous in healthcare. If you're a nurse,  
2 unfortunately, you're probably going to education  
3 almost every single day whether you like it or not.  
4 It may be on a new IV pump. It may be on a new  
5 glucometer. It may be on a multiple-dose vial. It  
6 may be on all kinds of topics.

7           So how do you sift that in? And I think  
8 that's an area where the manufacturing partners can  
9 continue to collaborate to say, "How can we bring  
10 this education to the forefront, to the bedside  
11 clinician, and actually help them improve the  
12 quality of care that they're able to provide to  
13 their patients?"

14           So I do want to spend a little bit of time  
15 talking about this. There's a tremendous  
16 difference -- just like with a medical device, if  
17 it's a single use and has to be discarded or if  
18 it's a multi-patient use and has to be reprocessed.  
19 The same principle really applies here.

20           So you really have two different categories  
21 that I would call your attention to. One is that  
22 single-use patient antiseptic that's really kind of

1       thrown away. You use it. It's instantly used, and  
2       it's discarded. So there's no risk for  
3       contamination between patients. There should be no  
4       risk with storage because it's sealed. It's stored  
5       properly. And it's going to be used for that one  
6       patient, so it's not going to be cross-pollinating,  
7       if you will, with flora.

8               The other issue, though, is that, especially  
9       outside of the hospital, in primary care offices,  
10       ambulatory surgery, there is a tremendous amount of  
11       multi-patient-use solutions out there. And so,  
12       that is something that is of concern to me because,  
13       when you have those larger solutions, you really  
14       have that opportunity, if you will, that it's  
15       really going to expose it.

16               Every time you go and access that solution,  
17       you're exposing it to air. You're exposing it to  
18       any other contaminants that might be present in the  
19       environment. And while there are bacteria  
20       everywhere, hopefully the antiseptic itself is  
21       going to be stored correctly. It's going to be  
22       dispensed correctly. And it's going to actually be

1 applied to the patient correctly. But those are  
2 three variables that the clinician has to control.  
3 And I think those are things that we can continue  
4 to improve.

5 So if you look at this, I think there would  
6 be a wise move to move towards those single-use,  
7 actually, antiseptics, which most of the  
8 antiseptics out there actually are in that  
9 category. And that will help eliminate another  
10 source of contamination.

11 When you look at some of the other  
12 steps -- so let's just say that products  
13 manufactured sterile, they're going out into the  
14 environment. They're used by clinicians. They  
15 have transportation. They're delivered to the  
16 hospital or whatever clinical environment that  
17 they're in. There's still an opportunity by the  
18 user to actually unfortunately use them  
19 incorrectly.

20 So again, going back to labeling, and  
21 clinical education, and requirements, there is an  
22 opportunity for collaboration here. And I think a

1 checklist, as Dr. Ryan mentioned, is an excellent  
2 idea. I think we've demonstrated that, in  
3 healthcare practice, that checklists are efficient.  
4 They work well. And they demonstrate good outcomes  
5 when they're adhered to.

6 So you think about training for skin  
7 antiseptics products. I think that's something  
8 where our partners at AORN and other organizations  
9 that really specialize in this actual procedure  
10 could have tremendous input on, and I certainly  
11 think that they would have a vested interest in  
12 doing so.

13 It's one of those things where you have to  
14 not only educate at the time that you come to work  
15 there, but you have to continue to educate. Things  
16 change. Products change. Antiseptics practices  
17 change, maybe the patient. You think about an  
18 average operating room patient. They may not be  
19 laying down on their back on that OR table. They  
20 may be in another position based off the procedure  
21 that's being performed.

22 So how do you adapt the education to

1 actually meet the specific needs of the patient?  
2 Because at the end of the day, we're trying to  
3 prevent that one infection in that one patient, and  
4 we have to take one patient at a time and make sure  
5 that the clinicians caring for that patient and  
6 actually using the antiseptic are doing so in an  
7 appropriate manner for that patient.

8 I think when you look at the AORN practices,  
9 they really, really stress aseptic technique. And  
10 I think that's an area where we have opportunity as  
11 a medical profession in the whole, really, to  
12 reeducate on what is aseptic technique, how do we  
13 minimize contamination to the patient, to the  
14 field, to the environment.

15 We go back to our roots with hand hygiene.  
16 Well, it's interesting that only 40 percent of  
17 healthcare providers practice hand hygiene when  
18 indicated. That means we have a 60 percent  
19 opportunity for improvement. And I think, through  
20 education, we can really beef up the proper use of  
21 antiseptics.

22 I also want to draw your attention, as we

1 draw to a close here, to some alternate site  
2 considerations. One of your questions was, where  
3 else are these products used? Now, this, to me, is  
4 a tremendous opportunity.

5           When you think about it, if you go to your  
6 private physician office, the average clinician in  
7 there is not a nurse. It's a medical assistant.  
8 And while those individuals certainly do receive  
9 training, they don't have the level of training,  
10 for example, that a nurse might have and certainly  
11 not one that a physician, or a physician assistant,  
12 or a nurse practitioner might have.

13           So we have an opportunity to educate some of  
14 these clinicians in these alternate care sites to  
15 be better advocates for the proper use of skin  
16 antiseptics and making sure that they're being  
17 consistent with the labeling instructions and  
18 following the manufacturer's indications.

19           That's something that I think, when you see  
20 dialysis centers, you think about the presence of  
21 dialysis patients, the prevalence of people going  
22 into ambulatory surgery. You've seen a tremendous

1 shift in surgical procedures actually moving  
2 outside of the hospital. So they're actually going  
3 to these outpatient centers where there's a  
4 tremendous volume of patients moving through these  
5 environments. And so, time is an element as well.  
6 So how do we make sure that we're maximizing  
7 patient safety and efficacy while meeting the time  
8 constraints that these clinicians have in these  
9 various settings?

10 So I think it's worth consideration for you  
11 that, as you look at opportunities to improve the  
12 use of these products, also consider our colleagues  
13 that are in alternate site settings that might not  
14 have the full resources, the educational support,  
15 that our colleagues in hospital environments have.

16 Last but not least, clinical staff training.  
17 I think we've reemphasized this all morning long,  
18 and I think that it's an important point. You can  
19 have the best product that, even if it was sterile,  
20 can be inappropriately used and contaminated. And  
21 I think that when you look at the data that's out  
22 there, when you follow instructions for use, when

1       you've explicitly followed manufacturers'  
2       instructions and labeling requirements, you should  
3       have a good outcome. And there are always  
4       exceptions to the rule, and I think there's  
5       opportunities for us to improve across the entire  
6       industry.

7               That being said, we need to do more to  
8       educate the users of these products, and I think  
9       that's where collaboration with industry and also  
10      our scientific partners like AORN and CDC can  
11      really come into play. I know that CDC, for  
12      example, is working on a new guideline specific to  
13      surgical site infections. This is a prime  
14      opportunity to take that new evidence-based work  
15      and actually educate further to it, so that the  
16      users of these products in the clinical setting are  
17      actually using them appropriately and really, fully  
18      understand how they're actually using these and  
19      what's the purpose.

20             Sometimes we just actually do things without  
21      understanding really the purpose behind them. And  
22      if we understand that the skin is not sterile,

1 cannot be sterilized safely with the patient,  
2 obviously, how do we maximize the efficacy of skin  
3 antiseptics products, things like aseptic  
4 dispensing, making sure that we're providing annual  
5 competency training, and then also proper storage?

6 I know one of the questions that came up  
7 was, can you date these products? And again, with  
8 a single use, single patient, you don't have to  
9 worry about that because they're immediately  
10 discarded. So there's no need to actually date the  
11 product when you opened it.

12 So when you look at some of these large  
13 solutions that are sitting on shelves in operating  
14 rooms, those have a much more tremendous risk for  
15 possible contamination.

16 These are my disclosures, and I will be  
17 happy to take any questions that you might have.

18 DR. FURNESS: Thank you very much.

19 Questions from the panel? Dr. Chang?

20 DR. CHANG: Thank you for your presentation  
21 and for actually responding to each of our  
22 questions --

1 DR. GARRETT: My pleasure

2 DR. CHANG: -- that was put out in the  
3 notice.

4 So two questions. Contemplating on  
5 single-use containers, can you please help me  
6 understand what, in your opinion, would be the  
7 ideal volume of solutions for each container?  
8 Because obviously, we have to keep in mind the  
9 different types of surgical procedures, and some  
10 may need more coverage.

11 DR. GARRETT: Right. So I would say the  
12 response to that question is twofold. One is to  
13 make sure that the appropriate amount of solution  
14 is used for the appropriate procedure. When you  
15 think -- one of the ideal properties of skin  
16 antiseptics that I talked about in, I think, the  
17 first three or four slides, was that it has to be  
18 non-irritating to the patient.

19 We know that if you coat the patient in  
20 antiseptic unnecessarily, you increase adverse  
21 events. Right? So you increase risk for skin  
22 irritation and things like that, especially when

1 dressings and things like that are inappropriately  
2 applied. So you have to put the appropriate mLs of  
3 solution on the patient, based off the clinical  
4 procedure, and as you mentioned, the coverage area.

