U.S. FOOD AND DRUG ADMINISTRATION

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GENERAL HOSPITAL AND PERSONAL USE DEVICES PANEL
OF THE
MEDICAL DEVICES ADVISORY COMMITTEE

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37th MEETING

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FRIDAY,
MAY 4, 2007

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The meeting convened at 8:00 a.m. at the Hilton Washington, DC North, 620 Perry Parkway, Gaithersburg, Maryland, William R. Jarvis, M.D., Chairman, presiding.

PANEL MEMBERS PRESENT:

WILLIAM R. JARVIS, MD, Chair
MATTHEW ARDUINO, MS, Dr.P.H., Consultant
HASSAN AZIZ, Ph.D., Consumer Representative
YADIN B. DAVID, EdD, PE, CCE, FAIMBE, FACCE, Member
CHARLES E. EDMISTON, JR., Ph.D., CIC, Consultant
JAMES J. GORDON, M.D., FACP, Member
ELIZABETH KRZYWDA, MSN, ANP, Member
FLURYANNE LEACH, RN, MS, CIC, Consultant
DEAN KEVIN LURIE, M.D., FACS, Member
MANGAIYARKARASI SANTHIRAJ, M.P.H., Member
DAVID K. SPINDELL, M.D., Industry Representative

FDA PARTICIPANTS:

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TERRELL CUNNINGHAM, RN, BSN, Infection Control Devices Branch
GEETHA C. JAYAN, Ph.D., INCB/DAGID/ODE
CHIU LIN, Ph.D.
SHEILA A. MURPHEY, M.D., Branch Chief, Infection Control Devices Branch
R. KAPIL PANGULURI, Ph.D., INCB/DAGID/ODE
MICHELLE RIOS, M.S., DAGID/ODE

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TOM PAGE, Director, Environmental & Regulatory Affairs, Cupron, Inc.
STEPHEN ROTHENBURGER, Ph.D., Ethicon
WAVA TRUSCOTT, Ph.D., Safe Life Corporation
DEREK WARNEKE, General Manager, MicroActive Corp.

PUBLIC SPEAKERS:

ROBIN BECK, BioBarrier
BRIAN HEIMBUCH, Air Force Research Laboratories
GEORGE LAVENTURE, Air Force Research Laboratories
KARL PERKES, Nelson Laboratories
SAMY RENGASAMY, NIOSH
MICHAEL J. SCAGLIONE, WRP
BOB WEBER, 3M

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8:05 a.m.

CHAIRMAN JARVIS: Good morning, everybody. One of our panelists, I believe, is probably stuck in traffic, but I think we'll go ahead and start. I'd like to call this 37th Meeting on the General Hospital and Personal Use Devices Panel to order. I'm Dr. William Jarvis, the Chairperson of the panel. I'm a healthcare epidemiologist by training. I'm President of Jason and Jarvis Associates, a consulting firm in healthcare epidemiology.

If you haven't already done so, please sign the attendance sheets that are on the tables by the door. And if you wish to address the panel during one of the open sessions, please provide your name to Ms. Ann Williams who's outside at the registration table. If you are presenting in any of the open sessions today and have not previously provided an electronic copy of your presentation to FDA, please arrange to do so with Ms. Williams.

I note for the record that the voting members present constitute a quorum, as required by 21

CFR Part 14. I would also like to add that the panel participating in the meeting today has received training in FDA device law and regulations.

Before starting, I'd like to go around and introduce all the members of the panel. If you'd please provide your name, area of expertise, position, and affiliation, we'll start right here.

DR. SPINDELL: I'm Dr. David Spindell. I'm the Industry Representative for the panel.

DR. AZIZ: I'm Dr. Hassan Aziz, and I'm the Consumer Representative.

MS. KRZYWDA: Elizabeth Krzywda from the Medical College of Wisconsin.

DR. ARDUINO: Matt Arduino, Lead Microbiologist from the Centers of Disease Control, Division of Healthcare Quality Promotion.

DR. DAVID: Yadin David, Director of Biomedical Engineering Department at Texas Children's Hospital.

LT. COLBURN: Lieutenant Scott Colburn from the Center of Devices and Radiological Health. I'm the Executive Secretary.

DR. EDMISTON: Charles Edmiston, Professor of Surgery and Hospital Epidemiologist at the Medical College of Wisconsin.

DR. GORDON: James Gordon, Assistant Professor of Medicine and Infectious Diseases, Wayne State, Detroit, Michigan.

MS. LEACH: Fluryanne Leach, Infection Control and Epidemiology Service, Walter Reed Army Medical Center.

MS. SANTHIRAJ: Mangaiy Santhiraj, Epidemiologist, Infection Control Practitioner at Hines VA Hospital, Chicago.

DR. LIN: I'm Chiu Lin. I'm the Director of Division of Anesthesiology, General Hospital, Infection Control and Dental Devices.

CHAIRMAN JARVIS: All right. Thank you very much. Just as a reminder, please silent your cell phones. And now Lieutenant Colburn, the Executive Secretary for the Circulatory System Devices Panel.

LT. COLBURN: Good morning, everyone. I'd like to read into the record the conflict of interest

statement. The Food and Drug Administration is convening today's meeting on the General Hospital and Personal Use Devices Panels, the Medical Devices Advisory Committee, under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the panel are special government employees, or SGEs, or regular federal employees from other agencies and are subject to the federal conflict of interest laws and regulations.

The following information on the status of this panel's compliance with the federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 United States Code 208 are being provided to the participants in today's meeting and to the public. FDA has determined that members and consultants of this panel are in compliance with federal ethics and conflict of interest laws. Under 18 United States Code 208, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it's determined that the agency's need for particular individual services

outweighs his or her potential financial conflict of interest.

Related to discussions of today's meeting, members and consultants of this panel who are special government employees have been screened for potential financial conflicts of interest in their own, as well as those imputed to them, including those of their employer, spouse, or minor child. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents, royalties, and primary employment.

Today's agenda involves a discussion of the general issues concerning scientific and clinical issues raised by the addition of antimicrobial agents to personal protective equipment, or PPE. The PPE to be discussed are surgical masks and respirators, medical gloves, and surgical isolation gowns. Based on the agenda for today's meeting and all financial interests reported by the panel members and consultants, no conflict of interest waivers have been issued.

Dr. David Spindell is serving as the Industry Representative acting on behalf of all related industry and is employed by Abbott Laboratories. This conflict of interest statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

We would like to remind members and consultants that if the discussions involve any products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the panel of any financial relationships that they may have with any friends of this issue. Thank you.

Now, before I turn the meeting back over to Dr. Jarvis, here are a few general announcements. Transcripts for today's meeting will be available from Neal Gross and Company and can be contacted at 202-234-4433. Information on purchasing videos of today's

meeting can be found on the table outside of the meeting room. Presenters to the panel who have not already done so should provide FDA with a hard copy of their remarks, including overheads. Thank you very much, and I'll turn it back over to Dr. Jarvis.

CHAIRMAN JARVIS: Thank you, Scott. To begin today's meeting, we're going to have some presentations by the Food and Drug Administration, starting with Dr. Murphey.

DR. MURPHEY: Ladies and gentlemen of the panel, good morning. This is a meeting of the General Hospital and Personal Use Devices Advisory Panel of the Medical Devices Advisory Committee of FDA is being asked to discuss antimicrobial agents on personal protective equipment, the scientific and clinical issues related to this. Am I audible to everyone? Good.

I'm Dr. Sheila Murphey. I'm the Branch Chief for the Infection Control Devices Branch in the Division of the Anesthesiology General Hospital Infection Control and Dental Devices in the Center for Devices and Radiologic Health. Today you will be

hearing presentations from several members of our branch, including myself, Ms. Michelle Rios, Mr. Terrell Cunningham, Dr. Kapil Panguluri, and Dr. Geetha Jayan. Dr. Katherine Spooner unfortunately is ill today, and I will be giving her presentation.

The Advisory Panel is asked to address the scientific and clinical issues raised by the incorporation of antimicrobial agents into personal protective equipment, or PPE. PPE include medical gloves, surgical masks and surgical respirators, and isolation and surgical gowns. PPE function as protective barrier devices.

FDA, to date, has not cleared any medical gloves or surgical masks or N95 respirators which incorporate antimicrobial agents. FDA is aware of just two surgical gowns cleared many years ago as parts of lines surgical textiles of various types, which included an antimicrobial agent.

FDA is aware that PPE which incorporate antimicrobial agents on those PPE are being marketed in other countries, and FDA believes that there may be interest in developing and marketing such products in

the United States. FDA believes that the addition of antimicrobial agents to PPE raises important scientific and clinical issues related to the safety and to the performance of such devices and, therefore, FDA wishes to seek the guidance of this Advisory Panel as it prepares for the review of PPE incorporating antimicrobial agents.

Devices cleared for marketing by FDA which incorporate antimicrobial agents have generally been devices associated with device-related infections, such as intravascular catheters, urinary catheters, ventricular catheters, etcetera. FDA has also cleared for marketing devices incorporating antimicrobial agents which may become contaminated during use over periods of days or longer, such as wound-care products.

FDA believes that there may be several important differences between personal protective equipment and devices previously cleared with antimicrobial agents. And FDA believes that these differences may be important to the potential review process for PPE which incorporate antimicrobial

agents.

Important characteristics of PPE in use include the fact that they are used for short periods of time. These are mostly single-use disposable devices. They are not associated with device-related nosocomial infections, although gloves, like human hands, can spread pathogens from one location to another when not removed and discarded between tasks, which would contaminate the gloves.

Can antimicrobial agents enhance the protective barrier function of PPE for the wearer of the PPE? Can antimicrobial agents prevent the spread of contamination by PPE, especially by medical gloves?

