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
## CONTENTS

<table>
<thead>
<tr>
<th>AGENDA ITEM</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welcome, Introductions and Opening Presentation</td>
<td>3</td>
</tr>
<tr>
<td>Scott Furness, PhD</td>
<td></td>
</tr>
<tr>
<td>Session I</td>
<td></td>
</tr>
<tr>
<td>Joyce Ryan, DNP, NP-BC RN</td>
<td>13</td>
</tr>
<tr>
<td>Tim Manthei</td>
<td>25</td>
</tr>
<tr>
<td>John Thomas, MS, PhD</td>
<td>55</td>
</tr>
<tr>
<td>J. Hudson Garrett, PhD, MSN, MPH, FHP</td>
<td>83</td>
</tr>
<tr>
<td>Session II</td>
<td></td>
</tr>
<tr>
<td>Jennifer Yttri, PhD</td>
<td>125</td>
</tr>
<tr>
<td>Bhaveen Kapadia, MD</td>
<td>135</td>
</tr>
<tr>
<td>Michelle Stevens, MD</td>
<td>146</td>
</tr>
<tr>
<td>Open Public Session</td>
<td>165</td>
</tr>
<tr>
<td>Closing Statement/Adjournment</td>
<td>177</td>
</tr>
</tbody>
</table>

---

*A Matter of Record*

(301) 890-4188
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.
today.

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

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

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

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

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

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

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

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

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

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

Please make sure you let us know if you're planning to do that, and there's a sign-up sheet at
the back of the registration desk. And we would
ask you to notify us of your intent prior to coming
back from the scheduled morning break.

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

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

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

Our goal for today's meeting is to have a
fair and open forum for individuals to present
their views without any interruption. I'll be
announcing the speaker's name and ask the speaker
to come to the podium. At the end of the speaker's
presentation, the panel members will be given time
to ask these speakers questions.

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

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

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

Contamination of patient preoperative skin
preparation occurs by two known mechanisms. The
first mechanism I would point to would be the
mechanism of intrinsic contamination. This occurs where microorganisms gain entry to the product during the manufacturing process and remain viable upon storage of the drug product. Avenues of entry for these bacterial contaminants have been found in pharmaceutical water supplies as well as from non-sterile antiseptic manufacturing environments.

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

With respect to our existing authority to address this concern, our current good manufacturing practice regulations require manufacturers to have appropriate procedures in place to prevent the presence of objectionable
organisms in drug products that are not manufactured as sterile. However, it should be pointed out that the microbial limits test that's currently in use by most manufacturers, which is actually a USP test, may not detect very low levels of microbial contamination. And even more significantly, it does not screen for the types of intrinsically antiseptic-resistant organisms that we've already seen in these products, such as Burkholderia cepacia, as well as Bacillus cereus.

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

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

Consequently, we have decided to hold this public hearing today to hear from interested
parties, including healthcare facilities, healthcare professionals, manufacturers, consumers, and others about ways that these issues might be addressed. And we would like feedback on the following questions, which are divided into two separate groups addressing intrinsic and extrinsic contamination.

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

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

Question number 3, are manufacturers currently producing or planning to produce sterile patient preoperative skin preparations? And if so, how will that be achieved, through terminal sterilization or some validated aseptic processing? We're very interested to hear about those different methods that could potentially be used.
Question number 4, what are the technical challenges in producing these sterile patient preoperative products? For a given manufacturer, how long will we expect such a switch to occur in order for this change to take place? And how could we possibly expect the market to change if all these products were to be required to be manufactured as sterile?

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

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

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

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

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

Question number 4, should patient preoperative skin preparations be marketed in single-use containers only? And what would be the technical and practical challenges associated with that?
Question number 5, can product labeling, for example, such as discard after a certain number of days after opening, be used to reduce the risk of adverse events associated with extrinsic contamination for these multiple-use products? And how could a discard-by date be established for these individual products? And how meaningful would it be in the context of current practices?

Lastly, question number 6, are healthcare facilities or other entities providing information or training on the safe use of these multiple-use patient preoperative skin preparations?

So with that, these are the questions we're very interested in hearing from each of the speakers. And with that, I will begin the presentation portion of this open public hearing. And I would like to call Joyce Ryan and Tim Manthei from Sage Products, Incorporated.

Presentation – Joyce Ryan

DR. RYAN: Good morning and thank you. I am Joyce Ryan, nurse practitioner. And I practice evidence-based medicine in clinical practice,
similar to all of you who are healthcare providers out there. I am also the director of clinical affairs at Sage Products. And Sage manufactures medical devices, including the 2 percent CHG cloth, and the products address hospital-acquired conditions. And that's pretty consistent with a preventive healthcare model.

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

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

So for those out there who are not healthcare providers, what is evidence-based
medicine? And evidence-based medicine is the conscientious, the explicit, the judicious use of current best evidence in making decisions about the care of our individual patients or patients as a group. It also allows for individual healthcare providers to utilize their clinical experience along with the best evidence from a systematic literature search. And evidence-based medicine also seeks to assess the strengths of the evidence while weighing the risks and the benefits of any type of treatment.

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

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

There is general agreement in healthcare
today that prevention is more effective than treatment. And healthcare providers are responsible for providing the best evidence in treating their patients utilizing evidence-based medicine.

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

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

So there has been a call to action for the elimination of hospital-acquired infections, and that has been by certain organizations, including APIC, SHEA, IDSA, as well as the CDC. These groups have put forth a consensus statement that's been
issued by these groups, and there is a plan for the
reduction of hospital-acquired infections. And
that will be done through the promotion of
adherence to evidence-based practices, and that
will be done through partnering and education.

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

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

Some of these organizations are the CDC,
SHEA, and AORN. And what they say specifically
with regards to the guidelines -- we can look at
the CDC recommendations and they require that
patients shower or bathe with an antiseptic agent
on at least the night before the operative day.
And we know that, according to a study by Mangram, where they utilized a clean versus a sterile surgical skin prep kit, there was really no benefit one versus the other.

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

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

According to an article in 2011, the comment is made that additional use of a cloth impregnated with chlorhexidine is more effective than simple showering. And that's fairly consistent with SHEA's recommendation that the chlorhexidine should remain on the skin.
So let's talk a little bit about the background. What are these preoperative skin preparations? And these preoperative skin preparations are over the counter, topical, antiseptic drug products, and they are used to reduce the bioburden on patients' skin prior to procedures, surgeries, and injections. And these products are used within healthcare facilities in a variety of settings, and they are also used in the home.

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

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

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

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

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

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

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

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

So envision this scenario. You have a patient who is at home the night before their surgery. So they or a family member is assisting them apply the pre-op preparation based on the recommendations. And they are doing it in this fashion.
They are applying it in a non-sterile way. Hopefully, their hands are clean. Or they could potentially be in the shower, applying the pre-op preparation with non-sterile water from the shower, from a non-sterile showerhead.

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

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

A study comparing clean and sterile surgical prep kits revealed that there was no difference in residual microbial skin flora between patients
prepped with each type. There was no difference.