5 I think that being said, I'm not personally  
6 aware of any data associated with those single-use  
7 dispensing solutions, regardless of the mLs -- I  
8 haven't personally seen any above 30 to 35 mLs;  
9 there may be some, so I don't want to say that's  
10 absolute -- that had been linked with that. And  
11 those are appropriate for the types of patients  
12 that we have.

13 Again, they're immediately used. They have  
14 special storage instructions, which everybody is  
15 familiar with. And then they're immediately  
16 discarded. And my concern is, if you have these  
17 large, multi-use dosing systems, if you will,  
18 you're creating an additional route of  
19 contamination because of the ability for things to  
20 contaminate every time you're accessing them.

21 DR. CHANG: One follow-up question --

22 DR. GARRETT: Sure.

1 DR. CHANG: -- not about the volume, but  
2 this pertains to the earlier part of your  
3 presentation. I think we all recognize that it's  
4 impossible to sterilize the skin, and it's  
5 certainly not possible to sterilize the entire OR.  
6 But thinking of a patient who might be  
7 immunocompromised and you're about to proceed to  
8 invasive procedures, how would one justify using on  
9 the patient a product that may introduce organisms  
10 that are not endogenous and possibly may be  
11 pathogenic?

12 DR. GARRETT: Sure. I think that's an  
13 excellent question, and one that, as an agency  
14 obviously concerned with patient safety, we have to  
15 ask routinely. I don't necessarily know that  
16 there's a scientific answer to that question. To  
17 me, I would be much more concerned with poor  
18 surgical technique than I would with the proper use  
19 of an antiseptic that was aseptically applied to  
20 the patient.

21 My personal opinion, I think that the risk  
22 of contamination, as we identified from the first

1 presentation, is extremely low, given the number of  
2 volume of procedures that take place in the United  
3 States annually. And so that's a very, very low  
4 statistical number.

5 That being said, I think we also have to  
6 continue to re-evaluate. Are we doing every single  
7 thing that we can, both as an FDA agency, CDC, and  
8 manufacturing partners, to properly protect the  
9 patient? But I think that when these antiseptics  
10 are used, you look at outcomes with CLABSIs and  
11 other things, the data speaks for itself. The  
12 antiseptics, when appropriately used, do actually  
13 improve patient outcomes. They decrease costs in  
14 the healthcare system, and they decrease mortality  
15 and morbidity.

16 So I think we have to continue to evaluate  
17 the education associated with those to ensure that  
18 we are doing the very best thing that we can for  
19 our patients.

20 DR. FURNESS: Dr. Kelman?

21 DR. KELMAN: A very interesting  
22 presentation, Dr. Garrett. I only have one

1 question. Could you think of any possible  
2 disadvantage to producing these products as  
3 sterile?

4 DR. GARRETT: Well, I think there's  
5 obviously the manufacturing piece, which colleagues  
6 from Sage had mentioned, and that's not my area of  
7 expertise. I will say, from a clinical  
8 perspective, if you go back to the AORN guidance,  
9 there's an opportunity, if you're using a sterile  
10 solution that is wet, to have strikethrough with  
11 your sterile barriers that you're wearing.

12 So I think from a clinical practice, you're  
13 actually asking the clinician in many cases to  
14 change their practice, especially if they're  
15 wearing sterile attire. And so, I think that is  
16 something that would have to be really studied, and  
17 work with colleagues at AORN and other groups to  
18 say, what would be the impact of your constituents  
19 in the OR setting to really adapt a change of that  
20 magnitude, because we certainly don't want to  
21 change practice unnecessarily if there's no benefit  
22 to the patient, of course. But, certainly, if

1 there was a benefit, I think that would require a  
2 tremendous amount of re-education.

3 DR. FURNESS: Thank you very much, Doctor.

4 DR. GARRETT: Thank you.

5 DR. FURNESS: Sorry. We have one more  
6 question. Dr. Shehab?

7 DR. SHEHAB: Sorry. Two comments and maybe  
8 a question. And I don't speak as neither a  
9 microbiologist nor a chemist. I am better known as  
10 a bean counter and epidemiologist, which is the  
11 lowest life form, probably. But as a bean counter,  
12 I can tell you that, epidemiologically, it's  
13 extremely challenging for us to be able to identify  
14 those surgical site infections that are due to  
15 contaminated products. And we may never be able to  
16 do it using our current surveillance capacity and  
17 perhaps outside of a clinical trial, just due to  
18 the complexity of the patients involved, the idea  
19 that the products may not be available after  
20 surgery or after injection.

21 So I just want to be careful because I've  
22 heard the absence of data cited as evidence; just

1 be careful that we don't do that once we're moving  
2 forward.

3 The other comment I had, I think we're  
4 asking about sterility at manufacture, not as the  
5 primary way to mitigate extrinsic contamination,  
6 but understanding that we -- and that we don't want  
7 to autoclave the patient, and we don't want to  
8 autoclave the skin.

9 What we do not want to do is introduce  
10 organisms, again, that we know are pathogenic into  
11 the patient and we know are causative infection,  
12 especially in patients who are immunocompromised or  
13 around catheters, where we know biofilms play an  
14 extremely important role. So we're not looking to  
15 autoclave the patient. We're looking just to  
16 minimize harm.

17 DR. GARRETT: Sure.

18 DR. SHEHAB: In that regard, you mentioned  
19 education is important. I agree education is  
20 extremely important. Part of, I think, the success  
21 of education with not reusing sterile syringes and  
22 needles is that those products are sterile. It's

1 easier to raise the threshold about proper asepsis  
2 and proper aseptic technique when you're dealing  
3 with inherently sterile products; the physician,  
4 the nurse, the medical provider knows, "Oh. These  
5 are sterile products. I need to handle them  
6 differently." And it's difficult to educate about  
7 that importance if you're dealing with something  
8 that we've already deemed is not important to be  
9 sterile, so use it any which way.

10 That's part of the reason we're trying to  
11 elevate the conversation about these products,  
12 because we do have a higher standard in the OR. We  
13 have a higher standard around dialysis catheters  
14 and in other areas that we use these. So education  
15 can only go so far.

16 It can only also go so far for single-use  
17 products used in the OR because that's not where  
18 the evidence tells us we see extrinsic  
19 contamination. We see extrinsic contamination  
20 mostly with multiple-use products used outside of  
21 the OR. So now we're talking about a whole  
22 different set of education, and there may not even

1 be a checklist. And if we're talking, again, about  
2 products that are not sterile, how do you explain  
3 the importance of treating them aseptically? Does  
4 that make sense?

5 DR. GARRETT: Yes. It absolutely makes  
6 sense.

7 DR. SHEHAB: It becomes a challenge to  
8 education. And I know you know those challenges  
9 very well in this field. So that's what we're  
10 trying to explore, is can we raise the standard for  
11 these products in a way that doesn't compromise  
12 their availability, that doesn't compromise their  
13 effectiveness? Because those aren't the things  
14 that we are arguing here.

15 So it becomes a different conversation about  
16 education that we have to have, and maybe one  
17 that's outside the OR and outside of single-use  
18 products. And in that regard, have you or have  
19 manufacturers, from your understanding, had a  
20 challenge producing single-use products because of  
21 the myriad of uses, including off-label uses, that  
22 might be in existence out there? Is there a

1 challenge to moving these products more into the  
2 single-use field?

3 I'm just wondering why there aren't more  
4 products in single-use form, which would mitigate a  
5 lot of the extrinsic contamination concerns.

6 DR. GARRETT: Absolutely. So I think you  
7 asked three questions, so I just want to make sure  
8 I got them all. The first was about the data  
9 source. You also asked a question about education  
10 outside of the OR. And I think that the third  
11 issue was really basically making sure that we move  
12 or acknowledge the value of a single use.

13 Is that fairly accurate?

14 So I happen to work very heavily with your  
15 division at CDC, so I'm very familiar with the NHSN  
16 dataset. And I think that CDC has made tremendous  
17 strides in moving towards looking at more public  
18 reporting, which I certainly support. I think  
19 transparency in healthcare is something that we  
20 should all demand as consumers of the service.

21 I do think that there's opportunity there.  
22 I just came back from the United Kingdom, and they

1 have a tremendous movement towards transparency in  
2 looking at surgical site infections and also making  
3 sure the definitions are very clear.

4           So I agree with you. I think we have  
5 opportunity to improve the data. I think we have a  
6 lot of data now that we're continuing to filter to  
7 and really pull out some best practices. So that's  
8 kind of my thought on the dataset.

9           As it relates to outpatient use, I think  
10 that you're seeing a tremendous movement. My  
11 procedure was done in an outpatient setting in a  
12 dermatologist's office by a medical assistant. She  
13 was the one that did the prep. The physician did  
14 not do the prep, had no idea how to do the prep,  
15 and that's fine.

16           But I do know that the medical assistant  
17 actually, when she pulled the antiseptic out,  
18 looked at it. It was a single-use antiseptic. She  
19 studied the instructions for use. Now, whether or  
20 not she did this because of, obviously, what I do  
21 for a living. That's a whole different story. But  
22 I do know she took extra care and attention to

1 describe to me, as the patient, what she was doing,  
2 what the importance of the skin antiseptics process  
3 was. And then she provided wound care instructions  
4 afterwards.