FDA is aware that there is great concern about the current incidents of hospital-acquired nosocomial infections and the efforts to reduce these. FDA is also aware of the concern about the increasing incidents of nosocomial infections caused by antibiotic-resistant pathogens, such as methicillin-resistant *Staph. aureus*, vancomycin-resistant *Enterococcus*, highly cephalosporin-resistant gram-negative rods, etcetera.

FDA is also aware of the concern of the difficulties in achieving complete compliance among healthcare personnel with such important infection-control measures as hand-washing and the appropriate use of PPE and proper aseptic technique during procedures. The increasing incidence of antimicrobial-resistant pathogens in both the hospital setting and the community, particularly MRSA, has also increased interest in appropriate prescribing patterns for systemic antibiotics.

Is there a potential role for antimicrobial agents on PPE in ameliorating such problems as the contact transfer of nosocomial pathogens in healthcare, the need for frequent hand-washing by healthcare personnel, the appropriate use of PPE by healthcare personnel? Are there risks associated with the use of antimicrobial agents on personal protective equipment? Could healthcare personnel wearing PPE with antimicrobial agents assume that the presence of the antimicrobial agent will prevent the adverse effects of the healthcare worker's failures to remove and discard contaminated PPE and

wash their hands when needed? Could there be risks associated with the use of antimicrobial agents on PPE? Could antimicrobial agents leach off or physically detach from the PPE? And what safety issues for patients or healthcare personnel could arise from the presence of these antimicrobial agents added to PPE? Can antimicrobial agents on PPE work quickly enough to actually inhibit the growth of or kill pathogens on the surface of PPE before a healthcare worker wearing that PPE moves from one patient care site to another or from one patient care task to another?

FDA reviewers will describe for the Advisory Panel our current review processes for PPE, current FDA thinking on data needed for antimicrobial agents added to non-PPE devices as we currently see them, performance testing issues noted in the review of antimicrobial agents on non-PPE devices, and the scientific and clinical issues which we think could be raised by the addition of antimicrobial agents to PPE for consideration by the panel. FDA will ask the panel to address after hearing from industry and

public speakers the questions which we have provided for you at place and will present to you before your deliberations.

Thank you. Our next speaker will be Ms. Michelle Rios from the Infection Control Devices Branch.

MS. RIOS: Good morning, ladies of gentlemen of the panel. My name is Michelle Rios. I am a Microbiologist for the Infection Control Branch in the Office of Device Evaluation. This morning, I will be speaking to you about the current pre-market approach to submission review for antimicrobial agents on medical devices other than PPE.

My presentation is divided into two parts. In the first part, I will provide you with an overview of the current review approach to medical devices other than PPE with added antimicrobial agents. The second part of my presentation will focus on the addition of antimicrobial agents to PPE, including the potential indications for PPE with antimicrobial agents and the issues for performance testing for antimicrobial agents on PPE. I will

conclude my presentation with a summary.

Before I start speaking to you about the current review approach of medical devices other than PPE with added antimicrobial agents, I will state that currently there is no cross-cutting guidance documents addressing the review of antimicrobial agents on medical devices. This overview will describe the current review approach as typically seen for medical devices other than PPE with added antimicrobial agents.

If we were to provide in different sections the contents of a typical pre-market notification for medical devices other than PPE with antimicrobial agents, the contents of this pre-market notification will be divided into four major parts. One, the information on the antimicrobial agent itself. Two, the information on the antimicrobial agent on the medical device. Three, the intended use, indication for use. And, four, evaluation of efficacy of the antimicrobial agent. Through my presentation, I will expand on each of these four major parts.

The manufacturers usually provide in the

content of a pre-market notification information on the antimicrobial agent itself, including what is the type of the antimicrobial agent added to the medical device and whether or not this antimicrobial agent has been previously approved by FDA. If so, what is the approved indication, and what is the effective concentration?

Over the years, FDA has approved different types of antimicrobial agents, such as systemic antibiotics, topical antimicrobials, or agents such as silver, crystal violet, or amical. For those agents not previously approved by the agency, manufacturers provide added information on the safety of this antimicrobial agent.

In addition to information on the antimicrobial agent itself, manufacturers also provide information on the antimicrobial agent on the medical device, including how this antimicrobial agent was applied to the medical device and where. Is it in the inner surface, in the outer surface, or is it embedded in the device material?

Manufacturers also provide the

antimicrobial agent release characteristics. Does the antimicrobial agent elute from the medical device to a different site, or is it bound permanently on the device material? For those antimicrobial agents which are leached off from the medical device, manufacturers demonstrate the special characteristics of the antimicrobial with qualitative methods, such as corrected zone of inhibition.

However, qualitative methods only are not sufficient to evaluate the antimicrobial agent release characteristics and, therefore, are usually correlated with quantitative methods. Manufacturers, therefore, quantify the amount of agent release over time.

In addition to the method of application, the location of the antimicrobial agent on the medical device, and the release characteristics of the antimicrobial, manufacturers also provide antimicrobial agent safety as it relates to the medical device, particularly the historical experience with the agent on other devices, the potential for interactions with the device material, and the potential for sensitization of the patient.

For the purpose of pre-market notification review, manufacturers provide the intended use indication for use, addressing each the device and the antimicrobial agent. The indication for use needs to relate to the function of the device and the function of the antimicrobial agent on the device. The amount of performance testing provided should support the indications for use.

Over the years, FDA has approved different types of medical devices with antimicrobial agents added on them. For example, catheters, implanted devices, dental devices, and wound-care products. The amount of performance testing provided in the context of a pre-market notification for a medical device will be dependent on the type of device. For example, manufacturers provide greater amount of performance testing for an implanted device when compared to the amount of data provided for a wound dressing simply because the implanted devices represent a greater risk to the user or wearer when compared to a wound dressing.

Performance data is not only dependent on

the type of device but also on the indication for use for the antimicrobial agent on the device. FDA has typically seen the following indication for use for the antimicrobial agent on a medical device: prevents contamination of the medical device during use; prevents colonization of microbes on the medical device; and prevents or reduces the incidence of device-related infections. FDA has also seen a preservative indication for the antimicrobial agent. Preservative is specific to multi-use products used repeatedly over days and relies on specialized performance testing. Since PPE are not, for the most part, multi-use products, the preservative indication may not be relevant to this panel meeting.

During my presentation, I will discuss the performance testing as typically seen for each of the other three indications for the antimicrobial agent. Before I start the discussion of performance testing per indication for the antimicrobial, I'll state that currently there are no FDA-recognized standard test method available to evaluate the antimicrobial efficacy on devices since the devices, antimicrobial

agents, and the indications for the antimicrobial agent vary so widely.

Since there is no specific standard for each type of device for each indication for the antimicrobial, FDA looks at information provided to support the indication for use in a case-by-case basis. For consistency through our reviews, FDA uses the same approaches for the evaluation of the device with the antimicrobial agent. And the approaches used for evaluation are: looking at the indication for use to determine whether or not this indication is supported with data. FDA also looks at the performance testing that evaluates the efficacy of the antimicrobial agent to determine whether or not the testing reflects the conditions of use of the device. FDA also looks at the testing to determine whether or not the pathogens used were clinically-relevant to the device, and whether or not the efficacy of the antimicrobial was evaluated using quantitative methods.

Also, FDA looks at the initial inoculum and the inoculum reduction to determine whether or not

it is clinically relevant. FDA also looks at the test article to determine whether or not the final finished device and not the device materials were evaluated. As previously said, the amount of performance data will be dependent on the indication for the antimicrobial agent on the device.

Now, we will move on and discuss the performance testing as typically seen for each indication for the antimicrobial agent. The first indication: prevent contamination of the medical device during use. Contamination does not refer to a specific in-use or clinical state. The factors to be considered in the pre-market review for the performance testing to support and prevent contamination indication are that the device bioburden is not often defined, there is no clinical correlation provided, and that the time frame in which contamination occurs varies with the device. This is why the efficacy of the antimicrobial to support this prevent contamination indication is usually supported only by individual testing.

The second indication is a prevent

microbial colonization on the medical device. The word colonization should be defined as it relates to the medical device as growth of organisms at a site in the absence of signs of infections. Colonization is usually quantified and related to clinical outcomes for the devices. Colonization refers to inserted or implanted devices. In addition to in vitro testing in the received submissions, in vivo or animal testing is also typically offered to study colonization in situ.

The third indication: prevent device-related infections. The word "infection" is a clinical event. Therefore, clinical studies can evaluate the reduction in the incidents of infections and can also evaluate the prevention of infections. In vivo and in vitro studies typically have been performed to evaluate the safety and likely efficacy of a potential clinical study.

Now, so far we have seen that the indication for the antimicrobial on a medical device will drive the amount of information provided in the context of a pre-market notification. The second part of my presentation is focused on the addition of

antimicrobial agent on personal protective equipment or PPE.

FDA has seen an increased interest from manufacturers to incorporate antimicrobial agents on PPE for different indications for the antimicrobial agent. Some indications for the antimicrobial agent on PPE as seen from public sources are enhanced protection against infectious microbes, prevents microorganisms from penetration or transfer, or prevents contamination during use.

The review criteria for PPE with antimicrobial agents could potentially be different from the review criteria for other devices with antimicrobial agents simply because of the special characteristics of these PPE devices. For example, PPE are mostly single use and disposable. They're used for short periods of time. They do not directly cause device-related infections. However, they can passively transfer pathogens from one site to another.

Now, these characteristics poses new challenges to manufacturers to develop new models to evaluate the efficacy of antimicrobial agent in the

final finished PPE. For example, how could device contamination be defined for each PPE? How could conventional antimicrobial testing reflect the conditions of use? Should incubation times for antimicrobial efficacy be modified for these type of devices? And how should testing address PPE whose antimicrobial agent is not on the surface of the device?