I think it's also important to note at this time

that non-sterile does not imply contaminated. It

implies that it's clean.

So it's important now to look at

contamination risks. And let's focus on them. And

thankfully, they are rare, but they can't be

minimized. There have been approximately 40

reports of contaminated products both intrinsically

and extrinsically. And certainly, any time a

patient has been harmed or there has been a

potential for harm, that needs to be addressed.

What we also know, though, is that

48 million procedures are performed in the U.S.

each year. Or we could say, since 1960, over

2 billion procedures have been performed. So if

there is 48 million procedures performed each year,

that means there is 48 million patients who are at

risk for a surgical site infection due to their own

endogenous skin flora. So it is imperative that we

reduce the bacterial burden on the patients' skin

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

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

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

These next slides, when we discuss the
challenges, I'm going to hand over to my colleague, Tim Manthei.

Presentation – Tim Manthei

MR. MANTHEI: Thank you, Dr. Ryan.

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

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

As you know, there is several different ways to manufacture sterile products. One of them is terminal sterilization. Steam sterilization for CHG is not practical. CHG starts to degrade at
about 40 degrees C and, in order to sterilize with
steam or an autoclave, you need to be at least
100 degrees C. So the molecule starts to degrade.

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

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

Another method is aseptic manufacturing.
There's very specific requirements for aseptic
manufacturing. In fact, the agency put out a
guideline, aseptic manufacturing of sterile drugs,
to help the overall industry understand what those
specific items are. And any time you manufacture
products aseptically, you have a sterile core, and
then all the pieces and parts, all the components,
have to come into that sterile core. And they have
to be sterilized.

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

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

EtO sterilization, we talked about, really
not practical. And aseptic processing with the varied components that we have today really does not lend itself to manufacturing, either.

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

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

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

We found if you use USP purified water or
better, that's where you should start with your bulk solution. Your facilities. We designed a facility that has engineering controls. It's an unclassified facility, but it has all the controls of a normal manufacturing pharma manufacturing facility: HVAC, walls, floors, ceiling, designed for cleanliness.

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

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

(No response.)

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

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

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

So, in summary, we all need to use evidence-based practice. That's standard for healthcare providers. But what we know now is that the non-
sterile products that are on the market work, and
the literature suggests that they work.

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

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

So we all understand why we're here today.
We are all motivated to protect patients and make
sure that they are kept safe. As a nurse, I am
intrinsically motivated to keep patients safe and offer the best care that I can. And as the agency and as manufacturing companies, they are motivated in the same way as well.

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

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

Perform a risk analysis because the effort to reduce the risk really should be commensurate with the frequency of the problem. So as healthcare providers, as the agency, as
manufacturers, it's important I think to plan and put our efforts where we can have the greatest impact for positive patient outcomes. Thank you.

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

Dr. Chang?

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

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

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

DR. RYAN: It was based on a literature
search, yes, and also based on Triad and Clinipad, looking at their information.

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

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

DR. RYAN: I think I'm going to open this up to anybody else who works at Sage Products who might have been there during that particular period of time and to maybe describe better how it was traced back. But I think my point here to this bullet point, you're talking about contaminated products, and this comment here is really related to non-contaminated products that have caused a problem.
DR. CHANG: Thank you. One last question.
How did you arrive at the conclusion that Triad and
Clinipad products were sterile products?

DR. RYAN: How did I arrive at that?

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

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

DR. FURNESS: Anyone else? Dr. Kelman?

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

So two issues. One is similar to
Dr. Chang's question, I think. When you say that
there's no risk demonstrated, do you mean that you
really think there's no risk or that there's no
evidence as to now developed as to that risk? In
other words, has anybody done root cause of
surgical site infections, to look back to the
presence or absence of sterile surgical skin
preparations?

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

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

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

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

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

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

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

DR. KELMAN: Thank you.

DR. FURNESS: Dr. Leonard-Segal?

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

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

DR. RYAN: Yes. I'll let Tim speak to the large volume, but I'll speak -- and we can take turns on this. I can answer certainly as a healthcare provider and as a nurse what training you undergo in the hospital setting, anyways, to learn proper technique based on the situation, whether it's going to be clean technique or sterile.
Also, we can probably address much better how we teach families and family members how to use a clean technique when they're using these products in the home. But as far as a nurse or another healthcare provider within a hospital system, you do learn the appropriate technique on how to use a product, whether it's sterile -- aseptic, or sterile, or clean.

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

DR. RYAN: I will let Tim address that. The product that we represent is actually a single-use
product, so I'll let Tim speak from a manufacturing standpoint on the larger volume.

MR. MANTHEI: Those are great comments.

And, really, what Dr. Ryan said, our product is a single-use product, so we don't make a multiple-use. So I really can't comment on the manufacturing process there or whether it should or shouldn't be used multiple times. But maybe somebody in the audience could.

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

MR. MANTHEI: Specifically, our in-house formulations. Two percent chlorhexidine is what that is. And as far as filtration, we have an additive in our product that is what actually gets filtered out, not the chlorhexidine itself.
DR. FURNESS: Thank you.

Any other questions? Dr. Shehab?

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

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

DR. SHEHAB: Okay.

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

DR. SHEHAB: Thank you. The second question
is, when intrinsic contamination has been identified among your products, has there been an overwhelming root cause? And the reason I ask, we understand that aseptic processing can be a challenge, and it sure seems to be a limitation to terminal sterilization.

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

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

The other thing, specifically on intrinsic challenges in the factory, what we've done since 2008 is we've put in QMS processes using CAPA and
drive the root cause. And so, we drive the root cause, and then we fix whatever we find was the issue. So that is very beneficial.

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

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

DR. FURNES: Dr. Chang?

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

MR. MANTHEI: Yes, I can. We tried that with our solution, and there's an additive that we
have in there that plugs the filter, at a .2 micron filter. So is it possible in other manufacturing solutions? I can't speak to that. But I can say that filtration is just one step in producing a sterile product. Right? If it's going into a sterile core, so an aseptic product, everything has to be sterile coming into that core, and then it has to be put together sterile, and end up sterile. Right? So there's a lot of pieces, parts, lot of components that have to come together besides just a sterile filtration step.

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

DR. FURNESS: Any other questions?

Dr. Furlong?

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

I'm curious what you think about how the
product is used, though, in the operating room. I agree that the showers and so on, before and after, are all in non-sterile settings. But when you think about the operating room, where you have sterile gowns, sterile gloves, sterile IV fluids, sterile complicated drugs in those IV fluids, sterile instruments, if the patient's eyes are closed with any topical ophthalmologic product, that is also sterile. And yet, the product that's placed on the person's abdomen -- say it's abdominal surgery -- may have pseudomonas aeruginosa in it.

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

DR. RYAN: Yes, and that's a great question because, in theory, that makes sense. You would think that if something could potentially be contaminated, obviously, that would be a risk to a
patient. So I agree, in theory, that does make sense. I think what we have to look at now is what does the clinical data say? Does the clinical data say that patients are at higher risk with a non-sterile or a sterile product? And we don't know. I don't know that there's been a significant amount of comparative studies that have looked at sterile versus non-sterile and determined that one is better than another.