5 I think that's a rarity to the rule. I  
6 think we have tremendous opportunity to partner  
7 with not just the FDA, but also the CDC and other  
8 scientific organizations to improve the quality of  
9 education in those settings. And you have to think  
10 about who is the audience? It may be a medical  
11 assistant. It may be a certified nursing  
12 assistant. It may not be somebody with more  
13 advanced skill. And so, I think that's something  
14 we have to consider, about what is the audience in  
15 which -- might be using these antiseptics.

16 I think the third issue that you brought up,  
17 PDI, we make single use. We do not make multi-dose  
18 things. And I feel very strongly that when you  
19 have that extra layer of, I guess, additional risk,  
20 it is concerning. And so I think that antiseptics  
21 personally should move more towards that  
22 single-use, single-patient dispensing system to

1 eliminate additional risk.

2 Sorry. Lots of questions.

3 DR. FURNESS: Dr. Leonard-Segal?

4 DR. LEONARD-SEGAL: Thank you for your  
5 presentation. It was very interesting.

6 DR. GARRETT: My pleasure.

7 DR. LEONARD-SEGAL: I think that I'm  
8 wondering, with all the education that's already  
9 out there -- and it seems like there's a fair  
10 amount of educational opportunity out there -- how  
11 did we get into the setting where people take these  
12 products and dilute them, add water to them, or  
13 sometimes non-sterile water -- I don't know what  
14 they're adding to them -- and then use them?

15 We've learned that this happens at dialysis  
16 centers and probably at a lot of other settings.  
17 And maybe, if there were no multi-use products  
18 available, this wouldn't happen. I don't know if  
19 it would or it wouldn't. But how do we get there?  
20 And is there anything going on now that's educating  
21 people not to do this? We certainly don't have  
22 data that says that these products work that way.

1           So how did that happen? It seems like such  
2 a huge educational challenge if people are still  
3 doing it.

4           DR. GARRETT: Right. I think your questions  
5 are extremely important. And, as I mentioned  
6 before, the concept of outpatient care has so  
7 significantly changed just in the last five years.  
8 We're dealing with so much more care that's more  
9 sophisticated outside of the four walls of the  
10 hospital.

11           You mentioned dialysis. I use that as a  
12 perfect example. I happen to be on the Infection  
13 Control Subcommittee for the National Renal  
14 Administrators. This is a tremendous challenge for  
15 them. They are saying that we have staff members  
16 in our institutions that are inappropriately using  
17 these products, and other products, and drugs, that  
18 are technicians.

19           It's so rare to actually find a nurse in a  
20 dialysis center. You may have one nurse there and  
21 multiple technicians. And so, I think that you  
22 have to look at the potential users and appliers of

1       these antiseptics and say, "What background do you  
2       have? What skill set do you currently have? What  
3       are the educational gaps?" And that's actually a  
4       program that's being developed right now to address  
5       that in the dialysis setting to say, "If you're  
6       going to be a dialysis technician, these are some  
7       of the basic principles of antiseptics that you must  
8       follow, an aseptic technique."

9                So that might be one example. I think  
10       there's an opportunity to take that type of model  
11       and bridge it outward in the other outpatient  
12       settings that you mentioned.

13               DR. LEONARD-SEGAL: Just in follow-up to  
14       that, I mean, I don't think that it seems that one  
15       would need to be a nurse or another kind of a  
16       healthcare provider beyond a technician to  
17       understand that one isn't supposed to dilute these  
18       products. And since it is common practice, I  
19       wonder if there is miseducation going on in a  
20       setting that we don't currently understand, where  
21       people are being taught to do this and aren't just  
22       doing it serendipitously.

1 DR. GARRETT: Right.

2 DR. LEONARD-SEGAL: Is that something that  
3 you know anything about?

4 DR. GARRETT: I am not personally aware, so  
5 I don't want to speak out of turn on that. I'm not  
6 personally aware of any education that would advise  
7 that, nor am I familiar with a tremendous amount of  
8 practice that does that. I certainly have heard  
9 about that in private physician practices and also  
10 in dialysis settings, as you mentioned.

11 In some of these environments, where  
12 turnover and care delivery cost is an important  
13 priority, I think that we need to transform that.  
14 And I think that's what value-based purchasing is  
15 doing, to say that we need to focus more on  
16 outcomes and doing the very best care for our  
17 patients. And I think that it doesn't matter who  
18 the provider is. We do need to place more emphasis  
19 on the appropriate use of these products and  
20 following instructions for use because, certainly,  
21 if the manufacturer's instructions do not advocate  
22 that, then you're adversely affecting the efficacy

1 of that product, as approved by the FDA. And so, I  
2 think we have more opportunity there.

3 DR. FURNESS: Thank you again, Dr. Garrett.

4 DR. GARRETT: Thank you.

5 DR. CHANG: Sorry. I have one more  
6 question.

7 (Laughter.)

8 DR. CHANG: Thanks for coming back to the  
9 podium. Earlier, we heard from Sage about the  
10 technical challenges associated with terminally  
11 sterilizing CHG. And I don't know which products  
12 that PDI makes, but I'm certain that you market  
13 alcohol products.

14 DR. GARRETT: We do

15 DR. CHANG: Yes. But what about povidone  
16 iodine products?

17 DR. GARRETT: We do.

18 DR. CHANG: So have you communicated with  
19 your manufacturing colleagues in the firm as to  
20 what challenges would there be for sterilizing  
21 these products?

22 DR. GARRETT: I am aware of challenges. To

1 be honest with you, I could not speak to those  
2 efficiently. So if that was an answer that you'd  
3 like some clarification to, I could get the  
4 appropriate colleague to do that. My background is  
5 in the clinical affairs arena, but I can certainly  
6 get you an answer to that question.

7 DR. CHANG: Thank you.

8 DR. GARRETT: No more questions?

9 (No response.)

10 DR. FURNESS: Thank you.

11 DR. GARRETT: Thank you.

12 DR. FURNESS: At this time, I'd like to call  
13 Dr. Jennifer Yttri.

14 **Presentation - Jennifer Yttri**

15 DR. YTTRI: I'm Dr. Jennifer Yttri, and I am  
16 speaking today on behalf of the National Research  
17 Center for Women and Families. Our organization  
18 does not accept funding from drug or device  
19 manufacturers, so I have no conflicts of interest  
20 in this matter.

21 Our non-profit research center includes  
22 scientists, medical, and public health experts who

1 analyze and review research on a range of health  
2 issues. I have a doctorate in immunology from  
3 Washington University in St. Louis.

4 In addition to conducting research and  
5 publishing our findings in medical journals, we  
6 provide objective and understandable information to  
7 patients, healthcare providers, and policymakers  
8 through briefings, continuing medical education,  
9 testimony, and other materials, and formats.

10 We have great respect for the FDA, and  
11 that's why our center's president is on the board  
12 of directors of two non-profit organizations,  
13 focused on providing additional resources to the  
14 FDA, the Alliance for a Stronger FDA and the  
15 congressionally-mandated Reagan-Udall Foundation.

16 Contamination of antiseptic products, we all  
17 realize, is a serious public health concern. High-  
18 profile cases such as the Triad Group's high risk  
19 recall of alcohol prep pads following the death of  
20 a child in Texas serve as warnings for the most  
21 severe cases. But even lower-risk recalls have the  
22 potential to severely harm patients. It is

1 imperative to take measures now to prevent future  
2 outbreaks.

3 Antiseptic-resistant microbes are not  
4 something that consumers think about. Consumers  
5 and physicians may not be aware that most  
6 antiseptic skin preparation products are not  
7 sterile, as some of us have admitted today.

8 Even if told, the associated risk might not  
9 be understood. If a product is intended to clean  
10 skin as an antiseptic, the logical conclusion is  
11 that contaminants are removed. They rely on the  
12 FDA to make sure that these products are maintained  
13 as safe.

14 Additionally, there is a large level of  
15 variance in the ability to detect or minimize  
16 potential contamination, especially at home and  
17 outside the hospital. It is challenging to  
18 maintain aseptic conditions, sterile water, and  
19 sterile containers.

20 Therefore, I think the FDA should focus on  
21 strategies that would improve manufacturing and  
22 outreach to prevent future outbreaks caused by the

1 use of antiseptic products.

2           There are several steps the FDA can take to  
3 better insure the safety of consumers who are  
4 exposed to antiseptic preoperative skin preparation  
5 devices. First, we support the recommendation of  
6 the August 2009 advisory committee in ensuring that  
7 all antiseptic preoperative skin preparation  
8 products are held to current good manufacturing  
9 practice standards. Sterile and non-sterile  
10 products have both been part of major recalls. So  
11 sterilization alone would give a potentially false  
12 sense of security to healthcare professionals and  
13 consumers.

14           The FDA has to strengthen monitoring of  
15 manufacturing facilities to ensure GMP compliance.  
16 Routine end-of-manufacturing testing for microbes  
17 should be required, and the FDA should also update  
18 their acceptable, non-sterile criteria.

19           More advanced screening processes have been  
20 developed that can detect lower levels of bacterial  
21 organisms than traditional cultured techniques.  
22 And the list of specified microorganisms to test

1 for needs to include any that have been associated  
2 with contamination outbreaks. By taking the steps  
3 to effectively monitor contamination during the  
4 manufacturing process, the number of outbreaks can  
5 be significantly reduced.