Now, to conclude my presentation, I will highlight some of the key points for each of the two parts of my presentation. From the first part of my presentation, we can summarize that, currently, the performance testing for antimicrobial agents on medical devices other than PPE considers the indication for the antimicrobial agent, the special characteristics of the device with the agent, and how antimicrobial activity testing reflects the conditions in which the device is used.

From the second part of my presentation, we can summarize that the performance testing for antimicrobial agents on PPE poses new challenges for testing based on the differences in PPE device

characteristics when compared to other cleared devices to which antimicrobials have already been added. This concludes my presentation. Thank you for your attention. Now I open the floor for Mr. Cunningham, who will be talking to you about medical gloves with antimicrobial agents.

MR. CUNNINGHAM: Thank you, Michelle. I am Terrell Cunningham, a nurse consultant and a reviewer in the Infection Control Branch of CDRH. Continuing our discussion of PPE, I'm here to discuss antimicrobial agents on medical gloves.

An overview. Our presentation will consist of review of CDC and OSHA requirements. We'll discuss the regulation and classification of medical gloves. We will look at the review process when we've added antimicrobial agents to medical gloves, and we will look at some of the safety considerations, and we will conclude with a summary.

Medical glove use is essential for hospital safety and infection control. Universal Precaution and the OSHA Bloodborne Pathogen Regulation have had a direct impact on medical glove usage. In

1987, the Center for Disease Control and Prevention recommended that healthcare workers use protective barriers when contact with blood and certain body fluids is anticipated. In 1991, U.S. Occupational Safety and Health Administration enacted the Bloodborne Pathogen Standard requiring the work practice control and protective clothing, including medical gloves, be used to minimize worker exposure to bloodborne pathogens.

Since the implementation of Universal Precaution, medical glove usage has skyrocketed. Approximately 39.2 billion pairs of medical gloves were imported into the United States during 2004. Medical gloves are one of the most frequently used medical devices cleared for market by FDA. Almost every patient that enters the healthcare system will come in direct contact with medical personnel wearing medical gloves.

Medical gloves are classified as Class I non-exempt medical devices. Different types of medical gloves include patient exam gloves, surgeons' gloves, glove liners, under-gloves, and finger cots.

Patient examination gloves are regulated under the Code of Federal Regulations. A patient exam glove is defined as a disposable device intended for medical purposes that is worn on the examiner's hand or fingers to prevent contamination between the patient and examiner. They are primarily non-sterile single-use disposable devices. The primary function of a patient exam glove is barrier protection. They protect the wearer of the glove from direct contact with blood and fluid-borne pathogens.

Surgeons' gloves are regulated under 21 CFR 878.4460. A surgeon's glove is defined as a device made of natural or synthetic rubber intended to be worn by operating room personnel to protect a surgical wound from contamination. They are sterile single-use disposable devices. The primary function of a surgeon's glove is barrier protection. They protect the patient from transmission of microorganisms and cross-infection.

Medical gloves are primarily made of natural rubber latex or synthetic polymers such as vinyl, polychloroprene, polyurethane, isopryl,

nitrile, or a various combination of polymers and co-polymers, such as listed for you. Medical gloves may also include other chemical additives and coatings. The barrier performance of medical gloves vary based on the type and quality of glove material, the length of time, and the conditions of use.

The current review process for medical gloves is based on the Glove Guidance Manual, the reference as listed. The guidance document describes FDA recommendations for information needed in a 510(k) submission for patient examination and surgeons' gloves.

The 510(k) process for medical gloves include the items listed before you. The review considerations include the water leak test. All medical gloves must pass the FDA water leak before they can be legally marketed. In addition to the pinhole test, gloves are tested for a variety of other characteristics, such as tensile strength, elongation, and physical dimensions. The physical dimensions are defined as specified in appropriate ASTM standards. Biocompatibility testing is also a requirement.

Medical gloves are skin-contact devices. We recommend the biocompatibility data include irritation and sensitization studies conducted on the final finished pre-shipment glove. Sterility evaluation is also recommended, as appropriate.

We will now look at the review considerations for medical gloves with antimicrobial agents added. How does the addition of an antimicrobial agent change the 510(k) review process? The agency is seeking the guidance from the panel to determine if the following proposed review considerations are appropriate. Should we consider the type of antimicrobial agent that is added and the intended use of the agent, the agent's mode and method of application, how and where the agent is applied? How important are the safety considerations that we have identified? Promotion indications? And, lastly, product performance testing.

Is the location of the agent on a glove an important factor for evaluation of medical glove safety? If the glove is coded or impregnated with an antimicrobial agent, the individual wearing the glove

may be at risk for potential exposure as a result of direct wearer contact. If the antimicrobial agent is applied by surface modification of the glove material, then the patient may be at risk for potential exposure due to patient contact from touching or direct contact with the surgical site.

In accordance with the FDA guidance document, safety considerations for review of medical gloves would include skin irritation and skin sensitization studies. Potential toxicity due to dermal exposure to the antimicrobial agent is also a safety consideration for the wearer of the glove. Gloves with antimicrobial agents may be worn while performing routine patient care activities; while doing routine procedures, such as preparing enteral feedings or while connecting a patient's intravenous connection system. Leaching of the chemical agent into the mucosa, open wounds, and/or other patient-care devices could occur.

The leaching off or physical detachment of the antimicrobial agent from the medical glove may result in delivery of the antimicrobial agent to

various body sites, the potential for adverse reaction to the antimicrobial agent. FDA believes that the effects of added antimicrobial agents on neonates, pediatric population, and other at-risk patient populations may need to be evaluated and included in device safety data for the medical glove.

Promotional indications for antimicrobial agents on medical gloves include the following: reduce hospital-acquired nosocomial infections, prevents cross-contamination, prevents pathogens from sticking to the glove, and prolongs the safety of the glove. Our question is: are these types of promotional indications appropriate?

We have just reviewed some of the proposed indications for adding an antimicrobial agent to medical gloves. The agency is seeking the guidance from the panel as to what are appropriate performance testing considerations. We propose that consideration be given to include in the following performance test protocols. We recommend evaluation of the final finished glove. Should testing mimic actual conditions of use? How important are including rapid

kill of microbials? And, lastly, shelf life and expiration test data. Dr. Murphey will address PPE performance testing in greater detail during her presentation.

In summary, I have briefly discussed FDA regulation and classification of medical gloves. We have addressed the addition of antimicrobial agents on medical gloves and the resultant and implications for the pre-market 510(k) review. The agency is seeking guidance from you, members of the panel, on how to best evaluate this product to ensure safety and effectiveness. We have proposed that review considerations include considering the indication of use of the product, the proposed benefits, product performance testing. We think that appropriate performance testing of medical gloves would be completed on the final finished pre-shipment gloves. FDA believes that suitable performance test data would support the effectiveness of the medical glove for the stated indicated intended use.

This concludes my presentation. Thank you for your attention. Next will be Dr. Panguluri.

DR. PANGULURI: Good morning, ladies and gentlemen of the panel. My name is Kapil Panguluri, and I'm a scientific reviewer at the Infection Control Division Branch of the ODE CDRH. My presentation is about the addition of antimicrobial agents on surgical masks and surgical N95 respirators.

This presentation will constitute two parts. In the first section, I will present a brief overview of the key issues of surgical masks and surgical N95 respirators, including their regulatory classifications, description of the device, comparison between a surgical mask and surgical N95 respirators, and FDA's 510(k) review process for surgical masks and respirators. In the second section of my presentation, I will provide a brief overview of surgical masks and N95 respirators with antimicrobial agents, including the site of application of antimicrobials on the mask and respirators, the safety and effectiveness concerns, indications for use, and performance testing.

Surgical masks are also known as laser masks, isolation masks, dental masks, and medical

procedure masks. They're regulated as Class II devices and are subject to pre-market notification.

Surgical masks may also be cleared as combination surgical masks and N95 respirators. These are regulated as Class II devices and are subject to pre-market notification.

Surgical masks with respirator performance features and certified by the National Institute of Occupational Safety and Health, NIOSH, and cleared by FDA becomes a surgical N95 respirator. Both the surgical masks and surgical N95 respirators are barrier devices. These devices are regulated under 21 CFR 878.4040 and, in this regulation, the devices are identified as surgical devices to be worn by operating room personnel during surgical procedures to protect both the surgical patient and operating room personnel from transfer of microorganisms, body fluids, and particulate material.

Here is a brief comparison between the surgical masks and surgical N95 respirators. Both surgical masks and surgical N95 respirators will reduce the risk of splashes of blood, body fluids,

secretions, and particles from reaching the mouth and nose of the wearer. Surgical N95 respirators may also reduce wearer's exposure to small airborne particles.

The surgical masks fit loosely to the face and are not designed for seal check. The surgical N95 respirators fit tightly to the face, and user seal check is required for each use.

Surgical masks and surgical N95 respirators are cleared for marketing by the FDA, which should meet the minimum performance specifications described in the surgical mask guidance document. This document will also be found at the web site listed here.

In the 510(k) review process, the FDA recommends that the submission contain description of the device and its intended use, comparison of the new device with the predicate device. FDA also recommends that the submission contain descriptive information, such as composition of the mask and respirators, specifications and dimensions, tensile strength, design features, and mask styles.

FDA has identified the risk to health

generally associated with the use of the surgical mask, and we recommend these risks be addressed in the 510(k) submission. Identified risks and recommended mitigation measures include fluid resistance, barrier for bacteria, which can be mitigated by both the particulate filtration efficiency testing and bacteria filtration efficiency testing.