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

But, in theory, I understand that question. It makes sense. But speaking to the challenges of making that product sterile, I think we need to think about the risk versus benefit. Is that patient best served by using the products that we know have clinical efficacy versus the potential slight risk that a product is contaminated? And
that's not to minimize at all the potential contamination, but the data that we have to date shows efficacy using the products manufactured as they are.

   DR. FURNESS: Dr. Leonard-Segal?

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

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

   Do you have any thoughts on putting this together with that background information, ways for us to think about this from an efficacy standpoint, knowing that we really don't have the clinical outcomes, and we know that they've been very hard
to get? So we've sorted accepted the practicality of it, but, yet, we have this safety risk.

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

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

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

   So I think that there's things that we can do up front, and it's the things that Tim mentioned
as well, is that increased education in making sure
we're addressing that extrinsic potential
contamination, because that's probably an easier
fix and can be done immediately.

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

DR. LEONARD-SEGAL: So I have one more
question, going back to the education part. So you
talked about a checklist, and checklists are always
a good idea. But I guess that we would be very
appreciative if you could provide us with some of
the elements that you think belong on that
checklist that go above and beyond the additional
training, the current training, that people have.
I think we'd be very interested in receiving that
information from you.

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

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

So I think a checklist has been helpful.
They have shown, certainly, some improvement. But
holding people accountable, but also giving that
autonomy to be able to speak up and address patient
safety as a group.
But I think increasing awareness, too, because there could be healthcare providers that are utilizing these pre-op preparations, but not really having a clear understanding of the ramifications of a breach in technique.

DR. FURNESS: Thank you very much.

Dr. Chang?

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

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

But oftentimes we are brought in when they
are implementing some type of initiative; say
they're going to implement chlorhexidine as a
pre-op preparation within the hospital system. So
our nurses are actually able to go into those
hospitals and help educate the other nurses that
are going to be the end users of these products.

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

DR. FURNESS: Dr. Hussong?

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

But several years ago, there was a recall on
some antiseptics. And the only reason it was
noticed is that the surgeon, when opening the
container, found the solution smelled putrid. And
it turned out bacteria had grown tremendously, to
great numbers.
There are bacteria that grow in many of these antiseptics. And my concern is that if you don't eliminate this bacteria, which means sterile, they will grow. And that does not seem acceptable in a surgical setting.

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

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

Based on the use of a product, can we
control time to keep that growth down, keep it
safe?

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

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

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

DR. HUSSONG: Thank you. I think that's a
really interesting concept, the pre-op versus
surgical, pre-surgical -- or, I'm sorry, operating room versus pre-op. Thank you.

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

DR. RYAN: Thank you.

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

Presentation – John Thomas

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

My issue is that, throughout my career, I've been involved in microbiology for almost 50 years now. And the reality is that my 50 years of microbiology led me to involve myself with wounds, particularly because I happened to serve as a captain in the United States Army during the
Vietnam War. And although I have been trained as a microbiologist, I found out that war environment and wounds for the wounded warrior are quite a bit different.

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

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

I'd also like to point out that as I started to develop this biofilm research consortium, that we wanted to make sure that we were, in the upper left-hand corner, dealing with biofilms in lungs.
and endotraches. And it's led us to understand about legislation. You cannot legislate compliance of use products, and that's an issue. And on the lower left-hand side, the idea that in chronic wounds, the development of a biofilm is critical in assessing what management style would work.

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

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

So what I'd like to do is, I'm a professor. You can tell. I was going to bring my puppets, but probably my wife said, "Don't you dare do that." I like to teach to students -- medical students, nursing students, pharmacy students -- with visualization because they remember a picture much
better than a particular statement. But I want to point out, every slide I ever start with starts out with this thought, "We live in a microbial world. You cannot legislate out the fact that bugs are around us, and, in fact, very helpful."

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

So here's my statement. We live in a microbial world. It is their world. It's an important environment that we deal with. And the world of defining this microbial world is changing. We are now using metagenomics. And I want you to realize that cluster analysis of microbes on a wound site is where it's at, single organism identification. To say that pseudomonas is going to be a pathogen and produce an outcome associated
with a bad scenario is not correct. We need to upgrade the assessment of bugs and disease process.

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

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

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

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

So, in reality, what I teach our students, our pharmacy students, our medical students, I teach them, point out to them, that in fact the normal flora that you address with products is in fact a part of our normal defense mechanism. And we teach our students today that normal skin flora is an organ system. It should be maintained with integrity so that cleaning it should, in fact, as we provide a protective environment for our
patients, should address the reality we need to
maintain some normal flora.

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

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

So I loved this slide when I was a freshman
in college, which, as I told you, was a long time
ago. I was told by a chemist -- gosh. As a
microbiologist, I hate chemists, but we must get
along. The reality is, I asked the professor how
should I prepare my first exam. And he said,
"Clearly, repetition is the mother of all learning." And the second point he said is, "Figures don't lie, but liars can figure."

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

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

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

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

The reality is, what we have done is we have so focused on standard microbes at a particular concentration, it's given us sort of a fail-safe method that may need to be replaced with the
reality of what happens in patients. And if you look at the difference of organisms in the list that's provided there, we are now saying to our colleagues, and to our physicians, and to you who work in this environment, that as a cluster analysis, as anti-Koch, we need to be with multiple species that have the ability to either maintain an environment or to produce an infectious environment. And it's a world that must be refocused because we've used the same tools for way, way, way too long.

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

There used to be floor mats on the floor. Do you remember those? And they were sticky, and
we'd pull off one piece of paper. And we used to say, "Shoe covers are absolutely mandatory," and a wide variety of old things that we don't do any more. But the reality is we still need to address the option of what happens when we follow protocol, and do we have a down-field outcome that can be measured appropriately?

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

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

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

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

On the lower right hand, middle right-hand side, we can associate whether the pattern of diffraction defines whether it's within WVU's same floor or different floors within the hospital. And then, ultimately, within West Virginia, is it a pattern of identification that is associated with a particular outbreak, which has occurred elsewhere?

After we've found a viable organism, it takes us about five seconds per organism.

So the tools are beginning to be developed, although I will point out to you that the United
States, in my assessment, is the slowest in the microbial world of assessing new methods into clinical reality. And I'm sort of embarrassed about that. I've been doing this almost 50 years, and when I go to Cardiff -- I just came back from Australia -- and look at the tools that these places are instituting for rapid detection of downstream outcomes, it's remarkable how slow and out of phase we are with the rest of the world. I'm a little bit embarrassed at times to have to say that.

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

What's going to happen, ladies and gentlemen? We're going to identify bugs by their phyla. When we came down to the, do you remember
the orders and the class, et cetera? You all said, "I'm going to forget my microbiology. I'm never going to do it again." We need to recognize how these group within each other.