6 Second, the FDA should remove ineffective  
7 antiseptic products from the market. For instance,  
8 benzoylcholine chloride-containing products have  
9 been recalled at high rates in comparison to other  
10 antiseptics. But these products are not currently  
11 approved by the FDA for use as an antiseptic. It  
12 seems that these products are actually causing more  
13 harm than benefit to patients. If it cannot be  
14 used appropriately, it shouldn't be used at all.

15 Third, as extrinsic contamination counts  
16 for the majority of contamination outbreaks, the  
17 FDA should require product packaging that would  
18 reduce extrinsic manipulation. We recommend that  
19 all products intended for use at home or in an  
20 outpatient facility be made as sterile as possible.  
21 These products should be packaged as single use and  
22 pre-diluted to the correct concentration so as to

1       avoid things like contamination from non-sterile  
2       water.

3               Methods for maintaining sterility should be  
4       as simple as possible, and the FDA should also  
5       require easy-to-understand instructions on how to  
6       appropriately use these products, including  
7       appropriate storage, any dilution or mixing -- none  
8       is needed -- and how to apply them appropriately.

9               Finally, while the majority of outbreaks  
10       seem to be related to extrinsic contamination,  
11       intrinsic contamination introduced during the  
12       manufacturing most likely accounts for a greater  
13       number of contaminated products on the market.

14              Large-scale recalls may sometimes be due to  
15       improper storage, but hundreds of millions of  
16       packages have been recalled in recent years because  
17       of poor manufacturing. Many of the antiseptic  
18       products being discussed today are cleared through  
19       the 510(k) process, and inspections and other  
20       monitoring are essential, but unfortunately are  
21       rare in the 510(k) process.

22              The FDA should require special controls such

1 as inspection of the manufacturing process prior to  
2 market release, submission of pre-marketing  
3 microbial testing, and maintenance of ISO and ASTM  
4 standards if available, regardless of device class.

5 Monitoring of microbial levels should also  
6 be continued as part of a required postmarket  
7 surveillance plan, rather than passively in  
8 response to serious problems. Patients are relying  
9 on you, the FDA, the regulatory agency, to protect  
10 them from contaminated antiseptic products.

11 Whether entrusting a physician to properly use an  
12 antiseptic device or using it themselves at home,  
13 most of these patients will not know if they are  
14 exposing themselves to potential harm. An improved  
15 set of guidelines for manufacturing and monitoring  
16 of microbial contamination will help reduce  
17 potentially lethal risk.

18 We urge you to help restore consumers'  
19 confidence in the FDA and in medical products sold  
20 in the United States by maintaining higher  
21 standards. Special controls are needed to keep  
22 these patients safe. Thank you.

1 DR. FURNESS: Thank you very much.

2 Questions from the panel? Dr. Leonard-Segal?

3 DR. LEONARD-SEGAL: Thank you for your  
4 presentation. I guess I have one question related  
5 to what I think I heard you say. Tell me if I  
6 misheard. I think you said the products should be  
7 as sterile as possible. What did you mean by that?

8 DR. YTTRI: What I meant is that there are  
9 certain manufacturing processes that you've heard  
10 about today, so there are limitations with the  
11 integrity of the drug products themselves, in terms  
12 of being able to sterilize them. But from our  
13 perspective, the ideal goal would be to have a  
14 completely sterile product.

15 If you're going to be using this in a home  
16 facility, yes, you are introducing potential  
17 contamination, based on your environment. But on  
18 the manufacturing level, that's where you can  
19 really limit any potential other sources of  
20 exposure.

21 So a patient itself is not going to be able  
22 to perform an aseptic technique. They're not going

1 to necessarily understand, "I should open this in  
2 this particular way," depending upon, of course,  
3 the education that we've discussed earlier.

4 What we've realized is that there are  
5 limitations to how sterile these products can be,  
6 but I think that concessions can be made in terms  
7 of the ways its packaging is done, in terms of the  
8 products within the packages, that can really help  
9 make these products safer.

10 DR. LEONARD-SEGAL: Can I follow up?

11 So as a follow-up to that, are you  
12 suggesting that, if a particular product with a  
13 particular active ingredient can be sterile, it  
14 should be sterile, but if it can't be sterile, that  
15 it should still be out there, but should be there  
16 under the best manufacturing practices that could  
17 be available?

18 DR. YTTRI: Correct. And I think, in the  
19 non-sterile case, we need to have better  
20 communication that that product is not sterile. So  
21 whether that be through labeling or education,  
22 those are both excellent options, but our current

1 practices are not really facilitating that  
2 knowledge.

3 DR. LEONARD-SEGAL: Would you make  
4 recommendations as to particular uses that would be  
5 different for the sterile versus the non-sterile,  
6 or could they all be used for the same things? And  
7 how would one choose? What advice would you be  
8 giving to a healthcare provider as to how to select  
9 one of these products, the sterile versus the non-  
10 sterile, for clinical use?

11 DR. YTTRI: I would say anything that is  
12 directly dependent upon a patient for use really  
13 needs to be in that sterile category. So if I am  
14 bringing it home, and I am treating myself or my  
15 family member is using it, if that sterile product  
16 is available, I believe that that's very important.

17 I also believe that, as we've discussed in  
18 the OR setting, it would make sense that that might  
19 be another situation where a sterile product is  
20 very important. But I think that the end judgment  
21 call should really be based on clinicians in terms  
22 of working with their patient populations.

1 DR. LEONARD-SEGAL: Thank you.

2 DR. FURNESS: Thank you very much.

3 I would now like to call Dr. Aaron Johnson.

4 **Presentation - Bhaveen Kapadia**

5 DR. KAPADIA: Hello. Good afternoon,  
6 everyone. My name is Dr. Bhaveen Kapadia. I'm  
7 here from the Rubin Institute of Advanced  
8 Orthopedics at Sinai Hospital here in Baltimore.  
9 And I want to thank the panel here for allowing me  
10 the opportunity to speak today.

11 Here are the disclosures of all the authors.  
12 So we're here to speak about whether or not  
13 antiseptic preoperative preparations require  
14 sterilization, and I wanted to focus more  
15 specifically on the process that we use at our  
16 institution alone.

17 At Sinai Hospital, we use 2 percent  
18 chlorhexidine gluconate impregnated cloths.  
19 They're disposable, single-use, ready-to-use  
20 cloths. They're a relatively easy application.  
21 Just wipe on. There's no rinsing involved with it.  
22 And it's a rapid-drying protocol as well.

1           The reason we've implemented this is,  
2 obviously, several health organizations have  
3 recommended using preoperative skin disinfection  
4 protocols either the night before or the morning of  
5 surgery. And a lot of emphasis has been put on  
6 using chlorhexidine gluconate specifically as the  
7 antiseptic of choice.

8           A study by Saltzman actually looked at  
9 chlorhexidine gluconate and compared it to other  
10 solutions such as iodine and found that there were  
11 significantly fewer positive cultures on the  
12 cutaneous site preoperatively when using  
13 chlorhexidine.

14           When looking at chlorhexidine cloth outcomes  
15 specifically, a study by Edmiston looked at  
16 2 percent chlorhexidine cloth and compared it to  
17 4 percent chlorhexidine scrubs. And what this has  
18 one was, essentially, they applied these solutions  
19 to the cutaneous sites, to several cutaneous sites  
20 preoperatively. And they subsequently cultured the  
21 skin for several hours afterwards. And what was  
22 found was that the cloth actually was capable of

1 reducing microbes for up to six hours, whereas the  
2 scrub itself was only effective for less than  
3 10 minutes.

4           There are several different applications to  
5 chlorhexidine gluconate. One of them is the shower  
6 method. What we've seen in our institution, as  
7 well as in literature, is that there's typically  
8 poor compliance with the liquid solution.

9 Furthermore, the application in the process that we  
10 use at our institution is a two-part application.

11           We recommend to our patients -- or we  
12 encourage our patients to use it the night before  
13 and the morning of surgery. And a couple of  
14 studies have actually confirmed that the two-part  
15 application actually significantly reduces more  
16 organisms than just the one-part application the  
17 morning of or the night before.

18           Furthermore, we've found that the two-part  
19 application actually helps to increase the  
20 chlorhexidine concentration on the skin more than  
21 just the one-part application itself.

22           Of course, there are concerns with

1 contamination. What are the potential sources that  
2 we can think about? Well, there's a lack of  
3 intrinsic antibacterial activity. There's  
4 incorrect mechanism of action, pathogens that could  
5 be resistant to the antiseptic agent, obviously  
6 inadequate concentration, and inadequate duration  
7 of action. Inadequate antiseptics, actually, could  
8 lead to increased risk for multi-drug-resistant  
9 pathogens as well, which is also a common concern.

10           There have been over 40 outbreaks that have  
11 been reported with contaminated antiseptics alone.  
12 Chlorhexidine has been reported to be contaminated  
13 with pseudomonas as well as a few other organisms.  
14 But if you look at the literature that's out there,  
15 a majority of them, up to 80 percent, were reported  
16 before 1990. And it seems that, based on the  
17 literature, looking through the reports, that the  
18 contamination was actually from the hospital or  
19 pharmacy itself, with the contamination of  
20 containers and water solutions as well.

21           We've seen that there have been only two  
22 reports after 2000. And what does that mean? So

1 basically we want to see what are the potential  
2 sources that we could have contamination of these  
3 preoperative solutions. Of course, you could have  
4 contaminated water sources, contaminated sources  
5 such as the cloth and material, as well as  
6 contaminated packaging from the manufacturing  
7 company itself.