Other performance characteristics include air exchange and flammability. Surgical masks include parts that have prolong contact with intact skin. FDA recommends that the 510(k) submission by all compatibility of the materials as described in the standard ISO 10993, Biological Evaluation of Medical Devices Part I, evaluation and testing for limited contact devices; that is contacting intact skin. N95 respirators are certified by NIOSH and FDA reviews and cleared through the 510(k) process as surgical N95 respirators. There will be certification for surgical N95 respirators in place of separate evaluations of filtration efficiency. Surgical N95 respirators are also evaluated for fluid resistance, flammability, and biocompatibility.

You have just heard the review process and the performance evaluation of surgical masks and surgical N95 respirators with all the antimicrobials. Naturally, the next question to ask is how does the addition of antimicrobial agents to the surgical masks and N95 respirators change the device review process? Well, it depends on the type and site of application of antimicrobials to the masks and respirators, the safety and effectiveness issues of the antimicrobial agent, the indications for use statement provided for the mask or the respirator with the antimicrobial agent, and the performance testing.

Antimicrobials can be drugs, chemicals, compounds, or metal ions. Typically, masks and respirators have three layers, and the antimicrobials can be either impregnated or coated under any of these three layers, outer, inner, or middle layers for the respirators.

Again, what kind of safety issues are we concerned about with the addition of antimicrobials to the masks and respirators? This will depend on the type of antimicrobial agents used; the antimicrobial

concentration; and the location of the agent, whether it is in the outer, inner, or middle layer of the mask or respirator filters.

The toxicity issues of concern due to the presence of antimicrobials in the filter elements are especially significant for masks and respirators. This is because the location of the antimicrobial agents, whether they're on the inner, outer, or middle layers, will be affected in a dynamic fashion by the force exerted on the filter elements due to the breathing process. Normal breathing when used have transfer effect on antimicrobial agents. As a result, they may become separated from the filter material and may be propelled into the oral and nasal respirator regions and to the ocular areas of the body.

So how could the safety for the oral, nasal, and ocular areas be addressed? Could the traditional evaluations, such as skin irritation and skin sensitization tests, are sufficient for evaluating the safety concerns? Or could the oral, nasal, and ocular mucosal assays of biocompatibility be of any use in evaluating the safety issues?

Multiple promotional indications for use are found in the public domains for antimicrobial masks and N95 respirators. Some of the examples include antimicrobial masks and respirators protect the filtration material from bacteria and fungi; protects against specific pathogens; antimicrobial agents in the filter material can isolate and kill microorganisms; elemental and metal ions in the device act as effective antimicrobial agents against viruses and bacteria.

The performance testing of the antimicrobial masks and respirators should support the indications for use. Some of the consents that we need your attention are should the antimicrobial effectiveness be evaluated by quantitative testing and for short time kills? When evaluating antimicrobial efficacy, how could one evaluate a mask and respirator with an antimicrobial present only on the interior layer of the filter? Would aerosol testing and surface contact evaluation be useful? Could the antimicrobial efficacy deficiency on the device change the prolonged storage period? If so, should this be

addressed? Presence of antimicrobial agents on the masks will require shelf-life labeling. Should performance testing be performed at the end of device shelf life? These topics will be covered in more detail by Dr. Sheila Murphey in her presentation that will soon follow.

This concludes my presentation. Thank you. Now I'm going to introduce Dr. Geetha Jayan to come to the podium to present her topic.

DR. JAYAN: Good morning, everyone. Can you hear me? I'm Geetha Jayan, and I'm a reviewer in the Infection Control Devices Branch at CDRH. Now, as Dr. Murphey said earlier, we are here today to address issues related to adding antimicrobial agents to personal protective equipments, or PPE. And the three PPE of interest to us today are medical gloves, masks, and gowns.

Mr. Cunningham and Dr. Panguluri already presented to you the issues that are specific to medical gloves and masks. Now we'll look at the issues that are specific to adding antimicrobial agents to medical gowns, and medical gowns include

surgical gowns and isolation gowns.

We will discuss this topic under two parts. First, we will look at some background information on the regulation and classification and FDA review process for gowns. Then, in the second part of our discussion, we will specifically look at issues related to adding antimicrobials to these devices.

So let us look at regulation and classification. As we see here, gowns are regulated as surgical apparel under the code of federal regulation. Examples for surgical apparel include surgical gowns, isolation gowns, surgical masks, etcetera. So as we see here, surgical apparel contains several devices. And depending on the review criteria, surgical apparel are classified into two classes, Class I and Class II.

Class II surgical apparel contains only surgical gowns and masks. So, obviously, all the other surgical apparel come under Class I. For example, isolation gowns are Class I surgical apparel. And as we see here, the Class I surgical apparel are

exempt from pre-market review by the FDA. Class II surgical apparel, on the other hand, are subject to pre-market review by the FDA. So surgical gowns are subject to pre-market FDA review.

So let us look at the review process for surgical gowns. FDA reviews surgical gowns through the 510(k) review process. Now, the information you see at the bottom of the screen is actually the reference to the FDA guidance document for surgical gowns, and the second one is the test standard for gowns. Now, coming back to the review process, as you can see here, the performance and safety testing information of the device is a very important part of this review process. So when antimicrobials are added to these devices, we have to consider how it could affect the safety and the performance information.

So let us look at the performance and safety information. First, we'll discuss the performance information. We look at two types of performance information: first, the barrier integrity; and, second, the physical and mechanical properties. And, actually, some of the physical and mechanical

properties also contribute to the barrier integrity of the gown. And we will look at each of these in more detail.

The barrier integrity. Now, as the name implies, the barrier integrity of the gowns is the ability of the gown to act as a barrier to resist blood and liquid penetration. The information at the bottom of the screen are some test methods to demonstrate the barrier integrity.

The next performance aspect is physical and mechanical properties. Here, you can see three important physical and mechanical properties for gowns. First, gowns should have the physical strength to resist tears and punctures. Second, the gown should be comfortable to wear. And, third, gowns should be safe for use in operating rooms.

So these are the performance aspects. The next important aspect is safety. As you know, gowns come in contact with the skin of the wearer, so they should not cause adverse reactions when they contact the skin. So biocompatibility is an important safety aspect for gowns. That is, the gowns should be non-

dermal irritants and non-dermal sensitizers.

Now, before we move any further, let us just recap where we stand. As you know, we are discussing issues related to adding antimicrobials to surgical and isolation gowns. This far, we were looking at the background information on the regulation, classification, and review of these devices.

Now, we'll move on to the second part of our discussion. That is, issues related to adding antimicrobials to these devices. We will discuss three aspects of this topic. First, we look at the potential performance indications for adding antimicrobials to these devices. Then we will see how this addition can affect the submission review or the 510(k) submission review. And then we will look at what are the safety and effectiveness considerations.

You can see here, I have an asterisk near potential performance indications, and that is to convey that these are not the indications that the FDA has seen. This is actually from public information sources for devices outside the U.S. market. So what

are these potential indications?

Here, you can see two important potential indications. One, enhanced protection of operating room patients and staff from infectious microbes and, second, prevent contact transmission of infectious microbes. Now, these are the potential indications for adding antimicrobial to gowns. From the FDA perspective, we also have to think about how this addition can affect the submission review and also how it can affect the safety and effectiveness of the device.

So how can it affect the submission review? Remember earlier we saw that isolation gowns are Class I surgical apparel, and they're exempt from pre-market review by the FDA. Now, when antimicrobials are added to isolation gowns, it can increase the safety considerations. So isolation gowns with added antimicrobials would be subject to pre-market review because the addition can trip the limitation for exemption from pre-market review.

So what are these safety considerations? For gowns, the safety considerations will depend

mainly on the method of application of the antimicrobial agent to the gown. So let us look at this aspect in more detail. So here the main question to ask is: is the antimicrobial agent woven into the gown fabric, or is it just coated on the surface of the gown? And if it is coated on the surface of the gown, we also have to ask is the coating on the outside of the gown, or is it on the inside of the gown?

And the safety issues here would be related to the antimicrobial agent leaching off from the gown, and, from the outside, it can get into a surgical site. And from the inside of the gown, it can leach off and get onto the skin of the wearer. So these are the safety aspects.

The next important aspect is effectiveness. Now, before we discuss the effectiveness aspect, if you recall, we saw that the primary function of gowns is to act as a barrier. So when antimicrobials or any material is added to gowns, the first question to ask is how would this addition affect the basic barrier performance of the gown? And

to put it very briefly, we can say that the addition should not compromise the barrier integrity of the device.

The next effectiveness aspect is related to the performance indications. Now, as we discussed earlier, adding antimicrobials to gowns would be to achieve some enhanced performance characteristics. So we have to ask what are these enhanced or what are these new performance indications? And the performance testing information of the new device should support these new performance indications.

Now, let us just recap and summarize what we've discussed so far. As you know, we were discussing about issues related to adding antimicrobials to gowns, and we discussed two aspects of this topic. First, we looked at some background information on the regulation and classification and FDA review of these devices. We also discussed how this background information is relevant when antimicrobials are added to these devices. Then, in the second part of our discussion, we specifically looked at the addition of antimicrobials to gowns, and

we also discussed how this addition could affect the submission review and the safety and effectiveness considerations.

Now, this brings us to the end of my presentation, and I thank you all for being a wonderful audience. Now I'd like to introduce our next speaker, Dr. Sheila Murphey.

DR. MURPHEY: Thank you. This presentation was prepared by Dr. Spooner, who put a great deal of work into it. Unfortunately, I'm going to have to present it for her. And this discussion is going to be about the performance testing and clinical implications of antimicrobial agents on personal protective equipment.

What clinical issues could be relevant to aspects of PPE performance testing? What considerations could influence antimicrobial efficacy testing and the organisms to be tested for a personal protective equipment to which antimicrobials have been added? How might PPE devices with antimicrobial agents impact healthcare facilities, providers, and patients? What are some of the relevant aspects of

performance testing?