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

The reality now is, in a time period of about five to seven days, this multi-species environment on skin, having received the environmental support, or lack thereof, produces,
as you go into the blue, the scheme of staging in
biofilms. And the biofilm formation that is part
of this assessment now is addressing multiple
issues.

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

(Cell phone rings.)

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

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

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

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

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

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

The need, from my perspective, is downhill. I want to know what you're going to do. Will it change the outcome of the patient population? And
we didn't go into it, but obviously one of the
issues of bugs and multiple species is what we call
colonization resistance. It's not your traditional
multi-resistant organism. It's multiple bugs
living with an extra polymeric substance. We call
that colonization resistance. That's a huge
problem for any group of bugs that has the
potential to live together. It's different than
what we have associated with one bug, one organism.

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

So my point is, in tracking and what we do
in West Virginia, versus what you do in Washington,
versus what you do in other states, we don't have
the tools that other countries are putting in place. That's where I'd like you to put your effort. Where is the method of tracking and maintaining data to get evidence to prove the benefit of what we're doing? We have so many loose ends that need to come together.

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

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

DR. FURNESS: Thank you.

Questions from the panel? Dr. Rogers?

DR. ROGERS: Thank you very much for that presentation. I'm just wondering, then, with what you've provided, do you feel that we should have more of a targeted approach to organisms prior to
surgeries, rather than sort of this mass --

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

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

So to answer your question, three bugs I would use; I would use staph, pseudomonas, and candida albicans. And here's the other point. Thank you for asking that question. Not every bug forms a good biofilm. Staph is not staph, is not
staph, is not staph. Pseudomonas is not pseudomonas. So we have these classic American-type culture collection isolates that we do query about sometimes.

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

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

Sir?

DR. FURNESS: Dr. Kelman?

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

(Laughter.)

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

DR. KELMAN: Based on your hypothesis, is there necessarily any value at all in preoperative
DR. THOMAS: There's a rule here in teaching. If you ask a professor a question he can't answer, that's a bad thing. Clearly, to maintain sepsis has been the goal of all of us, but to recognize the limitations of what it can be.

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

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

DR. FURNESS: Dr. Leonard-Segal?

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

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

DR. LEONARD-SEGAL: Thank you.
So with these biofilms as a potential risk, as a source of infection on their own, is there something that we ought to be looking at? I mean, we've been worried about contamination in the antiseptic, however it got there. Is there a way that we should be looking to study whether that contaminant is interactive somehow with a preexisting biofilm, such that it would be of particular risk?

DR. THOMAS: Great question.

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

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

So that's a really important point, is, are the bugs that we need to associate with, as addressed here, those that don't get along well?
Because if they don't get along well, they're not going to be able to compete with the organisms that are on the skin, and they will basically be refused.

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

Now, here's the problem. And I didn't go into this, but I love this. You are a biological microbiologic clock. Your flora changes with age. And at the flora that we'd looked at with a newborn versus the flora we'd looked at with my age is different. So you can't just assume that if we assay it at one time, it's going to have the same outcome. If that bug from the contaminated source has a challenge to a newborn versus a challenge to
an adult, and would they interact favorably or not
so, we have to test them, recognizing that you and
I are a biologic clock, and our bug pool is going
to change a bit. But we know now what those pools
are, so we can do that. But it would take some
sophisticated and specific challenges.

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

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

    Look. The presence of a bug does not
indicate it's a pathogen. And as our tools expand,
we're going to find bugs. We live in a microbial
world. So the issue isn't, are they there? The
issue is, are they there, and in an environment to
a patient, produce an outcome? And it's my opinion
that, most of the time, those bug combinations do not produce a bad outcome.

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

DR. FURNESS: Dr. Hussong?

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

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

DR. HUSSONG: Been there, done that.

I think it's very important, when you're talking about infectious potential with your
simplified calculation -- appreciate it -- our
concern here is large numbers of atypical
microorganisms that become an infectious dose.

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

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

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

DR. THOMAS: Give me my card back. And the
oral area is the issue. And without getting lost
and going too far, the bottom line is yes.
Maintenance of the bioburden of a particular site -- and they do vary -- is critical to the health of the patient for a variety of reasons.

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

We won't get lost here, but that's one of the issues that makes me madder than holy heck, is that our clinicians use the word "probiotic." It's like using the word "antibiotic." No one would send a patient out to buy an antibiotic. They would prescribe a particular type, given a particular dose, that's used for a particular time.
frame. But in the United States, unlike Europe, we have not decided whether probiotics are medical management or, in fact, food additives. And so, the reality is, there is no guidelines for using probiotics in the U.S.

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

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

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

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

DR. FURNESS: And we are running a little bit behind schedule, and I would suggest that we take our planned break at this point. And we'll
pick up at where we left off in 15 minutes. So that would be about 10:45. Thank you.

(Whereupon, a brief recess was taken.)

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

Presentation – Hudson Garrett

DR. GARRETT: Thank you very much.

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

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

So you can see my objectives here. I'd like
to go over a little bit of the clinical aspect of this. And I think some of the questions that were already asked this morning are very spot-on with some of the challenges that we see with this.

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

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

So when you think about healthcare-associated infections, each one of us could be a consumer. I was just a consumer of healthcare two weeks ago. I had a surgical incision made in the back of my neck, met a dermatologist for the first time, asked her some very specific questions, and she started to ask me, "Well, what do you do for a living?" when I started to ask this.
She actually did an outstanding job, I think, of following good practice for medicine. She applied the skin prep using a non-sterile technique. She applied the drape. She did all the things that she was supposed to do, and she took a tremendous amount of time at the end of the procedure and educated me, even knowing what I do for a living.

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

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

I know we have a colleague here from CMS, and I know that the Department of Health and Human
Services has put forth the HA action plan. And that's definitely something that we have to consider. And we know that healthcare is also delivered in a variety of other spaces outside of the four walls of the hospital.

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

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

When we think about the use of these types of products, we're really trying to target the transient flora in the epidermis. So we're never going to actually sterilize the skin. And I think that's a very important piece that we have to think
The whole purpose of this process is not to sterilize. I think we've acknowledged the role of good flora on the skin, but we also recognize that most of the infections actually come from the patients' own flora. They're not coming from sources outside of the patient.

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

So it's not just the four walls of the operating room in which these products are used. And so, we have to think about what types of clinicians might actually be using these products. What are their skillsets? What are their educational backgrounds? Are they exposed to
continuous education? And I think that's a question that we have a lot of opportunity to do in collaboration with the agency.

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

When we look at aseptic technique -- now, I mentioned to you before, I was just a consumer of healthcare. So the timeliness of this meeting is pretty ironic. But I think about the whole principle of aseptic technique in general. So what does that mean? Are we really accomplishing what
we're setting out to? What's our objective?

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

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

So when we look at antiseptics in general, no surprise to you it needs to be broad spectrum. So when it is applied to the patients' skin, what type of efficacy are we achieving? What type of log reduction are we actually seeking? There's not a magical number that says, if you achieve this log reduction, you're going to prevent a healthcare-
associated infection. And that, to me, is a
challenge that we need additional research. I know
we have a colleague here from DHQP at CDC, and
that's something that I always ask myself. What
else can we do to challenge ourselves to create
that resource, that evidence-based practice?