8 Now, is this enough to warrant  
9 sterilization? Well, we don't believe that  
10 sterilization is necessary for preoperative  
11 antiseptic preparations. Manufacturing facilities  
12 are typically low risk for harboring multi-drug-  
13 resistant organisms as compared to hospital  
14 institutions.

15 A property control management is necessary  
16 to make sure that input materials, such as cloths,  
17 packaging, and the fluids used to dilute, are  
18 actually sourced from non-contaminated suppliers.  
19 Rigorous quality control is necessary to ensure  
20 that cloths are tested for contamination. If there  
21 are any detect contaminants, the batches are held  
22 and reported.

1           The literature has not really demonstrated  
2           that there is any iatrogenic infection following  
3           the use of preoperative scrubs. I'm going to speak  
4           more specifically on the experience that we've had  
5           at our institution.

6           We've recently just conducted a prospective  
7           randomized trial, where we've used non-sterile  
8           chlorhexidine scrubs and compared to the patients  
9           who are not using them. The protocol that we used  
10          was the night before and morning of protocol. And  
11          what we found was that there were actually six  
12          infections in the group of patients not using  
13          chlorhexidine compared to 0 in the group that did  
14          use chlorhexidine gluconate the night before and  
15          the morning of. And they can see that's  
16          statistically significant as well.

17          We believe that sterilization may add an  
18          unnecessary process to the manufacturing company  
19          and could potentially increase the cost to the  
20          patient as well as to the institution, which could  
21          prevent its widespread distribution and potential  
22          benefits of helping to reduce the instances of

1 surgical site infections.

2 Surgical site infections are obviously a  
3 tremendous burden to the healthcare institution.  
4 They cost roughly \$129,000 per year for each event,  
5 and that's just for the year. I mean, some  
6 patients have multiple re-operations every couple  
7 of years, and that can add up as well.  
8 Furthermore, the preoperative preparation  
9 application itself is a non-sterile procedure.  
10 It's dependent on the patient environment.

11 This just a couple of more reports that  
12 we've had based on our retrospective reviews of  
13 total knee arthroplasty and total hip arthroplasty  
14 patients. What we've found is that patients not  
15 using chlorhexidine had a significantly higher  
16 infection rate than patients who used the  
17 chlorhexidine preparation protocol that I have  
18 mentioned. This is for the total hip arthroplasty  
19 patients. We see this a significant reduction in  
20 surgical site infections for both cohorts.

21 The literature has demonstrated some  
22 evidence of contaminated liquids, antiseptic

1 agents; however, it's uncertain whether this has  
2 occurred intrinsically or extrinsically. We  
3 believe that it's more likely the extrinsic  
4 contamination that could occur from dilution in the  
5 hospital environment and pharmacy environment that  
6 is more likely to do that, more specifically  
7 because the manufacturing agencies themselves are  
8 at low risk for harboring multi-drug-resistant  
9 organisms.

10 The clinical evidence from our hospital has  
11 demonstrated that no patients have had infections  
12 using chlorhexidine gluconate cloths, and these  
13 are, of course, non-sterile cloths that we have our  
14 patients use the night before morning of surgery.  
15 So we're just basing this on our clinical evidence  
16 that we've had from multiple retrospective reviews  
17 as well as a recent prospective randomized study.  
18 Thank you.

19 DR. FURNESS: Thank you very much.

20 Questions from the panel? Dr. Chang?

21 DR. CHANG: Thank you so much for your  
22 presentation. And I'm very glad to have a surgeon

1 in our audience. So a quick question about your  
2 reference to the Weber paper, which came out in  
3 2007. Have you independently performed another  
4 literature search? I know that, based on the Weber  
5 paper, there were only 2 reports since 2000.

6 Have you looked to see if there are any  
7 more?

8 DR. KAPADIA: Yes. We have.

9 DR. CHANG: Did you find any?

10 DR. KAPADIA: We did not find any more in  
11 our literature search.

12 DR. CHANG: Yes. I can tell you that there  
13 are more. And also, on slide 12, you mentioned  
14 some of the studies that you have conducted at  
15 Sinai. I'm sorry. I don't think it's the study.  
16 It's the one where you presented that there were  
17 six infections from the non-chlorhexidine use  
18 group.

19 DR. KAPADIA: Yes.

20 DR. CHANG: So help me understand what was  
21 the sample size for that particular study and  
22 whether it was powered adequately to detect any

1 statistically significant difference.

2 DR. KAPADIA: Yes, absolutely. So the study  
3 cohorts are 180 patients. They're prospectively  
4 randomized into each group, and we did have power  
5 to do this.

6 DR. CHANG: Also, just as a question of  
7 general practice, now, when you have a post-  
8 operative infection, have you yourself looked to  
9 see whether the antiseptic prep products may be the  
10 potential source? Have you actually done that? Or  
11 is that a hospital policy, recommending that it be  
12 done?

13 DR. KAPADIA: That's a very good question.  
14 It's a very difficult thing to try and determine,  
15 after the fact, what was the actual contaminating  
16 solution. Obviously, most surgical site infections  
17 are from the endogenous skin flora. So it's  
18 difficult to, at that point, determine whether or  
19 not it was the preoperative preparation we used.  
20 We're just basing it on our experience that we've  
21 seen no infections in the patients that have  
22 actually used this protocol.

1 DR. CHANG: And it would be difficult to be  
2 so confident that there wouldn't be any infection  
3 outbreaks. Correct?

4 DR. KAPADIA: Correct. As I said, it's  
5 difficult to really determine that after the fact.

6 DR. FURNESS: Yes. Go ahead.

7 DR. SHEHAB: I wondered, would the knowledge  
8 that these products, antiseptics, are sterile,  
9 change your behavior in the OR? I don't know if  
10 you have any experience outside the OR using these  
11 products.

12 DR. KAPADIA: I'm sorry. Did you mean  
13 specifically in the operating room as compared to  
14 preoperatively?

15 DR. SHEHAB: I guess both, but I guess the  
16 knowledge that they're sterile; how would that  
17 change your behavior as a surgeon, maybe, if any?

18 DR. KAPADIA: I don't know that it should  
19 really change the behavior. I mean, you should  
20 definitely follow the proper clinical guidelines  
21 and aseptic technique when performing surgery as  
22 well as draping, that sort of thing, prepping the

1 patient.

2 DR. FURNESS: Thank you very much.

3 DR. KAPADIA: Thank you.

4 DR. FURNESS: We'd now like to call Michelle  
5 Stevens.

6 **Presentation - Michelle Stevens**

7 DR. STEVENS: Good morning, Mr. Chairman,  
8 panel members. I'm Michelle Hall Stevens. I'm the  
9 chief medical officer for 3M's infection prevention  
10 division. And in addition to my role at 3M, I'm a  
11 practicing pediatric infectious disease specialist  
12 at the Children's Healthcare System in Minneapolis  
13 and St. Paul, where I was their hospital  
14 epidemiologist for 16 years before assuming my  
15 responsibilities at 3M.

16 On behalf of the more than 84,000 employees  
17 at 3M and our affiliate companies, it is my  
18 pleasure to be here at this public hearing and to  
19 share our point of view on this very important  
20 issue of safety of preoperative skin antiseptics,  
21 specifically to express our opinion whether sterile  
22 or aseptic processes should be incorporated into

1 manufacturing procedures for products intended for  
2 patient skin antiseptics prior to procedures.

3 Our extensive history in research and  
4 development, and marketing successfully products in  
5 this category informs our point of view, including  
6 work with iodine povacrylex, povidone iodine, and  
7 chlorhexidine in both aqueous- and alcohol-based  
8 formulations. So I'm pleased to be able to share  
9 our experience with you this morning.

10 So from our point of view, there are four  
11 points that I want to spend time on. I'll go over  
12 these very briefly and then have a slide on each  
13 one of these. First and foremost, and without  
14 compromise, patient safety is paramount and must  
15 remain central in all of our deliberations, and  
16 discussions, and decisions related to product  
17 design and manufacturing.

18 These products are intended to reduce risk  
19 of infection and optimize patient safety prior to  
20 procedures. Therefore, any decision on future  
21 process requirements must insure continued optimum  
22 patient safety.

1           Secondly, we also believe that the FDA  
2 enforcement of current good manufacturing practice  
3 regulations is of utmost importance, and we support  
4 that wholeheartedly. Confirmation of industry  
5 compliance to GCMPs (sic) -- or cGMPs, through  
6 audits and inspections will ensure that safe and  
7 efficacious products are released into the  
8 marketplace.

9           Thirdly, decisions affecting policy,  
10 regulations, and the resulting manufacturing  
11 standards for these products must be based on sound  
12 and reproducible science. And finally, 3M stands  
13 ready to collaborate and to support effective  
14 dialogue and result in implementation of processes  
15 that will prevent contamination of these products.

16           As we have seen over the past several  
17 decades, intrinsic and extrinsic contamination of  
18 antiseptic products occurs, and this can compromise  
19 patient safety. We've talked about the Weber  
20 review, and there have been publications since that  
21 review that have identified events where  
22 contaminations occurred.