FDA believes that performance testing should support the indications for use for the device, in this case with antimicrobial agents added. How could testing relate to the actual clinical use of PPE? Should we consider the length of time that these devices will actually be used? Should we consider the likely pathogens that will be encountered during the use of various devices, such as medical gloves, surgical masks, isolation gowns? Should we consider comparing the modified antimicrobial PPE with unmodified control devices as we examine their performance?

If terminal sterilization of PPE is performed, and this is relevant for surgical gowns and for surgical gloves, could this affect the antimicrobial properties of the added antimicrobial agent? Therefore, for PPE needing terminal sterilization, should performance testing, in fact, be performed on the post-sterilization pre-shipment device rather than a device which had not yet been sterilized?

Shelf-life determinations are not usually specified for PPE, unless the manufacturer should choose to do so. However, we can ask could the efficacy of an added antimicrobial agent on a PPE deteriorate over a lengthy period of storage of that device? Should the antimicrobial agent PPE shelf-life time, in fact, be determined? And should antimicrobial efficacy testing for submission be performed at the end of that determined device shelf life?

As noted earlier, there are no FDA-recognized standard methods for antimicrobial performance testing for either PPE or other medical devices. In general, antimicrobial performance testing can be quantitative with quantitative end points, such as time kill curves. It can also be qualitative in nature.

Quantitative methods. Here we have initial inocula that can be measured. We can decide whether or not the size of the inoculum may be clinically relevant. We can exactly measure the degree of inoculum reduction in the performance

testing. We understand the range of error in measurement in these assays rather well. We, of course, have to know that what we're seeing exceeds the range of error that we might expect just due to the assay itself. And the methods here are very similar to assays used in actual clinical practice. Therefore, they're fairly easy for clinicians to understand.

Qualitative testing may have somewhat limited value compared to quantitative testing. It does not provide a quantitative measurement of the degree of efficacy of the antimicrobial agent as it appears on the device, in this case personal protective equipment. Zone inhibition testing is one assay that is sometimes offered to us. Zone inhibition testing, as we see it offered for devices, often does not include the standardization used in clinical laboratories where, when we're looking at Kirby-Bauer assays, the release of the antimicrobial from the test material, its penetration into the media, and the correlation of the amount of antimicrobial agent present in the media has been

correlated with the clinical outcomes and also with quantitative testing. This is usually not done when zone of inhibition testing is offered to us for devices. Therefore, it's very difficult to interpret what a zone of inhibition means.

However, there is utility to this assay because it will show that the antimicrobial agent is, in fact, leaching off the device and into the media. And we feel that this may be an important piece of information that we should have for the antimicrobial agent added to a medical device, especially personal protective equipment.

In clinical practice, PPE are used for variable time frames. In the patient room where a nurse or a physician is examining the patient or providing care, gloves, isolation gowns, and surgical masks or surgical respirators are usually used for fairly short periods of time, measured in minutes or perhaps up to an hour or so for a given patient-caregiver encounter. In surgical procedures, however, surgical masks and surgical gowns and gloves may be used for periods of hours, depending on the type of

procedure. Should performance testing for PPE with added antimicrobial agents evaluate these time frames?

For other medical devices with added antimicrobial agents, we are usually seeing devices which are in place in patient care for very long periods of time, usually days. And the standard incubation times which are prevalent in ordinary antimicrobial performance testing, 18 to 24 hours on the average, seem rather appropriate for those situations. But the panel may wish to consider whether those time frames are as appropriate for personal protective equipment.

Typically, antimicrobial indications for devices have been supported by performance testing on bacteria and select fungi. Now, for bacteria activity against a reasonable spectrum of pathogens usually has some predictive value for looking at antimicrobial efficacy for closely-related bacterial species. In practice, when we have evaluated performance testing submitted for other devices, we don't look at performance tested against 20 to 30 or 40 different species. It is usually a somewhat more limited number

of species.

For fungi, usually performance testing only against clinically-relevant organisms is submitted, usually a small number. For instance, for respirators, if we're thinking of that, *Aspergillus* might be a very relevant pathogen. For medical gloves, we might be a little bit more interested in activity against Candida species. The range of clinically-relevant pathogens to be studied should be considered. Should the relevant pathogens tested vary by device depending on what that device is expected to encounter? Should testing and indications for use for performance testing be device-specific, particularly for PPE? Should we be looking at things differently for gloves or masks or gowns?

Antiviral activity against pathogenic viruses is not relevant for many medical devices. For instance, we don't see the sort of performance testing offered for intravascular catheters. However, antiviral activity may be relevant for surgical masks or N95 respirators. Now, antiviral agents typically have fairly narrow spectrums of activity. Therefore,

we would wish to ask should antiviral efficacy testing be performance specific; and, therefore, should the indications for use supported by such testing also be pathogen specific?

If an antimicrobial agent is placed in the interior layer of a mask or respirator rather than on the surface of the device, how could antimicrobial performance be assayed? When we look at other medical devices, very commonly the device itself, a piece of catheter, a piece of dressing, is dropped into liquid media, and, of course, the antimicrobial agent present on the device will hopefully leach out and deal with the inoculum present in that liquid media. If you're dealing with something in the middle of a complex layer of a set of layers, is that the best assay that one should use? Could demonstrating a reduction in an aerosol of infectious inoculum challenging a mask or respirator be more useful depending on the placement of the antimicrobial agent? And in the evaluation of efficacy, could comparison of a modified versus an unmodified device be useful in considering the endpoint?

What could potential clinical benefits of modified PPE actually be in clinical practice? Could we see a reduction in the passive transfer of microorganisms from one physical location to another? Could PPE with added antimicrobial agents enhance safety for the user by improving barrier protection? Could these devices increase protection of both the healthcare provider and the patients cared for?

How could potential benefits be clinically evaluated? Well, we could consider measuring rates of pathogen colonization in patients. We could monitor nosocomial infection rates during use of these devices, perhaps comparing to a control population in which modified devices were not used.

What potential clinical problems could be associated with modified PPE containing antimicrobial agents? Could the addition of antimicrobial agents onto PPE change the perception of infectious risk for both users and patients? Could modified devices provide false sense of security for healthcare workers? Could this reduce compliance with other proven infection control measures, such as hand-

washing? How could potential clinical problems relating to the addition of antimicrobial agents to PPE be accurately evaluated? We could consider doing observational studies of actual practices of healthcare personnel wearing PPE. We could observe hand-washing rates and hand-washing techniques. We could look at or otherwise measure compliance with the use of PPE. For instance, how fast are supplies consumed on an individual unit?

In summary, we think that performance testing for PPE may raise specific issues for consideration in evaluating such devices. What could appropriate performance testing time frames be for such devices? Should device-relevant pathogens be considered for performance testing? What test methods would be most useful in evaluating performance efficacy?

Modified PPE can certainly potentially offer potential clinical benefits. Can these clinical benefits be accurately measured and attributed to the use of PPE with added antimicrobial agents? Or is there a possibility that modified PPE could lead to

1 decreased compliance with existing infection-control
2 measures. Thank you very much.
3 Finally, I'd like to summarize our FDA
4 presentations. FDA has reviewed for the Advisory
5 Panel the current review process for PPE without
6 antimicrobial agents. We have reviewed for you our
7 current experience with evaluation of antimicrobial
8 agents on other devices and brought up selected
9 aspects of performance testing. We've pointed out
10 what potential indications for use for PPE with added
11 antimicrobial agents might be based on public
12 information.
13 The Advisory Panel will next hear
14 presentations from industry and public speakers. The
15 questions for the Advisory Panel will be presented to
16 the panel before your deliberations begin. Thank you.
17 Are there any questions for FDA? Yes?
18 DR. EDMISTON: I actually have this
19 question for Dr. Murphey and Dr. Lin. Let's suppose I
20 was a glove manufacturer and I had developed a glove
21 which, if MRSA or VRE were to adhere to the surface,
22 it was killed. And that would be one of my claims,

and I would have in vitro data to prove that. If, however, I said that this reduces the risk of nosocomial dissemination, would I have to demonstrate clinical data in terms of reduced colonization rates to an ICU study or some other study to validate that?

DR. MURPHEY: Well, as we have mentioned, we do expect for devices presented to FDA that the indications for use or intended use should be supported by appropriate performance testing. Now, I should mention that, given the fact that we haven't cleared many at all PPE with antimicrobial agents, only those two gowns back in the late 1970s, we do advise industry to come in and talk to FDA about their questions and about how they might support their product and what they should be putting in their 510(k) submission before actually doing it to make the process easier and to ask us any questions.

But as mentioned, yes, we would expect that a claim that this antimicrobial on this device could very rapidly kill MRSA or VRE might be adequately supported by in vitro performance testing. However, in vitro performance testing by itself

cannot measure the endpoint of patient colonization or patient infection. Therefore, it's very difficult to see how in vitro testing alone might support a clinical claim such as reducing infection or reducing or preventing colonization with a specific pathogen. I would think that, in that setting, a clinical trial might be desirable.

DR. EDMISTON: But it would depend to a great degree on the vendor's labeling intention, correct?

DR. MURPHEY: Yes, it would. That's correct.

DR. SPINDELL: Hi. In Michelle Rios' presentation, she mentioned there were three indications that, I guess, were under consideration, which was colonization, contamination, and infection. Would the FDA or the panel recommend to the FDA that, if a company was just going for the indication of a colonization, that there would be some information that that type of impact on colonization would impact infection rates? Or would the FDA consider solely the indication for colonization based on testing that it

did, indeed, inhibit colonization?