We know that it needs to be quick. If you
apply a skin antiseptic to a patient and it takes
an hour to dry, it's not necessarily going to be
the most appropriate antiseptic. It has to be easy
for the clinician to use. An example of this is,
if the products' instructions are so prohibitive
that it takes several minutes to read them, the
clinician's not going to adhere to them. And so, I
think we have an opportunity to have more
educational labeling that can actually be present
on these products as well and educate the actual
clinician. And I think we've also brought up a
good point this morning about the potential patient
that may be taking these products home from a
pharmacy or their outpatient setting and utilizing
them.
Persistence is one of those words. Well, what does that mean? Well, we know that if an antiseptic can continue to provide antiseptic properties on the patient’s skin, that that provides some benefit. Again, we don't know what that magical number is, but we do want it to obviously be compliant with the TFM.

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

So I told you that I had the opportunity to work with AORN on their guideline for a perioperative skin antisepsis, and they're very stringent about this. And just as Dr. Ryan mentioned earlier, the studies show that when
you're using preparations, there's really been no
difference between the application in a non-sterile
versus a sterile manner.

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

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

When you think about skin antisepsis, we've
spent a lot of time talking about surgical site
infections this morning, but another thing to think
about is central line-associated infections, which
these products are also used for. And if you think
about this, there are lots of opportunities for
bacteria to invade the skin. We certainly agree
that if you have intact skin, that's a great
natural barrier for microbial contamination.

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

When you think about CLABSI or blood serum
infections, I give you a statistic. Most
infections actually come from maintenance. So that
means it's not at the time of insertion. It's
actually at the time post-procedure that other
clinicians are actually caring for that site or that wound.

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

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

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

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

So I know some of the questions that were asked by the panel, if you think about, should these products be sterile, that's a fundamental question that you've asked. And I think it's a very good question and a very logical question to
I know one of the comments made earlier was that there's many sterile supplies and things like that, that are in the operating room setting. But the operating room itself is not a sterile environment. I mean, we try to make it as sterile as possible, but it's certainly not possible to make the entire room sterile. And so, when you think about skin antisepsis, again, the skin cannot be sterilized unless you autoclave it, as my previous colleague mentioned. And so, that's obviously something we can't do with the patient.

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

So while sterility does provide an added layer of benefit, it's certainly not going to eliminate the risk for contamination. You think about sterile products that come packaged today. I hate to pick on needles and syringes, but we have
needles and syringes that are clearly labeled single-use, sterile, disposable, for one patient, that, in this country, continue to be reused. And that's an issue for us that continues to cause adverse events. Poor user education, opportunity for improvement, opportunity for collaboration, and so, we have to think about that.

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

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

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

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

We also know that clinical education is
continuous in healthcare. If you're a nurse, unfortunately, you're probably going to education almost every single day whether you like it or not. It may be on a new IV pump. It may be on a new glucometer. It may be on a multiple-dose vial. It may be on all kinds of topics.

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

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

So you really have two different categories that I would call your attention to. One is that single-use patient antiseptic that's really kind of
thrown away. You use it. It's instantly used, and it's discarded. So there's no risk for contamination between patients. There should be no risk with storage because it's sealed. It's stored properly. And it's going to be used for that one patient, so it's not going to be cross-pollinating, if you will, with flora.

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

Every time you go and access that solution, you're exposing it to air. You're exposing it to any other contaminants that might be present in the environment. And while there are bacteria everywhere, hopefully the antiseptic itself is going to be stored correctly. It's going to be dispensed correctly. And it's going to actually be
applied to the patient correctly. But those are three variables that the clinician has to control. And I think those are things that we can continue to improve.

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

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

So again, going back to labeling, and clinical education, and requirements, there is an opportunity for collaboration here. And I think a
checklist, as Dr. Ryan mentioned, is an excellent idea. I think we've demonstrated that, in healthcare practice, that checklists are efficient. They work well. And they demonstrate good outcomes when they're adhered to.

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

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

So how do you adapt the education to
actually meet the specific needs of the patient? Because at the end of the day, we're trying to prevent that one infection in that one patient, and we have to take one patient at a time and make sure that the clinicians caring for that patient and actually using the antiseptic are doing so in an appropriate manner for that patient.

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

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

I also want to draw your attention, as we
draw to a close here, to some alternate site
considerations. One of your questions was, where
else are these products used? Now, this, to me, is
a tremendous opportunity.

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

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

That's something that I think, when you see
dialysis centers, you think about the presence of
dialysis patients, the prevalence of people going
into ambulatory surgery. You've seen a tremendous
shift in surgical procedures actually moving outside of the hospital. So they're actually going to these outpatient centers where there's a tremendous volume of patients moving through these environments. And so, time is an element as well. So how do we make sure that we're maximizing patient safety and efficacy while meeting the time constraints that these clinicians have in these various settings?

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

Last but not least, clinical staff training. I think we've reemphasized this all morning long, and I think that it's an important point. You can have the best product that, even if it was sterile, can be inappropriately used and contaminated. And I think that when you look at the data that's out there, when you follow instructions for use, when
you've explicitly followed manufacturers' instructions and labeling requirements, you should have a good outcome. And there are always exceptions to the rule, and I think there's opportunities for us to improve across the entire industry.

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

Sometimes we just actually do things without understanding really the purpose behind them. And if we understand that the skin is not sterile,
cannot be sterilized safely with the patient,

obviously, how do we maximize the efficacy of skin

antisepsis products, things like aseptic

dispensing, making sure that we're providing annual

competency training, and then also proper storage?

I know one of the questions that came up

was, can you date these products? And again, with

a single use, single patient, you don't have to

worry about that because they're immediately

discarded. So there's no need to actually date the

product when you opened it.

So when you look at some of these large

solutions that are sitting on shelves in operating

rooms, those have a much more tremendous risk for

possible contamination.

These are my disclosures, and I will be

happy to take any questions that you might have.

DR. FURNESS: Thank you very much.

Questions from the panel? Dr. Chang?

DR. CHANG: Thank you for your presentation

and for actually responding to each of our

questions --
DR. GARRETT: My pleasure

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

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

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

We know that if you coat the patient in antiseptic unnecessarily, you increase adverse events. Right? So you increase risk for skin irritation and things like that, especially when
dressings and things like that are inappropriately
applied. So you have to put the appropriate mLs of
solution on the patient, based off the clinical
procedure, and as you mentioned, the coverage area.

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

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

DR. CHANG: One follow-up question --

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

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

My personal opinion, I think that the risk
of contamination, as we identified from the first
presentation, is extremely low, given the number of volume of procedures that take place in the United States annually. And so that's a very, very low statistical number.

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

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

DR. FURNESS: Dr. Kelman?

DR. KELMAN: A very interesting presentation, Dr. Garrett. I only have one
question. Could you think of any possible
disadvantage to producing these products as
sterile?