1           When looking at the iodo-4 category of  
2 antiseptics, most contamination has been intrinsic  
3 and linked to contamination of the water source  
4 during the manufacturing process. For  
5 chlorhexidine-based products, most of the  
6 contamination has been extrinsic and linked to use  
7 error.

8           Most recently, there was the Triad recall in  
9 2011. That's freshest in our mind and, in this  
10 case, the FDA investigation identified numerous GMP  
11 deficiencies, including the lack of sterilization  
12 validation, the lack of validation of a purified  
13 water system, and the lack of bioburden control on  
14 incoming components, just to name a few.

15           In most cases, the intrinsic contaminations  
16 have been linked to failure to comply with GMP  
17 requirements. In terms of extrinsic contamination,  
18 bulk multi-use prep solutions are most at risk.  
19 We've heard dialogue about these bulk preps this  
20 morning, thus far. They are very difficult to  
21 manage in terms of maintaining sterilization or  
22 adequate -- or lack of contamination due to the

1 nature of the way they're used, due to multiple  
2 users and multiple uses for these products.

3 The microbial type and level of potential  
4 contamination upon opening cannot be predicted;  
5 therefore a use-by date cannot be validated to  
6 ensure the product has not been compromised.

7 As a result, single-use applicators are  
8 considered a best practice as recommended by the  
9 Association for Perioperative Registered Nurses.  
10 Single-use preps have a much lower risk of  
11 extrinsic contamination, and they also facilitate  
12 aseptic technique compliance. Additionally,  
13 single-use applicators provide an additional level  
14 of safety in the application of flammable, alcohol-  
15 based prep solutions, due to the control of volume.

16 So because recent recalls have resulted from  
17 identified deficiencies in following GMPs, we  
18 should assess the impact, how much of an impact,  
19 there would be from implementation of additional  
20 sterile processing requirements for antiseptic skin  
21 prep products. Even if we move to requiring  
22 sterility, it won't solve the problem if GMP is not

1 followed. So that will be an important thing to  
2 consider in the dialogue and decision-making  
3 process.

4 It is also important that manufacturers  
5 define the appropriate GMP, microbial control  
6 measures based on the product design, and the risk  
7 management principles that exist. And it's also  
8 important that they work very closely with the FDA  
9 in developing this process. There's accountability  
10 on the part of the manufacturer to do this.

11 In considering any path forward, we have to  
12 recognize that technical challenges exist relative  
13 to the sterilization or aseptic fill of antiseptic  
14 solutions. Assuming there's adherence to GMP and  
15 confirmation via regulatory oversight, it's still  
16 unclear whether the additional benefits would  
17 outweigh the technical and safety risks associated  
18 with sterile processing or aseptic fill.

19 So sound science must be behind the  
20 decisions affecting policy, regulations, and the  
21 resulting manufacturing standards, particularly as  
22 it relates to the technical and safety

1 considerations for standardizing the sterilization  
2 of antiseptic solutions.

3           When considering the three methods of  
4 standard sterilization, including high heat,  
5 ethylene oxide, and irradiation, each one of these  
6 poses a significant concern when used to process  
7 antiseptic solutions.

8           For example, heat application can create  
9 safety hazards associated with flammable components  
10 and alter specifications for container closure in  
11 order to accommodate the high internal pressures  
12 that are generated, in order to prevent evaporation  
13 and avoid active ingredient degradation.

14           With ethylene oxide, reactions with alcohol,  
15 iodide, and chloride produce new degradants and  
16 highly toxic byproducts, compromising patient and  
17 healthcare worker safety if they're present.

18           Provided that the primary container closure  
19 of the prep solution is impermeable to ethylene  
20 oxide, terminal EO sterilization of a finished  
21 patient prep product remains an acceptable means of  
22 providing a sterile applicator to the end user. It

1 should not be allowed to penetrate the applicator  
2 and affect the solution internally because it can  
3 affect the solution as mentioned.

4           Irradiation of any drug product or drug  
5 solution creates a high potential for degradation  
6 of the active molecule. And for this reason, per  
7 current FDA regulation, any drug sterilized by  
8 irradiation is given a new drug status.

9           So with these challenges associated with  
10 standard sterilization, we're left with aseptic  
11 manufacturing and non-standard sterilization  
12 options to consider. And with these options, there  
13 again are multiple technical challenges,  
14 manufacturing and regulatory challenges, that would  
15 come into play with the development, optimization,  
16 and validation of these methods.

17           Aseptic filling or non-standard  
18 sterilization may be feasible in some cases.  
19 However, a number of areas should be considered as  
20 we move down this path or if we consider moving  
21 down this path.

22           Implementing one of these methods is not a

1 short-term solution and will not resolve the  
2 immediate need to address GMP issues. When adding  
3 a terminal sterilization step or aseptic fill,  
4 retrospectively, the changes in the container  
5 closure material are designed and changes to the  
6 manufacturing equipment and the facilities would  
7 need to be required and considered in that  
8 decision-making process. It's also important to  
9 understand that aseptic fill does not achieve a 10  
10 to the minus 6 sterility assurance level.

11 As a result, there must be close and  
12 interactive collaboration with the FDA in order to  
13 ensure that these approaches can be implemented and  
14 validated, to achieve the appropriate sterility  
15 assurance levels.

16 So in closing, I'd like to reiterate the key  
17 points on this very important issue. We believe  
18 that following GMPs is of paramount importance for  
19 delivering safe and effective pre-op skin prep  
20 products to the market. This would apply whether  
21 sterile or a sterility requirement was incorporated  
22 into the manufacturing process or not. This will

1 remain central.

2           FDA should continue to focus resources on  
3 confirming industry compliance with the existing  
4 GMP-required regulations. If we can assume a  
5 compliance with GMP, then the implications of  
6 additional sterilization requirements must be  
7 completely understood, confirmed, and implemented  
8 as needed, based on good science. And we recommend  
9 that the FDA initiate the formation of an FDA  
10 industry working group to address this issue.  
11 There are stakeholders beyond industry, FDA, public  
12 health, consumers, that I think may all be worthy  
13 of participating in an effort such as this.

14           Finally, 3M welcomes the opportunity to lead  
15 the way for necessary collaboration on this  
16 important patient safety issue. I would like to  
17 thank you for the opportunity to be with you today  
18 and share our points of view. And we look forward  
19 to future discussions.

20           I'd like to ask a colleague of mine to come  
21 up for the question-and-answer period, if that's  
22 all right. Dianne Gibbs will be joining me up

1 here. She's a regulatory affairs manager.

2 DR. FURNESS: Thank you very much,  
3 Dr. Stevens.

4 I think I'll lead off with the questions  
5 this time. I have a clarification point I'd like  
6 to ask about, the challenges that you brought up  
7 about irradiation. Do you mean to say that all  
8 antiseptics are subject to degradation through the  
9 irradiation pathway?

10 MS. GIBBS: In 3M's looking at these  
11 different sterilization options, including  
12 irradiation, we do find degradation, even with  
13 alcoholic solution, plain alcohol solutions.

14 DR. FURNESS: Thank you.

15 Other panelists have questions?

16 DR. LEONARD-SEGAL: Hi. Could you please  
17 elaborate on this? You looked at alcohol and you  
18 looked at what else?

19 MS. GIBBS: We have considered the effects  
20 of radiation on iodo-4s, on chlorhexidine  
21 gluconate-based solutions with and without alcohol.  
22 Per the CFR reference up there from part 310, any

1 drug that is subjected to irradiation is given new  
2 drug status because of the potential for -- there's  
3 no reproducible way that you can be assured that,  
4 that same molecule is going to cleave in the same  
5 way time and time again when exposed to  
6 irradiation. So you don't know what you're going  
7 to be left with in a reproducible manner.

8 So what makes this more complicated is the  
9 dichotomy of regulatory approaches you have within  
10 this same category. So you have the monograph  
11 products and you have the NDA products.

12 So now I'm getting a little bit away from  
13 the irradiation question, but in applying any  
14 potential sterilization modality to that product,  
15 how do you vet that out to make sure that it's  
16 appropriately validated, designed to achieve the  
17 appropriate outcome?

18 As we have seen in the Triad recall, it was  
19 both sterile and non-sterile alcohol prep pads that  
20 were recalled. And one of the FDA citations in the  
21 43 was that sterilization process was not  
22 validated. Now, interestingly enough there, you do

1 have a gamma-irradiated alcohol prep pad that was  
2 still under the monograph. So it's kind of a  
3 difficult mix of products in the way that they're  
4 regulated.

5 DR. LEONARD-SEGAL: Yes. Actually, what you  
6 describe is a complicated regulatory paradigm that  
7 applies to many, many, many types of over-the-  
8 counter drugs in --

9 MS. GIBBS: All products.

10 DR. LEONARD-SEGAL: -- many, many, many  
11 different kinds of categories.

12 MS. GIBBS: Exactly.

13 DR. LEONARD-SEGAL: But focusing on this, it  
14 sounds like you've done some sort of background  
15 work, trying to figure out what active ingredients  
16 could be amenable to sterilization versus  
17 irradiation -- I mean, via irradiation. And so,  
18 you've looked at alcohol, povidone iodine, and  
19 chlorhexidine?

20 MS. GIBBS: At a very high level, we have  
21 discounted irradiation because of the degradants,  
22 because of the degradation.