DR. MURPHEY: Well, what we hope to convey to you, and I should also point out that these contamination, colonization, and infection are, to a degree, aggregate terms for indications for use. But they're really very relevant to the levels of performance testing that we usually see offered for these types of claims. If someone said to me, "Well, this device can prevent colonization," the first question that I would need to ask, because colonization is a somewhat vague term, is what is meant by colonization? It can mean different things in different settings. We can speak about patients colonized with methicillin-resistant Staph. aureus. We can talk about normal people colonized with ordinary Staph. aureus, and this usually refers to carriage in the nasal area or perhaps on the skin or other sites where the organism is persistently present, indeed growing at a low level, but absent any signs of inflammation or infection. But it is present, and, when we're talking about colonization of patients, we are usually talking about periods of days

to months, indeed sometimes years as we've seen it with very chronic colonization with Staph. aureus.

When we speak about colonization on devices, it has, in fact, varied with the device in question. I think we're probably most familiar with it in terms of the intravascular catheter as an example. A number of years ago, Dennis Mackey looked at what might be warning signs for an increased risk of infection related to a vascular catheter. We had known even before that, of course, that the length of time that the catheter was in place was clearly a risk factor for the eventual development of catheter-related infection.

So what was happening with the catheter prior to that event which we would prefer not to have happen? Well, he started looking at what happened to catheter tips when they came out of patients and culturing them in a semi-quantitative manner, and there are now a variety of ways that you can look at catheter tips. But his initial study which was published in 1980 in the New England Journal of Medicine showed that a colony count of 15 to 25

colony-forming units on a removed catheter tip correlated well with the outcome of clinical infection with patients. It was not, by any means, a 100-percent correlation, but it correlated well. And, indeed, that study has now been ruled into clinical practice. So when someone says, "Well, I'm going to look at colonization rates for vascular catheters," in fact, we have a pretty good idea, and they will tell us exactly what they're going to be looking for, and we have a very good idea of what it means clinically.

For other devices, we would ask the manufacturer that same question. What do you mean by colonization? How are you going to measure it? And are you aware of data correlating this with clinical events?

DR. SPINDELL: And that was exactly my question, and it feeds on Dr. Edmiston's question to a degree, was if a manufacturer was to come with the colonization claim, the expectation would be that there would be information on how that colonization impacts care, the end result, which is decreased infection or improved patient safety.

DR. MURPHEY: For vascular catheters and for other devices, as well, there are certainly a number of devices that have been cleared with claims for preventing or reducing colonization period. These have not necessarily gone on to clinical studies. Again, there is some data in the literature suggesting the relationship between those two states. But it depends on what it is that the manufacturer wants to claim, and I would say indirectly on what the medical community thinks that it knows.

We think we have a pretty good idea of what the term colonization means for vascular catheter. And vascular catheters have been cleared by FDA for that claim alone without studies showing changes in the incidents of infection. So they're not necessarily completely tied together. It depends on what it is that the manufacturer is seeking in terms of indications for use intended use. And, perhaps, indirectly, what does the manufacturer that whatever those claims are, how will those be interpreted by those that might choose to use that device?

DR. LURIE: Good morning. Kevin Lurie

from Surgery. Devices that have been discussed so far are barrier devices, and it seems that there's no contention that they don't adequately protect staff. I'm not aware of any studies that say that these barriers are inadequate for protecting staff. And it seems to me the discussion that I'm hearing is actually migrating to a different field of protecting a patient from essentially self-infection with their own microbes and whether the addition of these antimicrobials will improve, clinically change the patients' infections from self-infection. I don't see the relevance at all to indwelling catheters because indwelling catheters are a totally different animal than a barrier protection device, which we're talking about. And I'm wondering, as I heard the presentations on barrier functions, what this migration is and how we address the different described functions by the FDA, the barrier functions versus preventing self-infection from the patient with different antimicrobials.

DR. MURPHEY: Well, this, of course, is exactly why we're coming to you, our Advisory Panel.

Yes, we're very familiar with the barrier functions of these devices, and should they be offered to us in a modified form, we will, of course, be certain that they are substantially equivalent to the unmodified predicate devices in terms of their ability to carry out those barrier performance functions. What could antimicrobials add to PPE? That is the question. We're not the ones who will be adding the antimicrobial agents. It will be others who feel that these may add something to the value of these devices. I think the possible values come in probably two different categories: protecting the patient and protecting the healthcare worker. Gloves may be a good example of that. Gloves can certainly carry pathogens from one place to another. Perhaps, putting an antimicrobial on the outside might prevent that. If you put an antimicrobial agent on the inside of the glove, you're not protecting the patient. But the question would be if you had an antimicrobial agent in that site and you were wearing that glove and you were stuck with a bloody needle, could that antimicrobial agent offer some degree of protection

against the risk of infection from that percutaneous exposure? This is a question to which we do not know the answer, but we think that there may be an interest on the part of industry in trying to answer this question.

Another question is the addition of antimicrobial agents to surgical masks or surgical N95 respirators. These devices in normal use right now do not pose any risk to the patient. They are, however, a protection for the healthcare worker, as well as the patient. We think that there may be some interest in adding antimicrobial agents in hopes of enhancing the barrier function of these devices against ambient airborne pathogens. For instance, pandemic influenza. We think that may be driving some of the interest in adding antimicrobials to this type of personal protective equipment.

But as I say, the question as to why people would do this is one that FDA cannot directly answer. I think you can ask industry that. But we are aware that there appears to be great interest in this, and we know that such devices have been offered for

sale in other countries. Therefore, we think it's appropriate for us to prepare for how we might review such devices should they be presented to us.

If there are no further questions -- oh, I'm sorry.

MS. KRZYWDA: Sorry. Mr. Cunningham reminded us on the extent and volume that these devices would have on healthcare. Gloves, for example, billions of gloves. Does the FDA have any way to track the waste management and effects on the environment?

DR. MURPHEY: This is a very good question. At the moment, antimicrobial agents on devices as we have currently been clearing them have been considered to not pose a large enough hazard to the environment to warrant separate evaluation, as, for instance, might be considered for the use of antimicrobial agents in animal feed, and the Center for Veterinary Medicine does make such evaluations. However, the volumes of use of the various devices over time that FDA has cleared have been smaller than PPE.

However, I would point out to you that today and, in fact, for many years prior to today antimicrobial agents have been added to other products which are not medical products which are being used by the general product, are being used by consumers. We don't really have any idea or data on the volume of that use either in this country or in other countries. And it is my understanding that, at the moment at least, that's not something that's being tracked by Environmental Protection Agency. So at the moment, no, we have not given a great deal of thought to whether or not we need environmental impact statements for PPE with added antimicrobial agents.

DR. DAVID: I have a question relating to safety, specifically safety of the user. The average user of childbearing age in a hospital setting is raising an issue relating to migration or leaching off phenomena. Can you highlight what studies or MSDS is saying about the antimicrobial agent effect on the childbearing population?

DR. MURPHEY: Well, I think it's going to vary completely with the antimicrobial agent that is,

in fact, added to the device and whether or not it will leach off or physically detach from the device. I think this is a very valid question. For agents which have already been in use for other purposes, for instance we have vascular catheters with rifampin and minocycline added to them. Both drugs have been used in clinical practice as systemic agents for a long period of time. We know a lot about those drugs so that even if they were migrated off the device, we can make predictions about what might be the effect on the patient receiving such a device or the healthcare worker handling such a device as they insert it.

The same thing would be true for topical antimicrobial agents. If we saw a device presented to us for which we had no such experience, that would be a very large question for the sponsor of such a product. What, in fact, would be the safety? You're absolutely right, and this is why Mr. Cunningham raised the question of what about children, what about neonates, what about immunocompromised patients, what about the pregnant healthcare worker? Yes, these are very important considerations.

CHAIRMAN JARVIS: Are there any other questions?

DR. MURPHEY: If not, you'll have your opportunities again later. Thank you very much for your attention.

CHAIRMAN JARVIS: Thank you. Now we're going to take a break for about 15 minutes. I just want to re-emphasize that if there's anyone who wants to present in open hearing, if they please let either Ms. Williams or Lieutenant Colburn know during the break. We're going to break for about 15 minutes. By my watch, it's about 9:40, so if everybody come back, let's say, by 10:00.

(Whereupon, the foregoing matter went off the record at 9:41 a.m. and went back on the record at 10:06 a.m.)

CHAIRMAN JARVIS: Thank you. We will now proceed with the first open public hearing portion of the meeting. Public attendees are given the opportunity to address the panel and to present data information or view relevant to the meeting agenda. We have at least one speaker scheduled for this

session. Each speaker has been allotted a maximum of ten minutes to speak. In the interest of time, we ask each speaker to be as brief as possible and the panel to hold questions until everyone has presented.

Both the FDA and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee Meeting, FDA believes it important to understand the context of the individual's presentation. For this reason, FDA encourages you, the open public hearing speakers, at the beginning of your written or oral statement to advise the Committee of any financial relationships that you have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this

issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Our first speaker is going to be Brian Heinbuck of the Air Force Research Lab. Brian?

MR. HEINBUCK: I just signed up, so I thought I'd be later in the day. So let me just say, from a background standpoint, again, my name is Brian Heinbuck. I work in support of the Air Force Research Laboratory. We're located at the Panama City, Florida Tyndall Air Force Base. We are involved as a DoD lab in a lot of testing that's very relevant to what you all are talking about this morning, in particular what we would call as reactive material. It could be a respirator. It could be fabrics. It could be undergarments. It could be a variety of things but all in the basic category that falls into infection control. So infections that we may be looking at could be a bio-threat, a virus, or Anthrax, or something like that, that's different from the organisms that you may be concerned with, but generally infection control is how we could label it.

As part of the function of our lab, we do do third-party testing for the DoD for, again, respirators and reactive materials and all things that are, again, antimicrobial. My role and responsibilities as part of the group is to run the BSL-II lab, actually carry out the testing, and oversee the data analysis.