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

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

DR. FURNESS: Thank you very much, Doctor.

DR. GARRETT: Thank you.

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

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

So I just want to be careful because I've
heard the absence of data cited as evidence; just
be careful that we don't do that once we're moving forward.

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

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

DR. GARRETT: Sure.

DR. SHEHAB: In that regard, you mentioned education is important. I agree education is extremely important. Part of, I think, the success of education with not reusing sterile syringes and needles is that those products are sterile. It's
easier to raise the threshold about proper asepsis and proper aseptic technique when you're dealing with inherently sterile products; the physician, the nurse, the medical provider knows, "Oh. These are sterile products. I need to handle them differently." And it's difficult to educate about that importance if you're dealing with something that we've already deemed is not important to be sterile, so use it any which way.

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

It can only also go so far for single-use products used in the OR because that's not where the evidence tells us we see extrinsic contamination. We see extrinsic contamination mostly with multiple-use products used outside of the OR. So now we're talking about a whole different set of education, and there may not even
be a checklist. And if we're talking, again, about
products that are not sterile, how do you explain
the importance of treating them aseptically? Does
that make sense?

DR. GARRETT: Yes. It absolutely makes
sense.

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

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

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

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

Is that fairly accurate?

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

I do think that there's opportunity there. I just came back from the United Kingdom, and they
have a tremendous movement towards transparency in looking at surgical site infections and also making sure the definitions are very clear.

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

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

But I do know that the medical assistant actually, when she pulled the antiseptic out, looked at it. It was a single-use antiseptic. She studied the instructions for use. Now, whether or not she did this because of, obviously, what I do for a living. That's a whole different story. But I do know she took extra care and attention to
describe to me, as the patient, what she was doing, what the importance of the skin antisepsis process was. And then she provided wound care instructions afterwards.

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

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

Sorry. Lots of questions.

DR. FURNESS: Dr. Leonard-Segal?

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

DR. GARRETT: My pleasure.

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

We've learned that this happens at dialysis centers and probably at a lot of other settings. And maybe, if there were no multi-use products available, this wouldn't happen. I don't know if it would or it wouldn't. But how do we get there? And is there anything going on now that's educating people not to do this? We certainly don't have data that says that these products work that way.
So how did that happen? It seems like such a huge educational challenge if people are still doing it.

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

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

It's so rare to actually find a nurse in a dialysis center. You may have one nurse there and multiple technicians. And so, I think that you have to look at the potential users and appliers of
these antiseptics and say, "What background do you have? What skill set do you currently have? What are the educational gaps?" And that's actually a program that's being developed right now to address that in the dialysis setting to say, "If you're going to be a dialysis technician, these are some of the basic principles of antisepsis that you must follow, an aseptic technique."

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

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

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

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

In some of these environments, where turnover and care delivery cost is an important priority, I think that we need to transform that. And I think that's what value-based purchasing is doing, to say that we need to focus more on outcomes and doing the very best care for our patients. And I think that it doesn't matter who the provider is. We do need to place more emphasis on the appropriate use of these products and following instructions for use because, certainly, if the manufacturer's instructions do not advocate that, then you're adversely affecting the efficacy
of that product, as approved by the FDA. And so, I think we have more opportunity there.

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

DR. GARRETT: Thank you.

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

(Laughter.)

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

DR. GARRETT: We do.

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

DR. GARRETT: We do.

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

DR. GARRETT: I am aware of challenges. To
be honest with you, I could not speak to those
efficiently. So if that was an answer that you'd
like some clarification to, I could get the
appropriate colleague to do that. My background is
in the clinical affairs arena, but I can certainly
get you an answer to that question.

DR. CHANG: Thank you.

DR. GARRETT: No more questions?

(No response.)

DR. FURNESS: Thank you.

DR. GARRETT: Thank you.

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

Presentation – Jennifer Yttri

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

Our non-profit research center includes
scientists, medical, and public health experts who
analyze and review research on a range of health issues. I have a doctorate in immunology from Washington University in St. Louis.

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

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

Contamination of antiseptic products, we all realize, is a serious public health concern. High-profile cases such as the Triad Group's high risk recall of alcohol prep pads following the death of a child in Texas serve as warnings for the most severe cases. But even lower-risk recalls have the potential to severely harm patients. It is
imperative to take measures now to prevent future outbreaks.

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

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

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

Therefore, I think the FDA should focus on strategies that would improve manufacturing and outreach to prevent future outbreaks caused by the
use of antiseptic products.

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

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

More advanced screening processes have been developed that can detect lower levels of bacterial organisms than traditional cultured techniques. And the list of specified microorganisms to test
for needs to include any that have been associated with contamination outbreaks. By taking the steps to effectively monitor contamination during the manufacturing process, the number of outbreaks can be significantly reduced.

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

Third, as extrinsic contamination counts for the majority of contamination outbreaks, the FDA should require product packaging that would reduce extrinsic manipulation. We recommend that all products intended for use at home or in an outpatient facility be made as sterile as possible. These products should be packaged as single use and pre-diluted to the correct concentration so as to
avoid things like contamination from non-sterile water.

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

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

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

The FDA should require special controls such
as inspection of the manufacturing process prior to
market release, submission of pre-marketing
microbial testing, and maintenance of ISO and ASTM
standards if available, regardless of device class.

Monitoring of microbial levels should also
be continued as part of a required postmarket
surveillance plan, rather than passively in
response to serious problems. Patients are relying
on you, the FDA, the regulatory agency, to protect
them from contaminated antiseptic products.
Whether entrusting a physician to properly use an
antiseptic device or using it themselves at home,
most of these patients will not know if they are
exposing themselves to potential harm. An improved
set of guidelines for manufacturing and monitoring
of microbial contamination will help reduce
potentially lethal risk.

We urge you to help restore consumers'
confidence in the FDA and in medical products sold
in the United States by maintaining higher
standards. Special controls are needed to keep
these patients safe. Thank you.
DR. FURNESS: Thank you very much.

Questions from the panel? Dr. Leonard-Segal?

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

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

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

So a patient itself is not going to be able to perform an aseptic technique. They're not going
to necessarily understand, "I should open this in this particular way," depending upon, of course, the education that we've discussed earlier.

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

DR. LEONARD-SEGAL: Can I follow up?

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

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

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

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

I also believe that, as we've discussed in the OR setting, it would make sense that that might be another situation where a sterile product is very important. But I think that the end judgment call should really be based on clinicians in terms of working with their patient populations.
DR. LEONARD-SEGAL: Thank you.

DR. FURNESS: Thank you very much.

I would now like to call Dr. Aaron Johnson.

**Presentation - Bhaveen Kapadia**

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

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

At Sinai Hospital, we use 2 percent chlorhexidine gluconate impregnated cloths. They're disposable, single-use, ready-to-use cloths. They're a relatively easy application. Just wipe on. There's no rinsing involved with it. And it's a rapid-drying protocol as well.
The reason we've implemented this is, obviously, several health organizations have recommended using preoperative skin disinfection protocols either the night before or the morning of surgery. And a lot of emphasis has been put on using chlorhexidine gluconate specifically as the antiseptic of choice.