1 DR. LEONARD-SEGAL: In all of these?

2 MS. GIBBS: In all of these cases.

3 DR. LEONARD-SEGAL: -- three active  
4 ingredients?

5 MS. GIBBS: Yes. In the formulations  
6 specific to primarily iodine, alcohol,  
7 chlorhexidine gluconate alcohol.

8 DR. LEONARD-SEGAL: Okay.

9 DR. FURNESS: Dr. Furlong?

10 DR. FURLONG: Thank you for your  
11 presentation. I'm just curious about filtration  
12 methods. I'm not a microbiologist, but it seems  
13 like some of these products might be amenable to  
14 filtration without any destruction of the integrity  
15 of the product. Have you explored that option?

16 MS. GIBBS: We have done some exploration  
17 with filtration. The one thing I will say  
18 regarding filtration is that, with any microbial  
19 control that you apply to a solution -- and  
20 microbial control is important -- those  
21 methodologies that you choose should be based on  
22 product design and risk management principles.

1           So you may have a manufacturing process  
2 that, in and of itself -- there may be mixed  
3 processes, but then there may be processes that are  
4 subject to polymerization under very high heat, in  
5 which case additional sterile -- filtration  
6 wouldn't add any additional benefit.

7           So to create a list of what you must do  
8 wouldn't be applicable to all products to achieve  
9 the right end result. It really has to be an onus  
10 on the manufacturer to go through that design  
11 requirements, risk management principles, and what  
12 do you need to do to get to the end stage.

13           With that, I just want to reiterate one  
14 point that Michelle made. We've been talking about  
15 aseptic fill in the same context of terminal  
16 sterilization, and those don't achieve the same  
17 results. So I think it's important in whatever  
18 industry, FDA collaboration, for us to understand  
19 what is the end goal, because if it's aseptic fill,  
20 you're not getting to the sterility assurance  
21 level. You're getting to a contamination level of  
22 10 to the minus 3rd. And is that where you want to

1 be?

2           The technical challenges cannot be  
3 underemphasized regarding standard sterilization.  
4 So if you're looking at non-standard sterilization  
5 approaches, those approaches would need sound  
6 vetting with FDA. And because of the potential  
7 interactions of all the different formulations,  
8 there's no way that we could really even -- it  
9 would be very difficult to say, "Here's a protocol  
10 for this type of standard sterilization and what  
11 you should look for as far as degradants," or to  
12 have kind of a compendial, if you will. It would  
13 be very difficult. Plus, those non-standard  
14 sterilization modalities are going to be probably  
15 proprietary product by product.

16           DR. FURNESS: Dr. Hussong?

17           DR. HUSSONG: I have to agree that you can't  
18 just take one sterilization or sterile  
19 manufacturing procedure and apply it to all  
20 different types of drugs, antiseptics being among  
21 them. You take a large pharmaceutical  
22 manufacturer. They have hundreds of different

1 formulations and packages. And each one has to  
2 have a uniquely tailored sterilization process or  
3 sterile manufacturing process.

4 But at the same time, you have mentioned  
5 that the alcohol pads that are labeled sterile in  
6 their little foil packets are irradiated. So I  
7 think that there's an opportunity for technology to  
8 be studied and maybe moved forward. And I  
9 appreciate your offer for collaboration in that  
10 arena. The goal is a safe product, no harm.

11 MS. GIBBS: Absolutely

12 DR. HUSSONG: The question is, do we need to  
13 set a specification of sterile? And we can't do a  
14 sort of sterile or nearly sterile. It's either  
15 sterile or it's non-sterile. Now, in the non-  
16 sterile world, we can go for clean and very, very  
17 clean, but you have to set a limit.

18 Now, how we get there -- and that's the  
19 point you were making earlier about aseptic doesn't  
20 have a sterility assurance level. It has a  
21 contamination rate. That's all you can do. But we  
22 still label those products sterile. So if we can

1 work together on this, I'm sure we can get  
2 somewhere.

3 DR. FURNESS: Dr. Chang?

4 DR. CHANG: I have one question for  
5 Dr. Stevens. Since you're an epidemiologist, would  
6 you comment on how we could better fill the data  
7 gap right now as to how we better define the extent  
8 of whether there's any clinical problem.

9 DR. STEVENS: Define the problem?

10 DR. CHANG: Yes.

11 DR. STEVENS: I've thought about that, and I  
12 don't have a perfect answer. I think it would  
13 entail some collaboration with the CDC in terms of  
14 whether you could define a protocol for point  
15 prevalence testing of some sort. That could be  
16 done with participating healthcare systems and  
17 patients. It would be a big effort and would take  
18 a lot of collaboration.

19 DR. FURNESS: Go ahead.

20 DR. SHEHAB: You emphasized the importance  
21 of adhering to current good manufacturing practices  
22 in your presentation. I wondered, do you consider

1 the cGMPs as they are sufficient for delivering a  
2 safe antiseptic to the market, or is there room for  
3 improvement by way of building on those cGMPs for  
4 this specific product line?

5 DR. STEVENS: My comment or my answer  
6 related to that question is, we've not had a  
7 problem. We follow cGMPs, and we haven't had a  
8 problem with our products. So we're compliant. So  
9 we think it's important. It's part of our DNA at  
10 3M and our manufacturing facilities.

11 So I don't know, Dianne, if you have  
12 anything to add to that. The problems that have  
13 been published are related to gaps in following  
14 GMP. So that comes back to being a really  
15 important part of the process.

16 MS. GIBBS: I would just add that I don't  
17 think there's a way to write an all-inclusive  
18 regulation. So do I think that additional cGMPs  
19 need to be written? A lot of cGMPs aren't written.  
20 I mean, it's what is current practice.

21 But again, it goes back to product design,  
22 and risk management principles, and achieving the

1 spirit and intent of the GMP, so making sure that  
2 you get a safe and efficacious product to the  
3 market, whatever that may be for your product,  
4 based on its principles and design.

5 **Open Public Session**

6 DR. FURNESS: Thank you very much.

7 That is the close of the registered part of  
8 this hearing, and now we have two folks that have  
9 volunteered to make remarks during the open public  
10 session. The first speaker is Kevin Frey from the  
11 Association of Surgical Technologists.

12 MR. FREY: Good morning, afternoon. Thanks.  
13 First, I want to thank the FDA for thinking of the  
14 Association of Surgical Technologists. There is,  
15 as you know, lots of folks in the operating room.  
16 And sometimes we're kind of the hidden folks that  
17 help the surgeon out in there, so I really  
18 appreciate your inviting us here.

19 I have just a couple of comments, and I'll  
20 try and make this quick. I know a couple of folks  
21 have mentioned a lot about education and training.  
22 Obviously, I'm kind of speaking very specific to a

1 specific profession. But I'd also like to  
2 emphasize, in a way, that where education goes in  
3 our accredited programs, which may not occur in  
4 some other education and training programs, is we  
5 learn the skin prep, both didactic lab or mock OR,  
6 and in clinical rotation, and then obviously  
7 practice it in the operating room on a daily basis,  
8 a practitioner.

9           Some folks may learn the skin prep right  
10 then and there on a live patient. Obviously, to  
11 decrease error, it helps to know didactic combined  
12 with working, practicing it in a mock OR or lab,  
13 and obviously then moving into a clinical rotation  
14 setting.

15           So that just kind of speaks to some of the  
16 education and training that maybe could be  
17 emphasized. Some folks out there may have someone  
18 standing there that's been obviously doing skin  
19 preps for a long time, but they're training them  
20 right then and there on a live patient, maybe doing  
21 mock training, those type of things, and decrease  
22 the error in emphasizing that maybe in some of the

1 guidelines that come out of this meeting.

2 Another individual had mentioned about  
3 volume prep -- I forget -- the volume prep  
4 solution. Obviously, I mean, I think it'd be hard  
5 to call on a manufacturer to come up with -- say  
6 you're using a single-use prep. This one has  
7 12 ounces, but now, this one has a gallon. So  
8 we'll just kind of sling it over our shoulder and  
9 then we'll prep the patient.

10 You know, obviously, even though it  
11 increases the costs, you can open up another single  
12 prep solution, start at the skin incision site, and  
13 go from there. So I think that's just a comment on  
14 that.

15 Another comment on expiration date. In my  
16 experience, things in the OR have expiration dates,  
17 most single-use items and such. And I think it's  
18 important, again, for that to be emphasized, that  
19 there should be an expiration date, even on the  
20 single-use products. We have very large healthcare  
21 facilities that are given price breaks when they  
22 buy in bulk, and those items are sitting on the

1 shelf. And so, I think, from my end, I always  
2 check everything we use in the OR for an expiration  
3 date. So I think it's just important for the  
4 single-use products.

5           AST. I submitted this document, our  
6 recommended standards of practice for skin prep of  
7 the surgical patient, but we are undergoing a  
8 revision of it. And I just wanted to quickly say,  
9 we advocate the one-step, single-use skin prep.  
10 Reason being is, if Dr. Thomas is still in here, I  
11 remember the sticky mats also.

12           I also remember the days when we opened up a  
13 tray and poured out the paint solution and the  
14 scrub solution. Obviously, single use, it's  
15 obvious. The more steps you decrease in the OR,  
16 the less chance for human error. So we're  
17 advocating a single-use skin prep. It decreases,  
18 obviously, the human error factor.