So I was very glad to hear this morning these folks talk about testing because, in trying to do the testing for the Department of Defense and our customers, we also have very similar concerns about is the testing methodology relevant to the actual challenge condition, you know, what actually are we going to see in the field.

If you go and look at the current standards that are available for testing from the American Society for Testing and Materials and the American Association for Textiles Chemists and Colorists, the AATCC, these organizations publish test methods that are essentially water-based methods, so, you know, basically suspending microorganisms in water or applying a lot of water to the surfaces. What

you'll find in a lot of the reactive material work that we've done is that water can very much influence the performance of the antimicrobial. So if there's not a lot of water present in the actual exposure, you have to be careful in interpreting those results.

So, again, as part of our lab, we're involved in aerosol-based deposition testing and methodologies because, from a DoD perspective, that's the kind of deposition we'd expect in a real-time challenge. So the problem, though, is when you go and look for aerosol deposition standardized methods, there's none that exist out there. I think if you go back and look at ASTM, there's one very old standard that they use to challenge respirators with Staph. aureus with. It goes back quite a ways, and I'm not sure it's even on their books anymore.

So as part of our effort to begin with, the DoD, we are involved in two types of particle-deposition, aerosol-deposition challenges. One is to challenge materials and look for penetration of viable materials. So for our N95-type respirator or, in our particular case, we're looking at canisters or things

of that nature for penetration. Challenge upstream with viable particles and then look for how many viables come through.

As part of that work, we're collaborating with the Army, the Edgewood Chemical and Biological Center, to develop test methods for a standardized test method for looking at challenges for biological neutralization devices. So in that particular case, you could define biological and neutralization devices, any device that could have an active process to kill microorganisms, so an antimicrobial or, in our case, it may be a UV light source or gamma radiation or vaporized peroxide, or something of that nature. But the idea is still the same: put a challenge upstream, and what do you get downstream?

The problem is when you start looking at creating aerosols, there's a whole host of complexities that you have to take into account in the testing. One is particle size, agglomeration, protective factors, challenge concentration. All these things are very important but very hard to define an actual test. And you go from lab to lab and

you look at this lab testing with this particular device and this lab testing with another device, you get very different aerosols created which can dramatically effect the performance of the results. And if you do go through the literature, I mean we just did an exhaustive open literature research, and there's hundreds of papers out there on people creating biological aerosols for challenges. But, by and large, they're all very different from one another, so how do you standardize and how do you compare this result to that result? It becomes very difficult.

Another application that we're doing for bio-aerosols is aerosol deposition onto surfaces. So, again, for fabrics, it's going to be fairly straightforward because when you apply an aerosol to a fabric you can essentially draw the air through it and the particles impact, and it's very easy. But when you apply an aerosol to a solid surface, it becomes much more difficult because the air flow patterns go around the surface, and getting deposition can be very difficult, especially at concentrations that would be

relevant for testing.

So as part of another DoD effort through DARPA, which I forget that act and what it means, but we're applying, developing test methods for applying aerosols to solid surfaces. And then, finally, the last test method development that's going on that you all may or may not be aware of but it's certainly extremely relevant to your work is the Technical Support Working Group, the TSWG, which is a group combating terrorism, has just released a call for, it's basically a two-phased call looking for, one, developing test methods for applying bio-aerosols to PPE, in particular respirators, coming up with a standardized test method, and then looking at methods to decon PPE for re-use of N95-type respirators or surgical masks.

And then, finally, just for future thinking, new technologies are going to be coming along. We were talking about applying antimicrobials to PPE, but pretty soon someone is going to be coming to you folks and saying, "I've got technology to apply antimicrobials to the doorknobs and to the surfaces of

walls," and things like that. And the DoD is very active in those, as well. And, again, those become very difficult test methods, and you have to be able to have some idea of what your challenge is going to look like and how the test method actually relates to that.

So that's all I have and, certainly, will take questions at this point. If you want to wait, that's fine, too.

CHAIRMAN JARVIS: Let me just ask if there's going to be anybody else who wants to present in opening hearing. If you'd raise your hand. If not, why don't we go ahead and entertain questions now. I guess I'll start. I know this is probably unlikely, but do you have any idea of whether ASTM, the other organization you were talking about, military services and FDA are collaborating or working together or communicating together in any way or putting together any kind of task force so that the information that one learns could be applied to the other and more standardization actually could take place?

MR. HEINBUCK: Well, that's a great question, and I'm sure, as you know, you generally get very little communications between these different organizations. The best thing that I can talk to is in the TSWG proposal or the TSWG call for proposals that was just put out, there's collaboration. We're collaborating with the NIOSH, the National Personal Protective Technology Lab, so in putting forth a proposal to address that need for both testing and decon of PPE. So that's not a broad-ranging necessarily or high-level collaboration, but certainly you have a service lab in the Air Force Research Laboratory, NIOSH, and PPTL working together to try to develop the test method. Beyond that, I don't really -- you know, normally, like, in the ECDC effort we're doing for the Army, that's just a DoD effort, and I'm not entirely sure we talked about publishing and making that widely available, but I don't know the end results, what that will be.

CHAIRMAN JARVIS: Are there any other questions?

DR. LURIE: Obviously, the Department of

Defense's goals are different from the standard medical practice, and I'm wondering if you have any information on the toxicity of some of the agents that you do use not just for testing but on the users that may be involved in these products.

MR. HEINBUCK: Well, so there's a threat agent published, obviously, for the Department of Defense, and they're looking at a variety of threats, and these are all, you know, common knowledge. You've got Anthrax, you've got, you know, small pox, you've got a variety of bacterial and non-spore forming threats. So when we do our testing, again, we're looking at what's the minimum effective doses, things of that nature. For Anthrax, it's generally believed to be a high number of spores, eight to ten thousand, you know, maybe less than that, depending on which reference you want to believe. If you look at the viral threats, you look at much lower minimum effective doses. Generally, it's thought to be less than 10 virions that cause infection.

So when you look at, you know, from our standpoint, we look at the protective devices we have,

and we can look at the challenge to it, and it's a mathematical, you know, when you look at particulate penetration, you can do the math on it and figure out, well, do we really have protection there or not? But then you've got to go back a step further and look at what's the challenge really look like? You know, what's the particle size of this challenge? Because that's going to affect penetration. What's the protective factors? What's the length of viability in the aerosol state? And all those things play into the role when you're trying to determine protective factors.

But you mentioned another good point as far as testing microorganisms because there's a whole, well, I'm going to a meeting next week on what are the appropriate stimulus that we use to do the testing because, unless you're working in a BSL-III facility with high-level aerosol containment, you're not going to be Anthrax and small pox. So what are the safe organisms you can work with? And, generally, from the military's perspective, there is a list of microorganisms that we're working on. That will be

flushed out more next week, as well. But how that relates to the things that you're interested in as far as stimulus you could work on that are appropriate testing, microorganisms. You know, they're different animals I would say.

DR. EDMISTON: One of the questions that's going to come up is duration of activity, and if you look at the devices that have been approved by the FDA, central lines, Foley catheters, some other devices which are implanted, there have been papers published by independent investigators looking at duration of activity of these agents. How important do you perceive duration of activity with the short-term devices? Because there's really no guidance in this area unless you look towards that 1994 TFM for topical skin antiseptics. This clearly shows that, for an antiseptic, topical antiseptic, ten minutes, thirty minutes, and six hours is considered important duration. How do you perceive that on some of these other devices?

MR. HEINBUCK: Well, from a military application, so say a coating on the tents, duration

of kill could be, you know, it could go up to days to weeks because you could evacuate the tent and come back later. Say for undergarments and things of that nature that we put antimicrobial coatings on, that generally could happen very quickly and generally driven by the amount of moisture that's available.

For gloves and things like that, we're not really, we're learning of that here. That's things that we've not been overly intimately working on. But, certainly, if you have a PP device that you strip off and ten minutes after use, you know, I understand your question there. But from a military perspective, to where if I'm in the field and I wear a garment that has antimicrobial protection on it, they could be wearing that, you know, for hours or potentially longer than that before they actually would take it off. So it's, again, not the same type of correlation to what we're looking for and what you all are looking for in duration of kill, duration of time for kill.

DR. DAVID: In your testing methodology of the fabric or the solid surface, my understanding is that the agent, the antimicrobial agent, can be

applied on the outer shelf, the inner shelf, and in between. Can your test and model can differentiate what side of the barrier is being more effective?

MR. HEINBUCK: The test that we're working on right now for fabrics, so it could be fabrics or solid-surface coatings. For surface-bound, you can apply surface-bound microorganisms without getting penetration, or you can simply draw air through the fabric and get it embedded into the fabric, as well. So, yes, the test that we have could coat either side of the fabric or surface without any problems, or, from a filtration standpoint, if you wanted to know how much the military, you know, concerned about wind speeds and things like that, how much actually gets pushed through the fabric, we could evaluate that, as well.

CHAIRMAN JARVIS: Are there any other questions?

DR. GORDON: I think, from my perspective, the interest in the masses is really excellent. Also, from a hospital perspective, antimicrobacterial, antiviral, and so forth, protection. But with regard

to gloves and transmitting, I have some serious concerns about how it may affect behavior. You're supposed to be taking them off and how healthcare practice is so poor anyway.

But I'm curious what kind of speed are these, if you're breathing in organisms and you're breathing in microbacterium, and you're breathing in viral particles, do you have any data on how quickly these devices are effective at eradicating anything coming through?

MR. HEINBUCK: So if you look at, say, a normal HEPA filter, we've done a lot of tests on HEPA filters which would be personal protective or collective protection, and given the appropriate particle size so we know HEPA filters efficiently penetrated at the .3 micron particle size, when you apply a challenge of that size to the respirator, you'll get immediate penetration. There's no time delay. It's an open system, so you'll get a penetration instantaneously upon applying the challenge.