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

When looking at chlorhexidine cloth outcomes specifically, a study by Edmiston looked at 2 percent chlorhexidine cloth and compared it to 4 percent chlorhexidine scrubs. And what this has one was, essentially, they applied these solutions to the cutaneous sites, to several cutaneous sites preoperatively. And they subsequently cultured the skin for several hours afterwards. And what was found was that the cloth actually was capable of
reducing microbes for up to six hours, whereas the scrub itself was only effective for less than 10 minutes.

There are several different applications to chlorhexidine gluconate. One of them is the shower method. What we've seen in our institution, as well as in literature, is that there's typically poor compliance with the liquid solution. Furthermore, the application in the process that we use at our institution is a two-part application.

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

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

Of course, there are concerns with
contamination. What are the potential sources that we can think about? Well, there's a lack of intrinsic antibacterial activity. There's incorrect mechanism of action, pathogens that could be resistant to the antiseptic agent, obviously inadequate concentration, and inadequate duration of action. Inadequate antisepsis, actually, could lead to increased risk for multi-drug-resistant pathogens as well, which is also a common concern.

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

We've seen that there have been only two reports after 2000. And what does that mean? So
basically we want to see what are the potential sources that we could have contamination of these preoperative solutions. Of course, you could have contaminated water sources, contaminated sources such as the cloth and material, as well as contaminated packaging from the manufacturing company itself.

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

A property control management is necessary to make sure that input materials, such as cloths, packaging, and the fluids used to dilute, are actually sourced from non-contaminated suppliers. Rigorous quality control is necessary to ensure that cloths are tested for contamination. If there are any detect contaminants, the batches are held and reported.
The literature has not really demonstrated that there is any iatrogenic infection following the use of preoperative scrubs. I'm going to speak more specifically on the experience that we've had at our institution.

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

We believe that sterilization may add an unnecessary process to the manufacturing company and could potentially increase the cost to the patient as well as to the institution, which could prevent its widespread distribution and potential benefits of helping to reduce the instances of
surgical site infections.

Surgical site infections are obviously a tremendous burden to the healthcare institution. They cost roughly $129,000 per year for each event, and that's just for the year. I mean, some patients have multiple re-operations every couple of years, and that can add up as well.

Furthermore, the preoperative preparation application itself is a non-sterile procedure. It's dependent on the patient environment.

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

The literature has demonstrated some evidence of contaminated liquids, antiseptic
agents; however, it's uncertain whether this has occurred intrinsically or extrinsically. We believe that it's more likely the extrinsic contamination that could occur from dilution in the hospital environment and pharmacy environment that is more likely to do that, more specifically because the manufacturing agencies themselves are at low risk for harboring multi-drug-resistant organisms.

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

DR. FURNESS: Thank you very much.

Questions from the panel? Dr. Chang?

DR. CHANG: Thank you so much for your presentation. And I'm very glad to have a surgeon
in our audience. So a quick question about your reference to the Weber paper, which came out in 2007. Have you independently performed another literature search? I know that, based on the Weber paper, there were only 2 reports since 2000. Have you looked to see if there are any more?

DR. KAPADIA: Yes. We have.

DR. CHANG: Did you find any?

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

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

DR. KAPADIA: Yes.

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

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

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

DR. KAPADIA: That's a very good question. It's a very difficult thing to try and determine, after the fact, what was the actual contaminating solution. Obviously, most surgical site infections are from the endogenous skin flora. So it's difficult to, at that point, determine whether or not it was the preoperative preparation we used. We're just basing it on our experience that we've seen no infections in the patients that have actually used this protocol.
DR. CHANG: And it would be difficult to be so confident that there wouldn't be any infection outbreaks. Correct?

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

DR. FURNESS: Yes. Go ahead.

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

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

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

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

DR. FURNESS: Thank you very much.

DR. KAPADIA: Thank you.

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

Presentation – Michelle Stevens

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

On behalf of the more than 84,000 employees at 3M and our affiliate companies, it is my pleasure to be here at this public hearing and to share our point of view on this very important issue of safety of preoperative skin antiseptics, specifically to express our opinion whether sterile or aseptic processes should be incorporated into
manufacturing procedures for products intended for patient skin antisepsis prior to procedures.

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

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

These products are intended to reduce risk of infection and optimize patient safety prior to procedures. Therefore, any decision on future process requirements must insure continued optimum patient safety.
Secondly, we also believe that the FDA enforcement of current good manufacturing practice regulations is of utmost importance, and we support that wholeheartedly. Confirmation of industry compliance to GCMPs (sic) -- or cGMPs, through audits and inspections will ensure that safe and efficacious products are released into the marketplace.

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

As we have seen over the past several decades, intrinsic and extrinsic contamination of antiseptic products occurs, and this can compromise patient safety. We've talked about the Weber review, and there have been publications since that review that have identified events where contaminations occurred.
When looking at the iodo-4 category of antiseptics, most contamination has been intrinsic and linked to contamination of the water source during the manufacturing process. For chlorhexidine-based products, most of the contamination has been extrinsic and linked to use error.

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

In most cases, the intrinsic contaminations have been linked to failure to comply with GMP requirements. In terms of extrinsic contamination, bulk multi-use prep solutions are most at risk. We've heard dialogue about these bulk preps this morning, thus far. They are very difficult to manage in terms of maintaining sterilization or adequate -- or lack of contamination due to the
nature of the way they're used, due to multiple users and multiple uses for these products.

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

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

So because recent recalls have resulted from identified deficiencies in following GMPs, we should assess the impact, how much of an impact, there would be from implementation of additional sterile processing requirements for antiseptic skin prep products. Even if we move to requiring sterility, it won't solve the problem if GMP is not
followed. So that will be an important thing to consider in the dialogue and decision-making process.

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

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

So sound science must be behind the decisions affecting policy, regulations, and the resulting manufacturing standards, particularly as it relates to the technical and safety
considerations for standardizing the sterilization
of antiseptic solutions.

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

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

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

Provided that the primary container closure
of the prep solution is impermeable to ethylene
oxide, terminal EO sterilization of a finished
patient prep product remains an acceptable means of
providing a sterile applicator to the end user. It
should not be allowed to penetrate the applicator and affect the solution internally because it can affect the solution as mentioned.

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

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

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

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

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

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

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

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

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

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

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

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

DR. FURNESS: Thank you.

Other panelists have questions?

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

MS. GIBBS: We have considered the effects of radiation on iodo-4s, on chlorhexidine gluconate-based solutions with and without alcohol. Per the CFR reference up there from part 310, any
drug that is subjected to irradiation is given new
drug status because of the potential for -- there's
no reproducible way that you can be assured that,
that same molecule is going to cleave in the same
way time and time again when exposed to
irradiation. So you don't know what you're going
to be left with in a reproducible manner.