19           The last part of this, which I know is kind  
20 of more controversial, and I know a couple of those  
21 surgeons have mentioned this, as related to the  
22 GMPs, it's obviously very hard to trace, as someone

1       said, an SSI.

2               There's so much, as we all know, that goes  
3       on in surgery. You have an open wound, obviously,  
4       and everything. So it's very hard to go backwards  
5       and figure out where did the infection occur.  
6       There's some instances you can. You can come right  
7       out and say, "Oh. The surg tech screwed up and  
8       contaminated an instrument." But there are times  
9       when you just cannot figure it out.

10              So listening to this whole conversation, I  
11       would go two ways with this. One, it sounds like,  
12       emphasizing in guidance documents the good  
13       manufacturing practices, and if that needs to be  
14       beefed up a little bit more; but also, due to some  
15       data or maybe stats not totally there, working with  
16       obviously the FDA and the CDC to develop more  
17       studies and such to maybe produce stats that  
18       possibly could support sterilization of the skin  
19       prep products.

20              I'm sorry. One last thing. Also, don't  
21       forget, though, too, surgeons, not all -- and maybe  
22       this could be something in a guidance document,

1 too. As we know, in surgery, we build layers. I  
2 tell my students we build layers. So when we're  
3 draping, especially like in orthopedic procedures,  
4 there are drapes upon drapes upon drapes to create  
5 those barriers.

6 Now, often, some surgeons use what's called  
7 the Ioban drape. They impregnated iodine into the  
8 drape. So that also covers that skin that's  
9 showing through the fenestration of the drape and  
10 creates that one more barrier.

11 So if, by chance, you unfortunately used a  
12 skin prep solution that maybe had some  
13 contamination, you're at least doing some  
14 other -- the surgeon, along with the other surgical  
15 team, is doing some other steps to prevent that  
16 endogenous flora getting into the wound, and maybe  
17 consider adding onto guidance documents, promoting  
18 these other steps as a standard. Thank you.

19 DR. FURNESS: Thank you very much.

20 Questions from the panel? Dr. Leonard-  
21 Segal?

22 DR. LEONARD-SEGAL: Thank you for that.

1 Earlier today, we heard someone speak about  
2 checklists. Just out of curiosity, does your OR  
3 have a checklist on how to do these skin preps and  
4 how to work with these products? And if you do,  
5 what's on it? And if you don't, could you also  
6 tell us a little bit about what you think should be  
7 on there, based upon what you see as the largest  
8 maybe frequency of errors that are made in the OR  
9 skin prepping?

10 MR. FREY: First, I just want to say one  
11 thing. I work full-time for the Association of  
12 Surgical Technologists. I work in a couple of  
13 hospitals back in Colorado on just a PRN basis, and  
14 they're fairly small, like surgical centers. So  
15 I'm kind of speaking from both sides here.

16 The surgical centers that I work at,  
17 outpatient centers, don't have a checklist. AST  
18 advocates a checklist. We don't have one put  
19 together yet, but we're working on it, as an  
20 example. I don't know if that helps.

21 DR. LEONARD-SEGAL: Yes. And also, from  
22 your observation, what you know, what do you think

1 are the most common errors that are made, that  
2 might lead to extrinsic contamination in the  
3 operating suite?

4 MR. FREY: Okay. Let me think here. Can I  
5 get back to you on that? No. That's a hard one.

6 DR. LEONARD-SEGAL: I don't mean to put you  
7 on the spot. I'm just trying to gather some  
8 information.

9 MR. FREY: Yes. No. That's all right.  
10 Yes. It's a hard one. I mean, I guess, like you  
11 said, overall, the human error bit and where all  
12 that education and training comes in, when they're  
13 doing the open-gloving, those type of things,  
14 watching those type of things to make sure that  
15 contamination is not occurring at that point.

16 The skin prep itself, I don't want to  
17 simplify, but most people -- I think one gentleman  
18 said -- I think it may have been you, that even  
19 from nurse down to technician, it's pretty easy to  
20 train someone and tell them, "You start at the skin  
21 incision site and you go out," that type of thing,  
22 don't touch this; don't touch that.

1           So I think it's some of the things prior,  
2 leading up to that, proper application of putting  
3 on -- when you're open-gloving, those type of  
4 things. I don't know if that makes sense.

5           DR. LEONARD-SEGAL: Sure. Thank you.

6           DR. FURNESS: Thank you very much.

7           MR. FREY: Thank you.

8           DR. FURNESS: Our last speaker will be  
9 Patrick Carney from Public Citizen.

10          MR. CARNEY: Yes. I used to be involved in  
11 the industry, so I'm here for a personal reason  
12 now. I recently had two of my family that had  
13 surgical procedures done, so I'm aware of all this,  
14 most of it. So I have a question for the industry.  
15 I used to be in it, so my question is simple.

16                 There was a flammability issue with my  
17 brother-in-law. He was second-degree-burned by one  
18 of the products mentioned here. I won't mention  
19 the hospital because it's not important. I know  
20 that is an issue that wasn't mentioned today. I  
21 think it should be mentioned.

22                 Also, I think there was a lot of talk

1 about -- my aunt's having surgery. She has to have  
2 a peri-wash shower. She said, "Wait a minute.  
3 They told me I can't use this stuff around my eyes,  
4 around my ears. I can't use it on my urogenital  
5 area. I'm supposed to get a gynecological prep.  
6 Why am I using it?" The question. I said -- I  
7 didn't have an answer for her. I said, "Well, it's  
8 the policy, so you have to do it."

9 So my question is, as a public citizen, what  
10 are the manufacturers and the FDA doing to provide  
11 something that is non-flammable and non-toxic?

12 That's the only question I have. I'm not here to  
13 defend my former company or any company. I'm just  
14 saying, I think it's like, no one ever said there  
15 would be an iPhone. There is one now. Why can't  
16 there be made a sterile product that is not  
17 flammable, that is not toxic, that can be used on  
18 an open wound? Why? My question. Thank you.

19 DR. FURNESS: Thank you. Dr. Leonard-Segal?

20 DR. LEONARD-SEGAL: Well, thank you for your  
21 comment. We have focused today's meeting on the  
22 sterility issue. FDA, however, has been very

1 actively involved over the last several years,  
2 related to flammability issues, particularly with  
3 alcohol-containing skin preps. And FDA has been  
4 involved through their Safe Use initiative in  
5 meeting with all kinds of stakeholders to address  
6 this issue from everything, via educational  
7 campaigns, trying to enhance checklists in  
8 operating suits.

9 We have upgraded our labeling on products  
10 that contain alcohol preps to warn end users that  
11 they have to let these preps dry completely and  
12 that they need to avoid using them in areas where  
13 hair could get wet because that markedly extends  
14 the drying time of these products. There are  
15 warnings about using them near electrocautery  
16 devices that could cause them to burn.

17 We think that issues related to OR fires are  
18 very significant, although very rare. But when  
19 they happen, they can be devastating. And we're  
20 quite well aware of them. And we are working from  
21 all different kinds of perspectives to try to  
22 eliminate this problem if at all possible.

1           But today's meeting, we can't talk about all  
2 different topics. Right. So today's meeting is on  
3 the sterility issue and trying to decrease the risk  
4 of contamination, and to help people be as safe as  
5 possible when they have procedures using these  
6 products.

7           MR. CARNEY: (mic off - inaudible). Given  
8 that as an assumption, it is safe. And I think the  
9 next point is -- I'm sorry. The next point is make  
10 sure the product formulation is safe for where it  
11 is intended to be used. And based on two  
12 experiences in the last month, that was not the  
13 case.

14           So this is -- I'm talking real-world  
15 experiences to me. It just happened. How am I  
16 supposed to -- what am I supposed to do for a  
17 urological gynecological prep, and there is none?

18           My aunt. She's 79 years old. She needed a  
19 peri-op shower. She's a little obese. How do you  
20 get her clean? You got to wash her. It said don't  
21 wash your eyes. You got to wash something. What  
22 does she do? She has a dilemma. She called me. I

1 said, "I don't know. Just use some Ivory soap, I  
2 guess. I don't know."

3 I'm not being facetious. I'm just saying,  
4 at least she got something clean, some dirt off of  
5 her. She had to get some of the contaminants off  
6 her.

7 That's a personal point. That's why I took  
8 the time to come here today, because I think it's  
9 important for my own personal family, because if I  
10 have surgery, I damn well want to know what I'm  
11 getting put on me; I can tell you. If it's  
12 flammable, somebody better let it dry.

13 DR. LEONARD-SEGAL: Thank you. Thank you  
14 for your comments. We hear them loud and clear.

15 MR. CARNEY: Thank you. Appreciate it.

16 **Adjournment**

17 DR. FURNESS: And that brings to a close  
18 today's session. So the presentations, as I said  
19 before, will be posted to the docket after the  
20 meeting, and the transcripts will be available in  
21 approximately 30 days.

22 I wanted to reemphasize, we encourage

1 everyone to submit your comments as well as  
2 supportive data to the docket, and it will remain  
3 open until February 12th of 2013. Thanks very  
4 much. I think we had a great discussion and  
5 dialogue today. Thank you to all the presenters  
6 and to our panel of distinguished speakers today.  
7 Thank you.

8 (Whereupon, at 12:24 p.m., the meeting was  
9 adjourned.)

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