DR. GORDON: Oh, no, what I'm saying is

how long does it take for the antimicrobial to have an effect on any organisms that might get through? If it doesn't work for 20 minutes, then it's really go to be in the host, and it's really not going to be of much use anyway.

MR. HEINBUCK: Right. So then you talk to residence time of the microorganism in the filter as it's traveling through. That's a good question. We don't have a good answer to that at this point. We do know that we've done some testing for antimicrobial surfaces. We do get reduced penetration downstream of the filter compared to a normal HEPA device. So something is happening there to cause an orders of magnitude decrease in viability downstream. But, you know, you make a good point on the residence time, and I can't answer that question at this point.

DR. GORDON: Now, do these devices work so the organisms get caught in the filter itself, and then some eventually get through after staying in the filter for a period of time?

MR. HEINBUCK: That's an excellent question, and I don't think people have the answer to

that at this point.

CHAIRMAN JARVIS: Okay. Thank you very much.

MR. HEINBUCK: You're welcome.

CHAIRMAN JARVIS: I think now we'll continue with industry presentations. Each speaker will talk in the order that's on the agenda. Following the presentation, I'll ask if the panel has any points of clarification for the presentation they would like to be answered at that time. Otherwise, we can hold discussion until the very end.

And our first speaker is Tom Page from Cupron, Incorporated. Tom?

LT. COLBURN: While Mr. Page is getting ready, there is a clicker up there now for a slide advancement that was provided by Dr. Truscott. And just make sure you don't happen to take it back with you, or you can just use the computer to advance your slides.

MR. PAGE: Okay. Can everyone hear me? Okay. I'd like to, first of all, express my appreciation to the panel and to the FDA for this

meeting. I think, you know, for our company, but just in general, obviously, the topic of antimicrobial personal protective equipment is a topic which is increasingly becoming a current one. Many of the issues that have been addressed already by presenters Dr. Murphey, Ms. Rios, and others, are issues that we'd like to touch on, as well.

You know, I've been told that it's appropriate to introduce oneself and whatever associations one has. And, obviously, we're an industry representative. Cupron is basically a manufacturer of one product, which is a product with many, many potential uses. It's a fiber which is impregnated with a copper compound, cupric oxide, which is essentially a naturally-occurring form of copper with, essentially, broad-spectrum antimicrobial qualities, which is one of the reasons we're here today.

I'd like to sort of discuss three basic issues today. And these issues that I'm going to discuss, I mean, we've been given ten minutes each for the presentation, and obviously there's a limit to

what one can say in ten minutes. But the basic issues we'd like to touch on are, first of all, the value of antimicrobials in PPE beyond the protection of the wearer. And some of these issues have already been touched on.

The second issue is the risk of antimicrobial PPE leading to what is essentially a false sense of security in healthcare institutions. That's obviously an issue that's been touched on today, as well.

The third issue is the risk of creating resistant microbes. And, obviously, everybody is concerned with VRE and other resistant microbes. We'd like to just make a few remarks which have been sort of dealt with in more length in our written contents.

The first goes to the added value of antimicrobial PPE. Obviously, the easy sort of brass ring when it comes to PPE and antimicrobial PPE is to avoid cross contamination. In other words, if, let's say for example, a healthcare worker touches a source of antimicrobial contamination then touches another surface, including actual patients, obviously, you

know, to solve that problem you would need a very, very fast kill time for the microbes on that PPE. Let's say you're talking about a glove, which has been addressed by the FDA several times and sort of, because of this cross contamination issue, you know, which requires, I would guess, based on the data that we have, a matter of seconds in order to truly be effective at reducing all cross contamination.

Now, the question is are there other possible uses to, you know, for PPE, and, obviously, the issues have been raised already. But one of the things that one can say is that a dwell time of even, let's say, 15 to 45 minutes, you know, can potentially have some added value.

And what could that added value be? First, much PPE is worn for longer periods of time, and there's a bioburden issue. Again, bioburden, as was mentioned, you know, is a complex issue which is sort of one step removed from clinical reduction of nosocomial infections. However, you know, obviously, the inference is very strong that if you can reduce bioburden in a statistically-significant way, even

over a longer period of time, that could have several important effects. First, given that the wearers of PPE often wear it for a longer period of time, even when it's disposable and single use, over time, the reduction of bioburden and of microbes of various kinds on the surface of PPE can have an actual effect on cross contamination, especially given the issue of poor hygiene practices that have been touched on. One of the main causes identified in the literature of nosocomial infections is failure to implement basic practices such as hand-washing, and the source of nosocomial infections, in the literature at least, is identified as basically the flora on human beings which enters into the hospital environment.

The other issue is improper disposal. Obviously, to the extent that PPE is not disposed of properly, the wider it's used, which presumably would be extremely wide in the case of a possible epidemic or pandemic, improper disposable, given that the problem of improper hygiene practices and improper disposable seems to be widespread even among trained healthcare workers, it's to be presumed that PPE with

a longer dwell time, you know, an antimicrobial with a longer time of effectiveness, would have some incremental impact in addressing that issue.

So I guess, from our perspective, the solutions are not all or nothing solutions. In other words, nosocomial infections, it's been shown, are generally introduced by a combination of approaches, as we discussed in our written comments. And to the extent that antimicrobial PPE could be one element in the longer, in a much broader effort to combat the problem, that, in our view, would be appropriate.

I'd like to quickly address the issue of false sense of security. And, obviously, nobody can deny that if you build a better mousetrap, that mousetrap will potentially induce people to stop believing that they have mice. And that's not something that is particularly good. I'd like to make three points about that.

The first is it's important, in my view, to keep very modest claims and indications for use. In other words, not to try to sort of claim, you know, whoever is manufacturing the PPE, that somehow this is

the solution without more to very difficult epidemiological problems. Obviously, it's not. This is the flip-side of incremental solutions. You cannot throw out other approaches and important hygiene and disposal issues simply because you feel you have a good antimicrobial product.

The second issue is to have important warnings with any such PPE about good hygiene and disposal practices. I mean, without such warnings, you know, obviously, it's possible to make assumptions based on the nature of antimicrobial PPE, but somehow a person would need to stop, would be able to, once again, stop engaging in unsafe practices in order to protect themselves and others.

But I guess the third point is I think the bottom line, I mean all improved forms of PPE engender the risk of a false sense of security. In other words, if you wear surgical gloves or surgical masks, you know, when these were introduced, presumably and certainly people felt there was an additional level of protection. And this is something that is, in fact, the case. And, yet, we know that it's important to

comply with safe hygiene and disposal practices. So to the extent a false sense of security is an argument against antimicrobial PPE, it's basically an argument against any measure improving, potentially, the state of hygiene and bioburden.

Obviously, when it comes to antimicrobial PPE, one of the really hot-button issues is the issue of microbial resistance. Once again, the problem is increasingly a dire one. It arises, as we all know, from massive use of antimicrobials, including such antimicrobials as oral antibiotics in human and animal populations. And, obviously, this has led to a lot of very nasty microbes rearing their, I guess you can't speak of heads but rearing themselves in hospitals and elsewhere. And, you know, once again, coming from our perspective as a copper antimicrobial, which has been around in the biosphere, essentially, ever since the biosphere has existed and has been used in human environments for millennia without actually any significant resistance to copper over time, it would be, in our view, advisable to use such naturally-occurring, we're not the only ones, naturally-

occurring antimicrobials that have avoided microbial resistance over the millennia.

The example of copper, which we go into in great length in our written comments again, but copper acts using several mechanisms to make it very hard for microbes to actually evolve out of vulnerability to copper. What happens with soluble forms of copper, which we're not, is sometimes you have, as opposed to resistance, something called tolerance. Now, tolerance is the amount of copper that you actually have to use increases but not exponentially. In other words, if enough copper is actually used, even in soluble forms, and this has happened especially on farms with the use of copper sulphate, there's an increasing level of tolerance but not resistance. And the reason why is not worth going into here because it's a general meeting, and I don't want to throw people with copper.

But the main mechanism that should be I think focused on with antimicrobials, as opposed to things like triclosan which have led to very fast resistance and work in a very simple way, microbes are

very good at mutating away from. It's best to stick with antimicrobials that work simultaneously in several different ways to neutralize microbes such that mutations are much harder to achieve on the part of microbes.

So that, in brief -- I hope I didn't exceed my ten minutes. That, in brief, was what we . . .

CHAIRMAN JARVIS: Are there any questions?

DR. DAVID: My question is can you be more specific as to just microbial agent is the copper mechanism is specific to a certain bacteria or virus?

MR. PAGE: Well, we've been shown effective in laboratory testing against both gram-positive and gram-negative bacteria and a wide variety of viruses. Actually, we're now working with the FDA closely to develop testing that would be acceptable to the FDA. But, yes, we're a broad-spectrum and not just viruses and bacteria but also fungi, as well, and dust mites as well. I can tell you some of the mechanisms used, if that's of interest. I just don't want to spend time for the panel, you know, in ways

that's not of interest to the panel. That's all.

DR. DAVID: And you mentioned dwell time. You have any indication of initiation of spill faction?

MR. PAGE: Right. It really depends on how -- again, we have a technology that impregnates fibers with copper, and we also have another technology that coats fibers with copper, plates fibers with copper. Now, depending on the amount of copper and the ratio of copper fibers, I mean that dwell time can be a matter of a few minutes to a matter of a half an hour, depending on what is done with the fibers. I mean, basically, you know, the copper ions which are released are what actually does the, what actually kills the microbes.

But just very quickly, I'll essentially mention the ways, I mean if it's of interest, that the copper works. And the first way is denaturation of nucleic acids by binding to and/or disordering helical structures and by cross-linking between the nucleic acid strands. The second is alteration of proteins and inhibition of their biological assembly and