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

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

As we have seen in the Triad recall, it was
both sterile and non-sterile alcohol prep pads that
were recalled. And one of the FDA citations in the
43 was that sterilization process was not
validated. Now, interestingly enough there, you do
have a gamma-irradiated alcohol prep pad that was
still under the monograph. So it's kind of a
difficult mix of products in the way that they're
regulated.

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

MS. GIBBS: All products.

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

MS. GIBBS: Exactly.

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

MS. GIBBS: At a very high level, we have
discounted irradiation because of the degradants,
because of the degradation.
DR. LEONARD-SEGAL: In all of these?

MS. GIBBS: In all of these cases.

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

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

DR. LEONARD-SEGAL: Okay.

DR. FURNESS: Dr. Furlong?

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

MS. GIBBS: We have done some exploration with filtration. The one thing I will say regarding filtration is that, with any microbial control that you apply to a solution -- and microbial control is important -- those methodologies that you choose should be based on product design and risk management principles.
So you may have a manufacturing process that, in and of itself -- there may be mixed processes, but then there may be processes that are subject to polymerization under very high heat, in which case additional sterile -- filtration wouldn't add any additional benefit.

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

With that, I just want to reiterate one point that Michelle made. We've been talking about aseptic fill in the same context of terminal sterilization, and those don't achieve the same results. So I think it's important in whatever industry, FDA collaboration, for us to understand what is the end goal, because if it's aseptic fill, you're not getting to the sterility assurance level. You're getting to a contamination level of 10 to the minus 3rd. And is that where you want to
The technical challenges cannot be underemphasized regarding standard sterilization. So if you're looking at non-standard sterilization approaches, those approaches would need sound vetting with FDA. And because of the potential interactions of all the different formulations, there's no way that we could really even -- it would be very difficult to say, "Here's a protocol for this type of standard sterilization and what you should look for as far as degradants," or to have kind of a compendial, if you will. It would be very difficult. Plus, those non-standard sterilization modalities are going to be probably proprietary product by product.

DR. FURNESS: Dr. Hussong?

DR. HUSSONG: I have to agree that you can't just take one sterilization or sterile manufacturing procedure and apply it to all different types of drugs, antiseptics being among them. You take a large pharmaceutical manufacturer. They have hundreds of different
formulations and packages. And each one has to
have a uniquely tailored sterilization process or
sterile manufacturing process.

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

MS. GIBBS: Absolutely

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

Now, how we get there -- and that's the
point you were making earlier about aseptic doesn't
have a sterility assurance level. It has a
contamination rate. That's all you can do. But we
still label those products sterile. So if we can
work together on this, I'm sure we can get somewhere.

DR. FURNESS: Dr. Chang?

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

DR. STEVENS: Define the problem?

DR. CHANG: Yes.

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

DR. FURNESS: Go ahead.

DR. SHEHAB: You emphasized the importance of adhering to current good manufacturing practices in your presentation. I wondered, do you consider
the cGMPs as they are sufficient for delivering a safe antiseptic to the market, or is there room for improvement by way of building on those cGMPs for this specific product line?

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

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

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

But again, it goes back to product design, and risk management principles, and achieving the
spirit and intent of the GMP, so making sure that
you get a safe and efficacious product to the
market, whatever that may be for your product,
based on its principles and design.

Open Public Session

DR. FURNESS: Thank you very much.

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

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

I have just a couple of comments, and I'll
try and make this quick. I know a couple of folks
have mentioned a lot about education and training.
Obviously, I'm kind of speaking very specific to a
specific profession. But I'd also like to emphasize, in a way, that where education goes in our accredited programs, which may not occur in some other education and training programs, is we learn the skin prep, both didactic lab or mock OR, and in clinical rotation, and then obviously practice it in the operating room on a daily basis, a practitioner.

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

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

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

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

Another comment on expiration date. In my
experience, things in the OR have expiration dates,
most single-use items and such. And I think it's
important, again, for that to be emphasized, that
there should be an expiration date, even on the
single-use products. We have very large healthcare
facilities that are given price breaks when they
buy in bulk, and those items are sitting on the
shelf. And so, I think, from my end, I always check everything we use in the OR for an expiration date. So I think it's just important for the single-use products.

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

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

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

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

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

I'm sorry. One last thing. Also, don't forget, though, too, surgeons, not all -- and maybe this could be something in a guidance document,
too. As we know, in surgery, we build layers. I
tell my students we build layers. So when we're
draping, especially like in orthopedic procedures,
there are drapes upon drapes upon drapes to create
those barriers.

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

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

DR. FURNESS: Thank you very much.

Questions from the panel? Dr. Leonard-
Segal?

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

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

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

DR. LEONARD-SEGAL: Yes. And also, from your observation, what you know, what do you think
are the most common errors that are made, that
might lead to extrinsic contamination in the
operating suite?

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

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

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

The skin prep itself, I don't want to
simplify, but most people -- I think one gentleman
said -- I think it may have been you, that even
from nurse down to technician, it's pretty easy to
train someone and tell them, "You start at the skin
incision site and you go out," that type of thing,
don't touch this; don't touch that.
So I think it's some of the things prior, leading up to that, proper application of putting on -- when you're open-gloving, those type of things. I don't know if that makes sense.

DR. LEONARD-SEGAL: Sure. Thank you.

DR. FURNESS: Thank you very much.

MR. FREY: Thank you.

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

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

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

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

So my question is, as a public citizen, what are the manufacturers and the FDA doing to provide something that is non-flammable and non-toxic? That's the only question I have. I'm not here to defend my former company or any company. I'm just saying, I think it's like, no one ever said there would be an iPhone. There is one now. Why can't there be made a sterile product that is not flammable, that is not toxic, that can be used on an open wound? Why? My question. Thank you.

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

DR. LEONARD-SEGAL: Well, thank you for your comment. We have focused today's meeting on the sterility issue. FDA, however, has been very
actively involved over the last several years,
related to flammability issues, particularly with
alcohol-containing skin preps. And FDA has been
involved through their Safe Use initiative in
meeting with all kinds of stakeholders to address
this issue from everything, via educational
campaigns, trying to enhance checklists in
operating suits.

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

We think that issues related to OR fires are
very significant, although very rare. But when
they happen, they can be devastating. And we're
quite well aware of them. And we are working from
all different kinds of perspectives to try to
eliminate this problem if at all possible.
But today's meeting, we can't talk about all different topics. Right. So today's meeting is on the sterility issue and trying to decrease the risk of contamination, and to help people be as safe as possible when they have procedures using these products.

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

So this is -- I'm talking real-world experiences to me. It just happened. How am I supposed to -- what am I supposed to do for a urological gynecological prep, and there is none? My aunt. She's 79 years old. She needed a peri-op shower. She's a little obese. How do you get her clean? You got to wash her. It said don't wash your eyes. You got to wash something. What does she do? She has a dilemma. She called me. I
said, "I don't know. Just use some Ivory soap, I guess. I don't know."

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

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

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

MR. CARNEY: Thank you. Appreciate it.

Adjournment

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

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

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